Congenital Anomalies of the Upper Extremity

Etiology and Management

Donald R. Laub Jr.
Editor

Second Edition

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To the memory of Dr. Sondra Solomon and Dr. Toshihiko Ogino.

Preface

It is the greatest joy and honor of my career to use surgical skill caring for children. It is also a joy and honor to work with so many great scholars and clinicians in the preparation of this text.

Colchester, VT, USA — Donald R. Laub Jr.

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Part I

General Considerations

1 Embryology and Classification of Congenital Upper Limb Anomalies

Kathryn F. Ball, Michael A. Tonkin, and Kerby C. Oberg

Morphological Overview

In vertebrates, the limb bud starts as an accumulation of cells within the lateral plate mesoderm (LPM) forming an oblong, ventrolateral bulge on the body wall. The limb is a composite structure of cells from the lateral plate mesoderm (precursors of limb-associated skeletal tissues) and associated somites (muscle and vascular precursors). In humans, the upper limb bud appears during the fourth week of development around day 26 (Carnegie stage 12) and is located between somites 9 and 12 (Fig. 1.1a) [1, 2]. The limb emerges only in certain zones of the body, known as limb fields. The positions of limb fields are thought to be specified by a quantitative and/or qualitative combination of Hox transcription factors (see Fig. 1.1b) [3, 4].

By day 37 of development (Carnegie stage 16), the distal portion of the limb can be recognized as a handplate. At the same time there is progressive mesodermal condensation along the proximodistal axis forming the skeletal elements of the limb. By day 56 the major morphologic features of the limb are complete.

Limb Initiation

After the upper limb field has been specified, induction of the limb bud occurs. The cells of the LPM located within the limb fields maintain active proliferation, while non-limb field LPM begins to divide more slowly [5]. The proliferative mesenchymal cells of the emergent limb bud are derived from epithelialized LPM and must undergo epithelial to mesenchymal transition (EMT) to initiate limb bud formation [6]. Fibroblast growth factor 10 (Fgf10) is expressed broadly along the LPM in the early embryo, but just before the limb emerges, the domain of Fgf10 expression becomes restricted to the limb field. In chicken, the expression of *Tbx5* and *Wnt2b* in the LPM cells of the limb field are responsible for the induction of *Fgf10* in the presumptive limb (see Fig. 1.2) [7–9]. Studies suggest that *Tbx5* expression can be induced and regulated by Hox transcription factors, suggesting a role for *Hox* genes in both positioning the limb field and initiating limb outgrowth [4, 10]. Fgf10, through its receptor Fgfr2b, has been shown to induce *Wnt3* and *Wnt3a* in prospective

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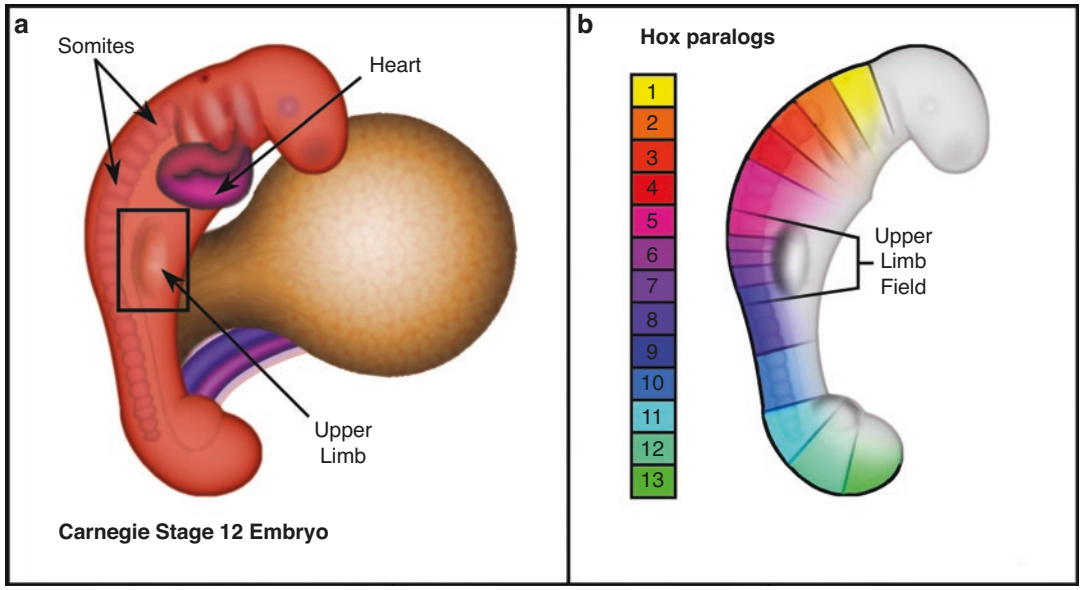

Fig. 1.1 Human embryo at stage of limb initiation and presumed Hox positioning. (**a**) Depiction of an emerging upper limb bud (boxed) in Carnegie stage 12 embryo. (**b**) Hox genes establish upper limb position and polarity. (Courtesy of K.C. Oberg and Loma Linda University)

mouse and chick limb ectoderm, respectively [11–13]. Concurrently, bone morphogenetic protein (Bmp) signaling in the ventral ectoderm induces β-catenin competency in cells of the presumptive apical ectodermal ridge (AER) at the dorsal-ventral boundary [14, 15]; for a comprehensive review of Fgf10 in limb development, see [16]. In turn, Wnt3 or Wnt3a induces *Fgf8* in a Wnt/β-catenin-dependent manner in the precursor cells of the AER [7, 11]. Fgf8 secreted from the recently formed AER maintains the expression of *Fgf10* in the mesoderm, establishing a positive regulatory loop that maintains proximodistal growth [7, 11].

Another signaling molecule that is fundamental to the induction of the limb bud appears to be retinoic acid (RA), the active metabolite of vitamin A. This molecule is produced in the somites of the embryo by the enzyme Raldh2 [17–19]. RA restricts the early expression of Fgf8 within the heart field, which, in turn, permits the expression of *Tbx5* in the limb field to initiate forelimb development [20, 21]. Furthermore, RA has been shown to regulate the expression of *Hox* genes both in vitro and in vivo, which may contribute to limb field induction and/or positioning (see Fig. 1.2) [22, 23].

Signaling Centers

Between the fourth and eighth weeks of development, the limb bud undergoes growth and differentiation to transform it into a fully patterned limb. This process can be described in terms of three coordinate axes: proximodistal (PD), anteroposterior or radioulnar (AP/RU), and dorsoventral (DV) modulated by three signaling centers [24].

Along the PD axis, the AER appears as thickened ectoderm overlying the distal edge of the limb bud [25]. The AER is the signaling center that regulates PD growth through Fgf signaling. Excision of the AER in chicken embryos at successive stages of limb development results in progressive limb truncations [26].

The signaling center for the AP/RU axis is the zone of polarizing activity (ZPA), a cluster of mesodermal cells located at the distal posterior

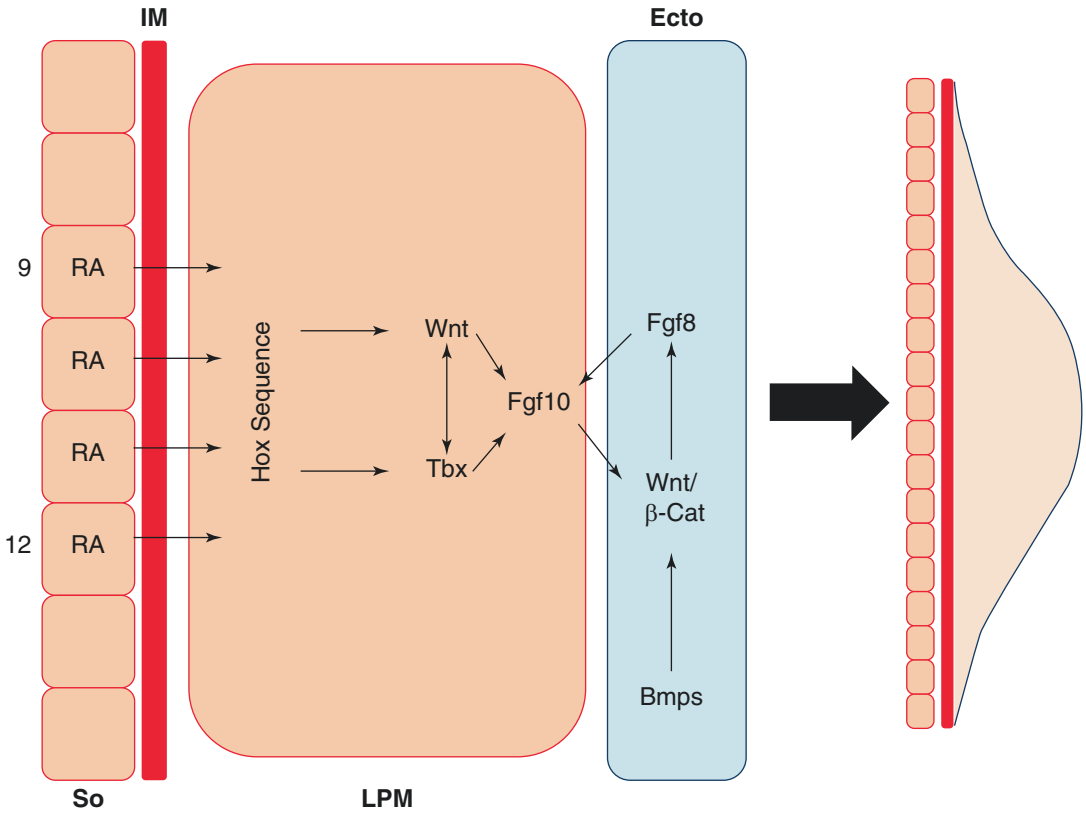

Fig. 1.2 Molecular pathways involved in limb induction. Depiction of the tissues involved in the initiation of the right upper limb bud emerging from lateral plate mesoderm (LPM) at somite (So) levels 9–12. Molecular interactions between LPM and ectoderm (Ecto) are also illustrated. IM intermediate mesoderm. (Courtesy of K.C. Oberg and Loma Linda University)

(ulnar) margin. The ZPA directs AP/RU patterning and Shh is the signaling molecule that mediates its function. Both mice (*Shh* knock-out) that lack Shh function or mutant chickens (oligozeugodactyly (*Ozd*) mutants) that fail to have limb-specific Shh expression show marked loss of posterior (ulnar) elements [27, 28].

Dorsal, non-AER ectoderm directs DV patterning with Wnt7a as the signaling molecule that promotes dorsalization. Excision and rotation of the dorsal ectoderm results in the formation of dorsal structures within the ventral aspect of the limb [29].

Patterned Development Along Coordinate Axes

Pattern formation is a process by which the cells are sequentially specified, determined, and then differentiated to form the morphological structures of the limb. In this section we will focus on how the process of patterning is accomplished along each axis as directed by the signaling centers and the associated molecular pathways, recognizing that the molecular cascades of these three axes are operating concurrently to coordinate development.

Proximodistal Patterning (PD)

The upper limb can be divided into three different segments along the PD axis (Fig. 1.3): (1) the proximal segment or stylopod where the skeletal elements of the humerus develop, (2) the intermediate segment or zeugopod where the radius and ulna form, and (3) the distal segment or autopod where the carpals, metacarpals, and digits form.

Patterning along the PD axis begins during limb initiation with the formation of the AER, stratified ectoderm at the distal dorsoventral boundary of the developing limb bud. The AER secretes Fgfs, the molecules primarily responsible for PD patterning. Fgf8 is the first and functionally most important Fgf secreted from the AER during induction and is maintained until the AER regresses, when the drafts of the last phalanges are formed. *Fgf4*, *Fgf9*, and *Fgf17* are activated sequentially in the posterior AER and expand to the anterior aspect as the limb develops [30, 31]. Classical experiments in chick embryos showed that AER removal abated distal limb outgrowth and resulted in truncations that corresponded to the timing of AER removal; in other words, the later the AER removal, the more distal the truncation [26]. Moreover, Fgf-soaked beads were able to restore limb bud outgrowth and patterning after AER removal, indicating that Fgfs are the functional signaling factors of the AER [32, 33].

Among the different *Fgfs* expressed, *Fgf8* is thought to be the main AER signal, while *Fgf4*, *Fgf9*, and *Fgf17* are considered secondary or redundant [34, 35]. This concept is supported from experiments with *Fgf8* knock-out mice that showed smaller AERs, delayed limb bud outgrowth, and loss of some skeletal elements [30, 36]. In contrast, knock-out mice for *Fgf4*, *Fgf9*, and/or *Fgf17* did not develop limb anomalies. Interestingly, *Fgf4* expression in *Fgf8* knock-out

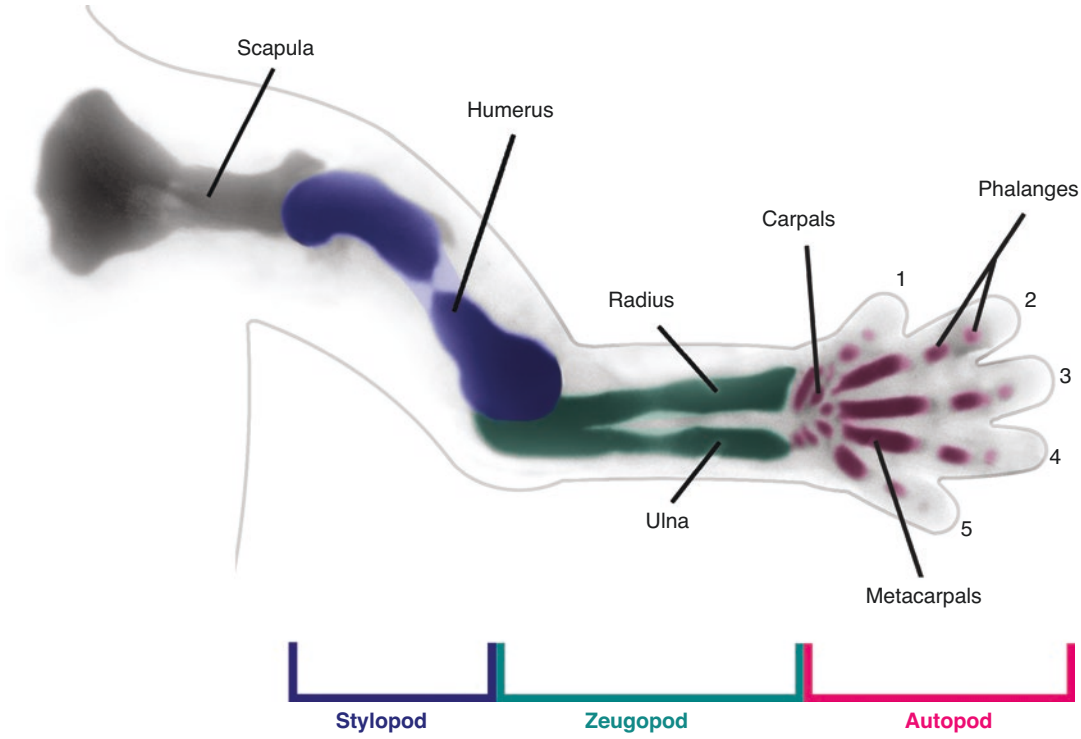

Fig. 1.3 Limb elements. The upper limb consists of a limb girdle or shoulder and three limb segments known as the stylopod, which contains the humerus (colored blue), the zeugopod, which includes the radius and ulna (colored green), and the autopod or handplate (colored magenta). (Courtesy of K.C. Oberg and Loma Linda University)

mice was upregulated, suggesting that redundant expression may have lessened the phenotype of these mutants. This was confirmed by the removal of both *Fgf4* and *Fgf8* that resulted in a worse phenotype with notably smaller limb buds [36, 37].

Several models have been proposed for PD patterning. The progress zone model proposes that mesenchymal cell fate is determined by the length of time spent under the direct influence of the AER in a proliferative region called the progress zone (PZ) [38, 39]. The early specification model [40] postulates that the PD identities are specified early and the different progenitor pools expand sequentially as the limb grows. The differentiation front model suggests that the AER maintains mesenchymal cells in an undifferentiated state; as the limb expands, the cells that are no longer under the influence of the AER differentiate [41].

However, the accumulating evidence supports an alternative model. The two-signal model [34, 42] proposes that two opposing signals pattern the limb along the PD axis: RA emanating from the flank will specify a proximal fate, while Fgfs from the AER will specify a distal fate (Fig. 1.4a) [43, 44]. In somites, Raldh2 oxidizes retinol to form RA which can act locally in the proximal limb buds to promote the expression of Meis1 and Meis2. The expression of Meis1/Meis2 and Shox2 defines the proximal limb segment and where the humerus (stylopod) will develop. Distally, Fgf signaling induces 5′*Hoxa* genes (*Hoxa11*, *Hoxa13*) and limits distal *Meis1*/*Meis2* expression. Although the mechanism for this repression is not fully understood, it is known that Fgf8 signaling induces the expression of *Cyp26b1* in the distal mesenchyme of the limb bud; the product of this gene oxidizes RA into a non-active form, thus clearing the distal region of active RA (see Fig. 1.4c) [45]. In addition, recent evidence indicates that polycomb repressor complex 1 (PCR1) members are necessary for RA inhibition in the distal limb bud, and that RA and

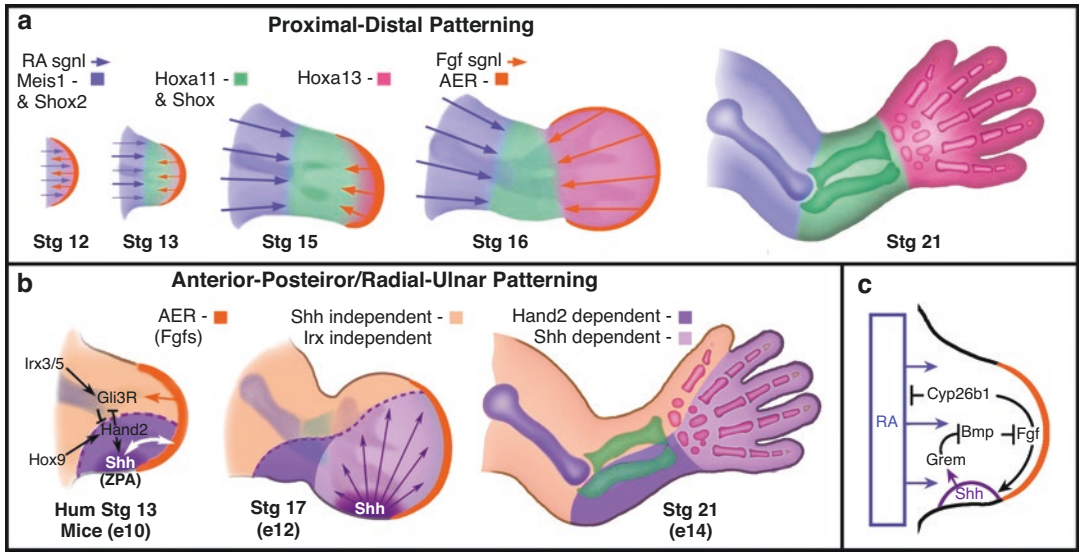

Fig. 1.4 Molecular pathways regulating proximodistal and anteroposterior/radioulnar axes. (**a**) Progressive segment specification along the proximodistal axis based on the two-signal model with RA-related proximalizing signals countered by distalizing Fgf signals. Outgrowth separates the signals and an intermediate zone is formed. Mies1 and Shox2 are restricted to the stylopod, Hoxa11 and Shox are markers for the zeugopod, and Hoxa13 delimits the handplate boundaries. (**b**) Opposing gradients of Gli3 repressor (Gli3R) and Shh-maintained full-length Gli3 activator establish boundaries between the radius and ulna in the zeugopod and the thumb and ulnar digits in the autopod or hand. (**c**) Some of the molecular interactions that maintain and terminate Shh expression in the ZPA (→ indicates positive regulation, while ⊣ indicates inhibition). (Courtesy of K.C. Oberg and Loma Linda University)

PCR1 appear to have antagonistic roles in *Meis2* regulation [46]. Some have questioned RA's role as a proximalizing agent [20], and further investigations are warranted to clarify whether RA or another factor influenced by RA is the proximalizing signal. As the limb elongates, a gap between the proximal and distal signals develops. This establishes an intermediate region demarcated by Hoxa11 and Shox expression where the radius and ulna will form (zeugopod). Fgf will maintain Hoxa13 expression in the distal limb bud defining the handplate (autopod) (see Fig. 1.4a).

Anteroposterior/Radioulnar Patterning (AP/RU)

The limb along the AP/RU axis is divided into two segments: the anterior (radial), comprised of the thumb and radius, and the posterior (ulnar) with the ulna and ulnar digits (digits two through five) [47].

Patterned development along the AP/RU axis is regulated by the ZPA, a cluster of mesenchymal cells maintained in the distal posterior/ulnar aspect of the developing limb (see Fig. 1.4b). The ZPA was discovered in 1968 through grafting experiments in chick limb buds [48]. In these experiments, grafts from the distal posterior/ulnar mesenchyme were excised from one group of chicks and then inserted into the distal anterior/radial aspect of another group of chicks. The limbs that developed from these grafts demonstrated mirror-image duplication of structures [48–50]. RA was found to be the first molecule that mimicked ZPA grafts when applied to the distal anterior/radial aspect of the limb bud [51–54]. Later it was shown that Shh was the molecule responsible for the phenotype induced by RA [55].

Shh is critical to the correct developmental pattern of the distal limb, the forearm (zeugopod), and the hand (autopod). This is demonstrated in *Shh* knock-out mice, which have a correctly developed stylopod, a single skeletal element (radius) for the zeugopod, and a minimal autopod. In the upper limb, the autopod forms as a small cartilage condensation [27, 56], while in the lower limb, the autopod consists of a single digit with two phalanges [27, 56].

AP/RU polarity is initiated by axial Hox gene segmentation [57] followed by anterior expression of Irx3/5 [58] and induction of Hand2 in the posterior/ulnar half of the limb bud by Hox9 paralogs [57]. Hand2 is required for Shh induction and Shh maintains Hand2 expression [59, 60]. Hand2 has also been shown to directly interact with a limb-specific Shh regulatory region, the ZPA regulatory sequence (ZRS) [61]. Similarly, distal Hoxd (Hoxd10–13) transcription factors also interact with the ZRS, and evidence suggests that their initial phase of limb bud expression helps to localize Shh expression (Fig. 1.5) [62].

The first or initial phase of distal Hoxd expression in the limb bud occurs in a nested collinear (corresponding to their gene order) fashion along the anteroposterior axis, with Hoxd10 exhibiting the broadest initial expression domain. The expression of each successively more distal Hoxd gene is nested within the previous gene's expression domain (see Fig. 1.5). Hoxd13, the terminal transcription factor in the Hoxd cluster, has the most restricted expression domain within the distal posterior or ulnar aspect of the limb bud overlapping the ZPA. This first phase of distal Hoxd expression plays a role in localizing Shh expression and temporally corresponds to specification of the forearm or zeugopod.

Shh signal transduction uses the Gli family of transcription factors (Gli1, Gli2, and Gli3), and the role of Shh in AP/RU axis patterning has been characterized largely through Gli knock-out mice. *Gli3* mutant mice are polydactylous without digit identity while the zeugopod is perfectly formed [63, 64]. Remarkably, the limbs of the double knock-out mice for both *Gli3* and *Shh* were indistinguishable from the *Gli3* mutant alone [65, 66], including a normally formed ulna. However, in the absence of Gli3 and Hand2 (and therefore its downstream target Shh), the same digit phenotype was present, and the zeugopod was also symmetrical with loss of ulnar identity [61]. Collectively, these findings suggest that

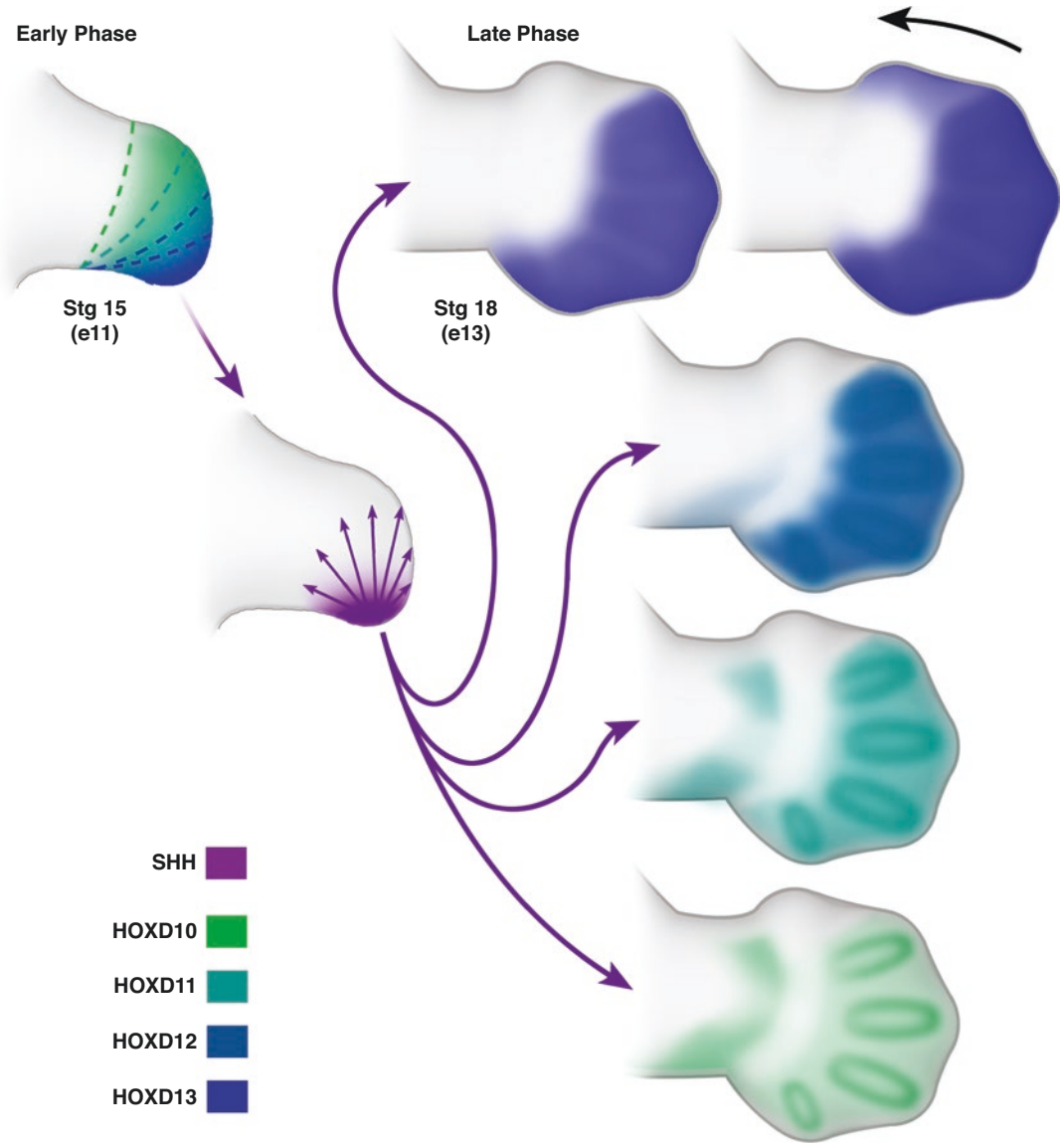

Fig. 1.5 Distal Hoxd genes are expressed in the limb bud in two phases**.** In the early phase, there is a nested collinear expression pattern. Dotted lines highlight the boundaries of expression, from broadest expression of Hoxd10 (green) to the most restricted of Hoxd13 (blue). In the late phase, Hoxd expression demonstrates quantitative reverse collinearity with progressively more robust expression. Initially in the late phase Hoxd13 is restricted from the thumb domain, but eventually Hoxa13 recruits Hoxd13 to extend into the thumb domain (upper left corner). (Courtesy of K.C. Oberg and Loma Linda University)

Hand2 patterns the zeugopod or forearm and the principal function of Shh is to establish digit number and identity through Gli3 (see Fig. 1.4b).

Molecular studies demonstrate that Shh signaling prevents the post-translational processing of full-length Gli3 protein into a short form (Gli3R), which functions as a strong repressor of Shh target genes. Secreted Shh diffusing from the ZPA establishes a posterior to anterior concentration gradient of full-length Gli3 with a comple-

mentary gradient of Gli3R being the highest in the anterior limb bud where Shh signaling is minimal (see Fig. 1.4b) [66]. In the absence of *Shh*, the level of Gli3R is uniform along the AP/RU axis. The elevated levels of Gli3R, unopposed by Shh, are accompanied by an increase in the apoptotic rate of the limb mesenchyme [65, 67]. Thus, the AP/RU gradient of Gli3R and its reciprocal full-length Gli3 activator are responsible for conveying pattern information along this axis. However, it remains unclear whether the critical patterning signal is the absolute level of Gli3R or the relative levels between the repressor and the activator forms [65, 66]. Collectively, these data help to characterize the role of Shh in AP/RU patterning, which at least in part is to regulate the form and function of its transcription factor, Gli3.

Dorsoventral Patterning (DV)

Patterning along this axis is regulated by signals from the non-AER ectoderm that surrounds the limb mesenchyme. The dorsal and ventral areas are defined by the expression of two different genes: *Wnt7a* in the dorsal ectoderm and *En-1* in the ventral ectoderm (Fig. 1.6). *Wnt7a* signaling defines the dorsal fate of the limb structures [68], while *En-1* restricts *Wnt7a* expression to the dorsal ectoderm, preventing the dorsalization of ventral limb tissues [69, 70]. It is not yet known how *Wnt7a* is induced in the presumptive limb ectoderm; however, there is evidence that Bmp and Wnt canonical signaling are responsible for the induction of *En-1* in the ventral ectoderm. Knock-out mice have further elaborated their functional roles. *Wnt7a* mutants have bi-ventral limbs, while *En-1* mutants have bi-dorsal limbs [71, 72]. Interestingly, double-compound mutant mice for *En-1* and *Wnt7a* display a bi-ventral phenotype, suggesting that the default limb phenotype is ventral and establishing Wnt7a's role as the dorsalizing signaling molecule of the limb DV axis [71].

Additional studies demonstrate that *Wnt7a* manifests its function through the induction of *Lmx1b* in the underlying dorsal mesoderm. Lmx1b function is both sufficient and necessary for the induction of dorsal fates. In chicken and mice, ventral *Lmx1b* expression led to bi-dorsal limbs, whereas its inactivation resulted in bi-ventral limbs [68, 71, 73, 74]. Recently Lmx1b targets were identified including genes involved with cell proliferation, extracellular matrix production, angiogenesis, musculoskeletal development, and axonal guidance [75], indicating the array of targets needed to dorsalize the limb.

Integration of Axis-Related Signaling

The three signaling centers coordinate patterned limb development through interactions between their molecular signaling cascades. One of the most studied interactions is the interaction between the ZPA and the AER. Shh signaling from the ZPA induces the expression of Gremlin1 in the adjacent mesenchyme that underlies the AER [30]. Gremlin1 is an antagonist of Bmp signaling, repressing *Bmp* expression in the mesenchyme [76, 77]. Although Bmp signaling is needed in limb and AER induction [78, 79], mesenchymal Bmp inhibits the expression of AER-associated Fgfs and increases mesenchymal cell death [78, 79]. Thus, Shh through Gremlin1 prevents these Bmp-associated functions to maintain Fgf expression. Correspondingly, Fgf8 secretion into the mesenchyme upregulates Lhx2 expression to maintain Shh secretion from the ZPA forming a positive feedback loop that supports continued limb growth and patterning [80]. Termination of this reciprocal loop has been proposed as the mechanism that stops limb outgrowth once the appropriate size has been achieved [81]. Alternatively, Pickering and coworkers suggest an intrinsic cell cycle timer as a primary mechanism to terminate limb outgrowth [82].

Integration also occurs between other axes. *Wnt7a* knock-out mice show a reduction in *Shh* expression [68] with a loss of the posterior digits (corresponding to the little finger). In chickens, elimination of the dorsal ectoderm of the limb showed similar results [83, 84]. These findings suggest that Wnt7a signaling from the dorsal

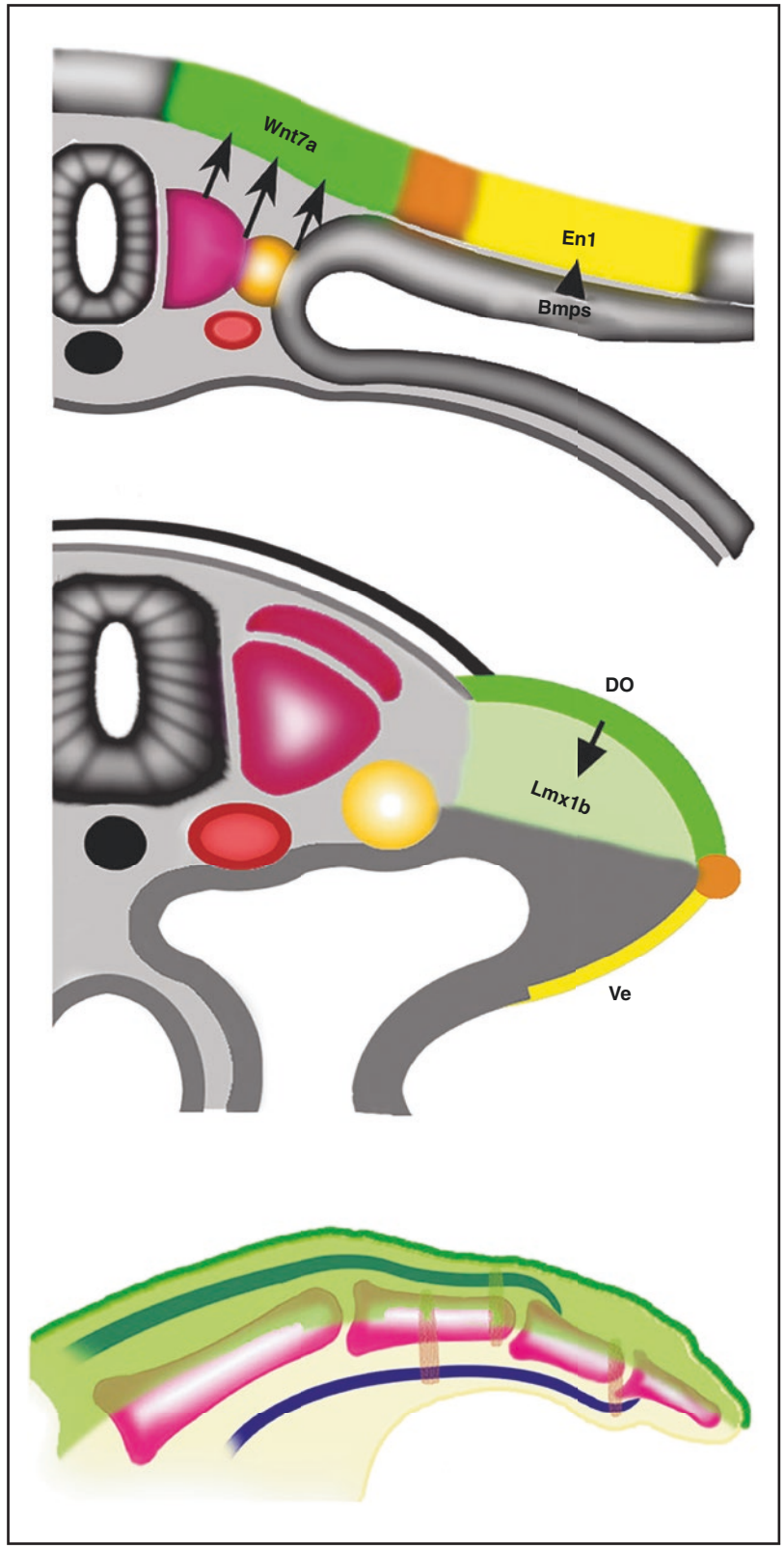

Fig. 1.6 Molecular pathways regulating the dorsoventral axis. From top to bottom, unknown factors in somites and/or intermediate mesoderm initiate Wnt7a expression in medial dorsal ectoderm. Bmps induce the expression of En1 in what will become the ventral ectoderm establishing the dorsal-ventral boundary where the AER will form (orange). Wnt7a will induce Lmx1b in the underlying mesoderm to dorsalize developing tendons, joints, and soft tissues. (Courtesy of K.C. Oberg and Loma Linda University)

ectoderm is capable of inducing or maintaining Shh expression in the ZPA [68]. Although the characterization of pathways that interconnect these three signaling centers is incomplete, it is intuitive that interaction between them is crucial for the proper development of a patterned limb.

Pathway integration begins at the level of genomic regulation. Cis-regulatory modules (CRMs) are sequences of regulatory DNA that determine the precise location and level of gene expression. Although CRMs are often a substantial distance away from their target gene, they regulate expression by interacting with the gene's promoter. In order for CRMs and promoters to interact, they have to be close in 3-dimensional space, even if they are millions of bases apart. Topologically associated domains (TADs) are portions of the genome which have folded into compact clusters or neighborhoods in which these interactions take place [85]. Each TAD has distinct boundaries (CTCF binding sites) that keep CRMs from regulating genes in other TADs [86].

The signaling factor for the AP/RU axis, Shh, is regulated by the ZRS through a CRM-promoter interaction. The ZRS is a limb-specific CRM necessary for *Shh* expression [87, 88]. Deletion of the ZRS results in a limb phenotype similar to conditional *Shh* knock-out mice [28]. Although the ZRS is located about 1 Mb upstream of the *Shh* promoter, in intron 5 of the *Lmbr1* gene, both sequences are located in the same TAD and co-localize in limb mesenchymal cells that are actively producing Shh [89]. Single nucleotide variations (SNVs) within the ZRS can disrupt normal AP/RU patterning that lead to ectopic anterior Shh expression and radial polydactylies such as triphalangeal thumb, mirror-image polydactyly, triphalangeal thumb-polysyndactyly syndrome (TPT-PS), and syndactyly type IV [90, 91]. Regulation of Fgf8 expression from the AER is complicated and involves five CRMs; these span 200 kb in a gene dense region and reside with Fgf8 in the same TAD. Disruption of these CRMs in the dactylin gene is known to interfere with AER function, causing split-hand/foot malformation [92]. Likewise, about 80 kb upstream of the Lmx1b promoter within the same TAD, *Lmx1b*-associated CRMs, called LARM1/LARM2, regulate *Lmx1b* levels, and disruption of these CRMs have been linked to incomplete dorsalization and nail-patella syndrome [75] (Haro et al_article in revision).

Handplate Patterning

The handplate or autopod is the distal-most element of the limb and the last to form. It is composed of digits (fingers) and wrist bones. The axis-related pathways converge in the handplate to form the most complicated, pattern-rich structures of limb development. Hoxa13, the terminal transcription factor of the Hoxa cluster, is confined to the handplate, demarcating its proximal boundary along the PD axis (see Fig. 1.4a) [93, 94]. Concurrently, along the AP/RU axis, a second "late" Shh-regulated phase of distal Hoxd expression (that corresponds with digit formation) is generated that partially reverses the Hoxd expression domains, i.e., reverse collinearity (see Fig. 1.5) [95]. More importantly, there is progressive expression intensity, with Hoxd13 exhibiting the most robust expression within the digits and Hoxd10 exhibiting the least intense expression, in what has been termed quantitative collinearity [96]. Along the DV axis, expression of Lmx1b, the dorsalizing Wnt7a-mediated transcription factor, becomes restricted to dorsal tendons and joint-associated tissues (see Fig. 1.6) [97].

Establishing Digit Number

In addition to regulating the second phase of Hoxd gene expression in the limb bud, Shh-expressing ZPA cells also make a direct contribution to digit development. Fate mapping studies have demonstrated that descendants from Shh-expressing cells of the ZPA populate digits 5 and 4 and half of digit 3. The cells of digit 5 have had the longest exposure to Shh and at higher levels, while the cells of digit 2 are only affected by diffusion of Shh [98, 99]. Moreover, premature arrest in *Shh* expression causes a reduction in the number of digits corresponding to the stage and

duration of arrest. With normal Shh levels, the order of condensation is d4, d2, d5, and d3, and with the premature arrest in Shh, the loss follows a predictable order, where digit 3 is lost first, followed by d5, d2, and d4 [100]. Studies of digit duplication in chicken wings by *Shh* misexpression show that the most posterior/ulnar digits need higher Shh concentrations and longer exposure times than the more anterior digits [101].

Experiments in chicken show that Shh integrates both proliferation and specification of digit precursors and that Shh expression is controlled by cell proliferation [100, 102]. These data prompted two models to explain how digit morphology and number are achieved. The biphasic model suggests that an early phase specifies digit number and potential morphology and a second proliferative phase allows for digit growth and final morphologic determination [100]. The growth-morphogen model posits that both Shh concentration and exposure duration progressively expand the limb to specify digit number and morphology [102].

Although a Shh concentration gradient can account for some features of digit morphogenesis, it does not fully explain the repeating digit-interdigit pattern. Experiments out of Marian Ros' laboratory found that compound gene deletions of *Hoxa13* (the terminal *Hoxa* gene demarcating the handplate), *Hoxd11–13* (the Shh-dependent *Hox* genes of the AP/RU axis), and *Gli3* (the gene mediating Shh activity along the AP/RU axis) exposed an intrinsic self-organizing mechanism (ISOM) in mice involved in digit patterning [103]. Progressive reduction of the *Hox* gene dosage in the absence of Gli3 progressively increased digit numbers (up to 14 digits) that was not accompanied by a corresponding increase in handplate size; thus, the digits were increasingly thinner and shorter.

Alan Turing developed a mathematical diffusion-reaction model to account for repetitive self-organizing patterns, such as stripes or spots in animal skin and fur [104]. This model considers two molecules, an activator and inhibitor, which diffuse into a field of cells. The activator auto-inhibits itself and upregulates its own inhibitor. In contrast, the model's inhibitor suppresses the activator and auto-inhibits its own expression (Fig. 1.7). Small random molecular variations of activator and inhibitor eventually lead to a stable pattern.

The Turing mechanism in the handplate involves three main components: Bmp, Sox9, and Wnt, with Bmp as the activator, Wnt as the inhibitor, and Sox9 cartilage condensation as the terminal readout of the intrinsic Turing mechanism [105]. As noted above, Hoxa/d transcription factors and AER-related Fgfs are required to inform the intrinsic Turing mechanism and establish the common digit/interdigit pattern of pentadactyly. Shh is thought to contribute to the Turing mechanism by expanding the domain of the handplate to accommodate five digits [106].

Defining Digit-Specific Morphology

Once the number of digits has been established, each digit must then acquire its specific morphology, i.e., thumb, index finger, etc. At the distal end of each digit is a cluster of cells called the phalanx-forming region (PFR) or digital crescent that, with progressive digital outgrowth, regulates *Sox9* expression and chondrogenesis, thereby shaping phalangeal morphology (Fig. 1.8) [107–109]. The PFR also maintains digit-associated Fgf expression in the overlying AER during digit outgrowth [107].

Although the mechanisms are not fully characterized, evidence suggests that Shh plays a pivotal role in defining digit-specific morphology for digits 2–5 (the Shh-dependent digits). Three Shh-regulated gradients converge to define the appropriate size and number of phalanges. The Shh-dependent Hoxd10–13 transcription factors within the developing digits interact directly with Gli3 [110]. However, the form of Gli3 present at each digit varies based on the Shh-regulated Gli3R/Gli3 activator counter-gradients [111]. In addition, Shh induces a Bmp gradient that is also known to regulate digit morphology [109, 112]. The signals that determine digit morphology are conveyed to the PFR through the adjacent posterior interdigital tissue [107, 109] and through Fgf and Wnt proteins secreted from the overlying

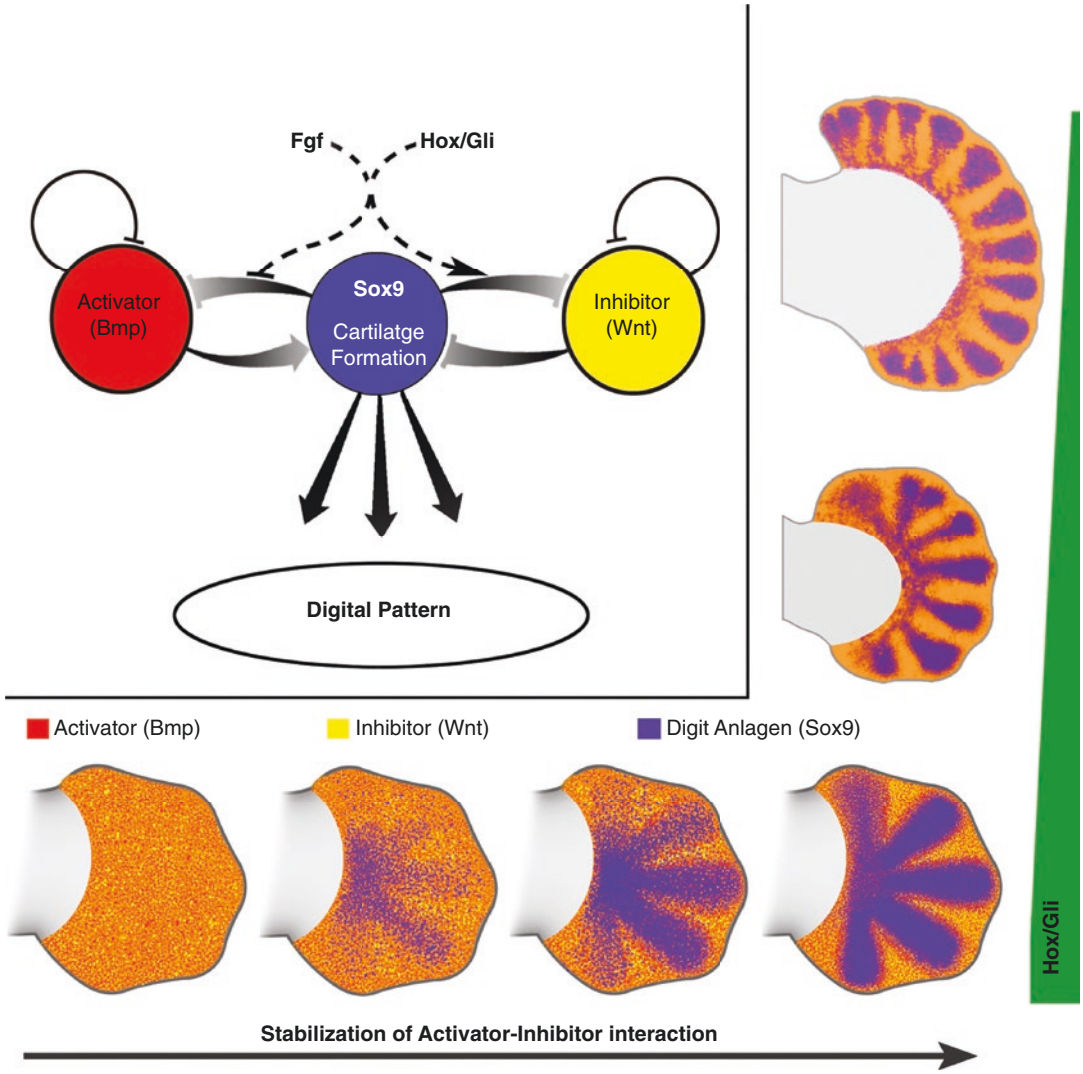

Fig. 1.7 Turing-like patterning in limbs. In the upper left-hand corner is a diagram of the diffusion-driven instability model with an activator and inhibitor modulated by Fgf and Hox/Gli. In the model described by Sheth et al. (2012), Fgf from the apical ectodermal ridge (AER) promotes a radial stripe pattern from this intrinsic self-organizing mechanism (ISOM) and ultimately regulates digit length, while Fgf in concert with distal Hox and Gli transcription factors limits the number of digits. The bottom of the illustration has a series of handplates that show the rapid progression from fluctuating activator-inhibitor interaction (noise) to a stabilized five-digit pattern. On the right, progressive loss of digit suppressing Hox/Gli transcription factors (green bar) causes an increase in the number of digits patterned by the ISOM. (Courtesy of K.C. Oberg and Loma Linda University)

AER [108, 113–116]. Changes in the interdigital BMP levels or swapping interdigital mesenchyme can transform digit morphology [107, 109].

The thumb is a distinctly different digit in its shape, position, and structure [91]. It is Shh-independent, has high levels of Gli3R, and has a compilation of genes expressed within its domain that is dissimilar from other digits (Fig. 1.9). *Hoxa13* is expressed within the entire handplate [93, 94] and overlaps the expression of *Tbx5*, which extends into the carpal and thumb domains but not into the domains of the ulnar digits (digits 2–5) [117]. In the presence of Gli3R, Hoxa13 expression is required to recruit the late extension

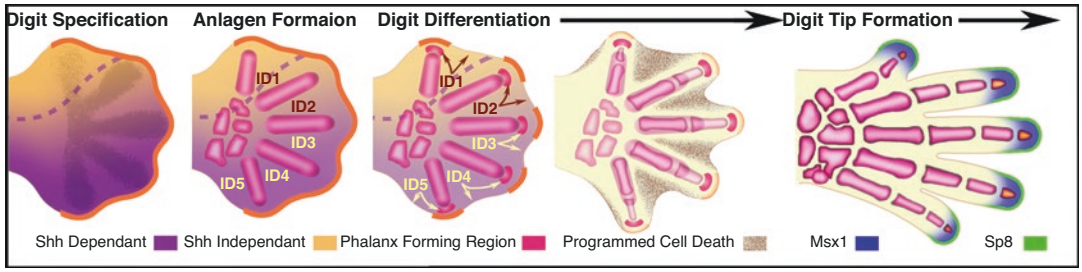

Fig. 1.8 Molecular pathways regulating digit development. After establishing digit number and the Shh-dependent/Shh-independent domains (boundaries indicated by dashed line), digit morphologies are specified. Interdigital mesoderm as illustrated (ID1–ID5) regulates regression of the overlying AER (orange) and digit morphologies of the adjacent anterior condensing digit via the phalanx-forming region (PFR; cyan) capping the distal tip of each anlagen. The PFR, in concert with the AER, determines phalanx size, length, and joint position. The interdigital tissue subsequently undergoes Bmp-mediated programmed cell death (speckled regions). As the AER overlying the digit regresses, the distal or ungual phalanx begins to form and is demarcated by expression of mesodermal Msx1 (blue) and ectodermal Sp8 (green). (Modified from [242]. Courtesy of K.C. Oberg and Loma Linda University)

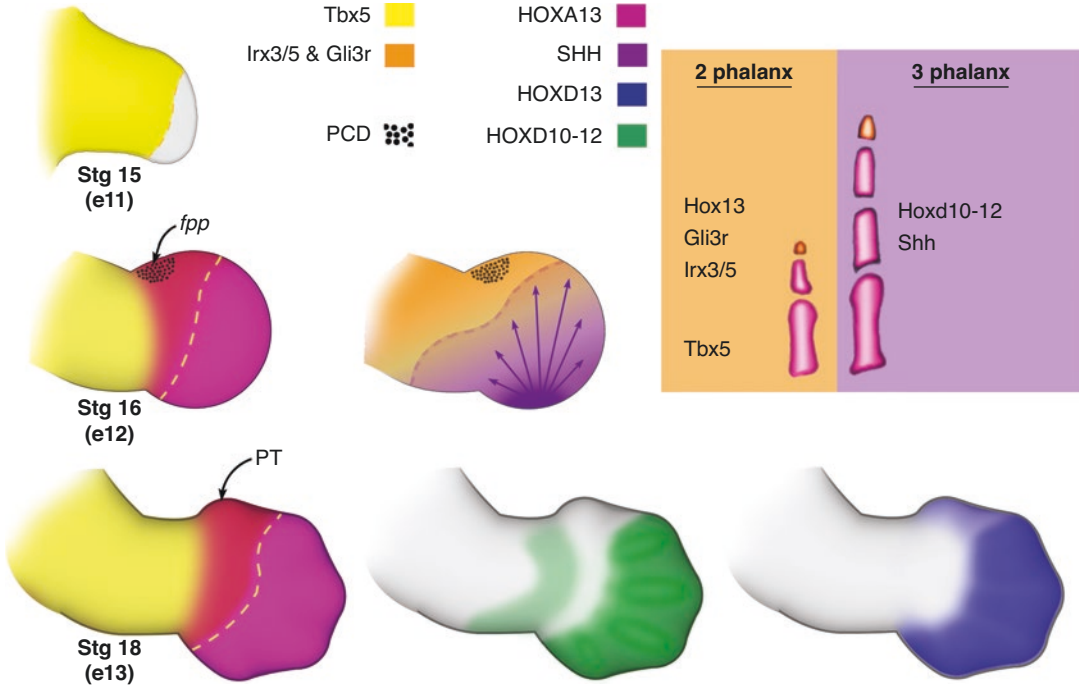

Fig. 1.9 Molecular regulation of thumb patterning. The presumptive thumb domain (PT) is defined by the overlapping expression of Tbx5, Gli3R, Hoxa13, and Hoxd13. The other Hoxd transcription factors (10–12) have overlapping expression domains in presumptive digits 2–5, but are restricted from the thumb domain. Note that the Hoxd genes are also restricted from the developing carpal region. (Modified from [91]. Courtesy of K.C. Oberg and Loma Linda University)

of Hoxd13 into the thumb domain [118]. Moreover, the thumb domain is accentuated by the lack of Shh-regulated *Hoxd10–12* expression [119]. The absence of *Hoxd10–12* expression has been used as a marker of "thumbness" across species [120, 121]. Interestingly, the wrist is also

a zone with limited Hox protein expression (see the illustration in Fig. 1.9 associated with Hoxd12 expression). Experiments with mouse mutants that express low levels of Hox proteins showed transformations of metacarpal bones to carpal-like elements [122]. Thus, Tbx5 and low levels of Hox transcription factors may limit the size of the carpal bones, while the distal Hoxd transcription factors are thought to elongate digits [93, 117, 123]. The thumb with a low initial level of Hox gene expression coupled with the later extension of Hoxd13 into the thumb domain may account for this proximally shifted small digit with two rather than three phalanges [118].

The terminal phalanges differ structurally from other phalanges: they are cone-shaped and associated with a surface modification at the dorsal tip called the unguis or nail, which is dense, keratinized epithelium that protects the tip of the digit. Terminal phalanges also differ in their development, with ossification beginning at the distal tapered tip of the cartilage model rather than forming a collar around the mid-shaft [124]. As the AER regresses, the terminal phalanges begin to form [114, 125]. Sp8, a specificity protein transcription factor that mediates Wnt signaling, is expressed in the distal tip ectoderm [124, 126] and appears to direct dorsal signals to form the nail. In mice with a reduction in Sp8 levels, dorsal dimelia forms [127]. The distal tip mesoderm also expresses Bambi, a Bmp inhibitor, and Msx1, a transcription factor that is thought to provide regenerative competency to fingertips [124, 128, 129].

Interdigital Cell Death

In the interdigit mesenchyme, Bmp signaling induces cell apoptosis, in part, by repressing Fgf expression in the overlying ectoderm [130]. Restriction of Indian hedgehog (Ihh) to the digit domain is also critical for allowing interdigital cell death, and extension of this proliferation/survival factor into the interdigital domain blocks apoptosis, resulting in syndactyly [131]. RA also appears to play a principal role in regulating interdigital cell death. *Rdh10* knock-out mice, which fail to convert precursors to RA, show interdigital webbing and a reduction in the expression of *Bmp7* [132]. RA beads are capable of inducing *Bmp* expression and cell death when implanted in the interdigit regions [133]. Weatherbee and coworkers have also suggested that the levels of Gremlin1, a Shh-regulated factor that inhibits Bmps, correlate with the degree of webbing across species [134]. Hedgehog and RA signals may work in concert to signal digit morphology and interdigital cell death, respectively.

Limb Differentiation

While the limb is growing and acquiring its overall shape, cells from both ectoderm and mesoderm begin to differentiate into the various tissues required for limb function. The differentiation process is tightly regulated by signaling molecules of the three axes. Although we will discuss the different tissues separately (vessels, muscle, bone, cartilage, and nervous tissue), these processes are occurring concurrently, with several signaling molecules shared across tissues.

Limb Vasculogenesis

Vascularization begins with the transformation of mesenchymal cells into hemangioblasts [135]. Upregulation of the E26 transformation-specific variant 2 (Etv2) transcription factor is the earliest indicator of vascular transformation [136, 137]. Bmp, Notch, and Wnt signaling regulate the general mesodermal expression of Etv2, while Nkx2.5 and Sry mediate organ-specific (heart and gonad, respectively) expression [137, 138]. Etv2, in turn, induces the expression of *Flk1* (also known as Vegf-receptor 2), the functional marker of hemangioblasts that confers the capacity to respond to vascular endothelial growth factor (Vegf) [138, 139]. Embryos that lack *Flk1* die around day 9 without any vascular development [140, 141]. Hypoxia-inducible factor 1 alpha (Hif-1α), sensing the local demands for oxygen in the growing tissue, induces *Vegf*

[142]. Bmp4 conjointly with Vegf differentiates hemangioblasts into angioblasts (CD31-, CD34-, Flk1-positive cells), the precursors of vascular tissue [143, 144].

Angioblasts within the developing limb bud are derived from limb mesenchyme and cells that migrate from adjacent somites [145]. In the emerging limb bud, angioblasts aggregate and differentiate into vascular channels to form the primitive capillary plexuses [144, 146, 147]. This process, known as vasculogenesis, is under the control of Vegf [148]. New vessels will sprout from these rudimentary vessels in response to local environmental and chemotactic factors, in a process termed angiogenesis. During angiogenesis, Notch-Delta signaling limits the number of sprouting "tip" cells to support directional outgrowth and remodeling [149, 150]. Interestingly, many of the molecules directing angiogenesis are also involved in axonal guidance (ephrins/Eph receptors, Slit/Robo signaling, Netrins, Semiphorins, etc.) [151]. This may, in part, explain the parallel pathways taken by these tissues to form neurovascular bundles.

As cartilage anlagen form within the central limb bud, the capillary network undergoes remodeling by angiogenesis forming definitive vessels from proximal to distal. In addition to Vegf and Notch signaling, angiopoietin/Tie signaling is involved in this second stage of vessel formation/remodeling [152, 153]. Around Carnegie stage 13 (day 28 post-fertilization), remodeling forms a central limb artery (the primitive subclavian artery) that connects with the dorsal aorta (Fig. 1.10a); concurrently, two peripheral veins form to drain into the posterior cardinal system [146, 154]. The endothelial cells from these remodeled vessels secrete platelet-derived growth factor (Pdgf), which recruits smooth muscle cells and pericytes to surround the growing vessels [155]. Arteries and veins differ in the thickness of surrounding smooth muscle and pericytes. In addition, arteries can be identified by their expression of ephrin B2, while veins are defined by their expression of Eph-B4 receptors [156].

RA plays an important role in vascular development, but its role requires further investigation [157]. In the absence of RA synthesis, vascular development is disrupted [158]. Alternatively, experiments with mice lacking Cyp26, an RA-degrading enzyme, showed an underdeveloped vasculature that did not progress beyond primitive plexuses [159, 160]. The data suggests that excess RA can have an inhibitory function on the expression of *Flk1*, thus halting the development of vessels [159, 160]. Endothelium expresses Cyp26 and may function to precisely regulate the level of RA [159], thereby promoting angiogenesis. Thus, deficiencies and excesses of RA disrupt vascular development, suggesting that RA participates in the fine-tuning of the vascular pattern.

Progressive proximal-to-distal remodeling of limb vessels continues as the limb develops with primitive capillary plexuses persisting in the distal limb until about Carnegie stage 19 (post-fertilization day 48). By Carnegie stage 21 (post-fertilization day 52), the major vessels and general architecture are completed [161, 162]. The vascular network develops arteries, capillaries, and veins. The low-pressure venous system is not able to collect all of the fluid distributed to the tissues by the higher-pressured arterial system; therefore, a second low-pressure vascular system, the lymphatics, forms. The lymphatic vessels also arise from angioblasts that are derived from LPM and somites [145]. Although a unique homeodomain transcription factor, Prox1, distinguishes lymphatics from arterial or venous vessels, the same signaling molecules that direct artery and vein formation likewise appear to control lymphatic vascular development [156].

Limb Skeletogenesis

The limb skeleton is derived from lateral plate mesoderm, and its development can be described in two steps: (1) chondrogenesis, the process of mesenchymal condensation and chondrocyte differentiation to form endochondral anlagen; and (2) endochondral ossification, the progressive transformation of the cartilage anlagen into the bones of the growing limb. The formation of joints is a related but separate process.

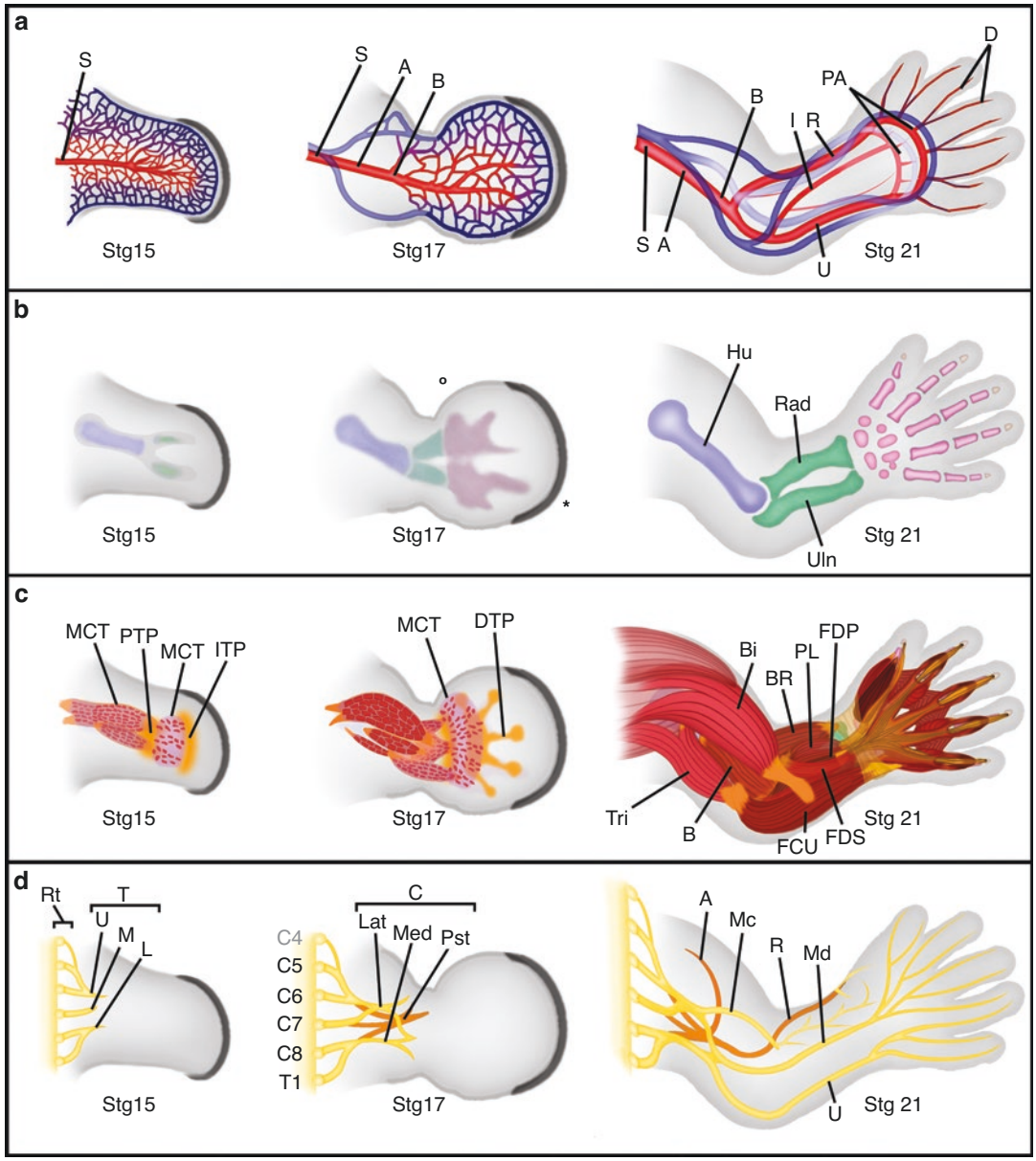

Fig. 1.10 Differentiation of limb tissues. Progressive differentiation of limb tissues from stage 15 (post-fertilization day 35) to stage 21 (day 52 near the end of the embryonic period). (**a**) Vascular differentiation showing the formation and remodeling of the subclavian (S), axillary (A), brachial (B), interosseous (I), radial (R), ulnar (U), palmar arch (PA), and digital (D) arteries. (**b**) Progressive skeletal differentiation showing anlagen condensation and definition for the humerus (Hu), radius (Rad), ulna (Uln), carpi, and digits. (**c**) Progressive muscle differentiation begins with myocyte migration, guided by muscle connective tissue (MCT) and tendon primordia: first the MCT of the upper arm (stylopod) and proximal tendon primordium (PTP), then the MCT of the forearm (zeugopod) and intermediate tendon primordium (IPT), and finally the MCT of the handplate and distal tendon primordium (DTP). Secondary myocyte migration and subsequent proliferation within the fascicles define muscle groups. Triceps (Tri), biceps (Bi), brachialis (B), brachioradialis (BR), flexor carpi ulnaris (FCU), palmaris longus (PL), flexor digitorum superficialis (FDS), and flexor digitorum profundus (FDP). (**d**) Progressive differentiation of limb nerves. The nerve roots (Rt) from cranial 4 through thoracic nerve 1 coalesce to form the upper (U), the middle (M), and lower (L) nerve trunks (T) as they enter the limb bud. Further rearrangements define the lateral (Lat), median (Med), and posterior (Pst) cords (C). As the muscles differentiate and require innervation, major nerves are formed – axillary (A), musculocutaneous (Mc), radial (R), median (Md), and ulnar (U). (Modified from [230]. Courtesy of K.C. Oberg and Loma Linda University)

Ectodermal and AER-related Wnt and Fgf signals maintain mesenchyme in an undifferentiated state, limiting differentiation of the peripheral and digit tip mesenchyme [163]. As the limb bud enlarges, the central mesenchyme escapes the influence of Wnt/Fgf signaling, cell adhesion molecules are upregulated, and the cells aggregate, condense, and begin to express Sox9, a high-mobility group transcription factor. Upregulation of Sox9 is the first indication of chondrogenesis [164]. Patterning signals established by distalizing AER-related Fgfs, dorsalizing Wnt7a, and posteriorizing Shh define the segment-specific anlagen and coordinate its patterned morphogenesis.

As the cells condense, vessels within the condensate regress and the mesenchyme becomes hypoxic [165]. The hypoxic mesenchyme upregulates Hif-1α, which in turn further promotes Sox9 expression. However, Sox9 alone is not sufficient for normal chondrocyte differentiation, and additional Sox transcription factors are needed [166, 167]. The chondrogenic trio of Sox9, Sox5, and Sox6 control chondrogenic differentiation, chondrocyte proliferation, and cartilage maintenance. Differentiation is evidenced by type II collagen production and chondrocyte hypertrophy. In addition, an antichondrogenic SoxC trio (Sox4, Sox11, Sox12), together with Irx 1 and 2, define the boundaries of the cartilage anlagen [168, 169].

Bmp signaling also plays a role in the condensation and differentiation of cartilage anlagen. Studies using constitutively activated and dominant-negative constructs in chicks show that signaling through Bmp receptor 1B (BMPR-1B) supports cartilage condensation [170]. The induction of Noggin, a potent inhibitor of Bmps, in the limb bud results in the complete absence of mesenchymal condensation, while the absence of Noggin induces expansion of mesenchymal condensations [131, 171]. Similarly in mice, knockout of Bmp receptors 1a and 1b (*BmpR1a*, *BmpR1b*) impairs chondrocyte differentiation and Sox5/Sox6/Sox9 expression [172].

The ablation of individual Bmp proteins instead of their receptors does not prevent chondrogenesis in mice but rather delays the process [78]. This finding suggests that Bmps have a redundant function in chondrogenesis and that a threshold level of Bmp is needed to trigger the induction of Sox 5/Sox6/Sox9 and promote anlagen condensation. Despite the delay in cartilage condensation, individual Bmp knock-out mice exhibit normal endochondral ossification [78] (for a full review of the role of Bmp in skeletogenesis and embryonic development, see [173]).

In contrast to Bmp, RA limits the expression and activity of *Sox9* [174, 175]. Experiments with *Cyp26b1* knock-out mice demonstrate impaired RA clearance. The elevated level of RA in the limb arrests or restricts cells to a prechondrocytic state and aborts cartilage formation and skeletal progression [176]. Interestingly, Bmp signaling counters this activity by inhibiting *Raldh2*, a gene that encodes for an RA-synthesizing enzyme [177]. Thus, Bmps utilize direct and indirect pathways to promote chondrogenesis.

As with other aspects of limb development, chondrogenesis progresses in a proximal-to-distal fashion. By Carnegie stage 15 (35 days post-fertilization), the humerus, radius, and ulna anlagen are evident as a "Y"-shaped condensation (see Fig. 1.10b) [178]. During the next week of gestation (post-fertilization days 36–42), condensations form within the handplate. A consistent order of digital condensations in vertebrates has been demonstrated with digit 4 forming first [179, 180], followed by digit 2, digit 5, digit 3, and finally the thumb or digit 1 [100]. Forming last appears to have put the thumb at increased risk, being the most common digit disrupted in malformation syndromes [91]. By Carnegie stage 21, the cartilaginous pattern is established.

Endochondral ossification is mediated in large part by the Runx2 transcription factor that differentiates precursors into osteoblasts and promotes chondrocyte hypertrophy [181]. In addition, Sp7 (also called Osterix), another specificity protein transcription factor, mediates osteocyte maturation, collagen I production, and bone matrix deposition [182]. Sp7 works in concert with another transcription factor, ATF4, to maintain osteocyte function [183]. The ossification of long bones is also characterized by an epiphyseal plate that forms between the diaphysis (shaft) and epiphysis (ends). The epiphyseal plate is a growth

center responsible for longitudinal growth. At the epiphyseal plate, cartilage proliferation forms regular columns of chondrocytes. These chondrocytes undergo hypertrophy, maturation, and apoptosis with subsequent ossification. These steps are tightly regulated by Runx2, Twist1, Ihh (and Gli3), Vegf, Bmp, and Fgf signaling [184].

Endochondral ossification transforms the cartilage models into bone. Primary ossification begins as a collar around the diaphyses of all limb long bones except the distal phalanges. Ossification in distal phalanges starts at the distal tip then progresses proximally over the cartilaginous model [124]. There is a consistent sequence to the formation of primary ossification centers in the upper limb. The first anlagen to begin ossification are the humerus (Carnegie stage 23, post-fertilization day 56 or 8 weeks gestation), followed by the radius, ulna, distal phalanges, metacarpals, proximal phalanges, and finally middle phalanges by 10 weeks post-fertilization [185]. Notably, George L. Streeter, the embryologist entrusted with characterizing the Carnegie collection of human gestations in the 1940s, regarded humeral ossification as the sine qua non of the beginning of the fetal period. Thus, the initiation of limb long bone ossification with the formation of primary ossification centers is a fetal endeavor.

Ossification of carpal bones does not start until around the time of birth [186]. The initiation of carpal ossification also follows a typical sequence beginning with the capitate and hamate (the ulnar aspect of the distal row) and ending with the trapezium, trapezoid (the radial aspect of the distal row), and the scaphoid (the radial aspect of the proximal row) [186]. Formation of secondary ossification centers within the epiphyses of the long bones also occurs postnatally. The characteristic pattern of hand and wrist ossification is a useful tool in assessing skeletal maturity in children. Prior to puberty, a sex-related difference is evident in hand and wrist ossification; in girls, formation of primary ossification centers is completed at around 6 years of age, whereas in boys, it is completed around 8 years of age [186].

The expression of the distal Hoxa transcription factors, Hoxa10, Hoxa11 and Hoxa13, correlates with the stylopod (arm), the zeugopod (forearm), and autopod (hand), respectively [94]. Synovial joints form within the developing skeletal anlagen at the boundaries between these three skeletal segments.

Morphologically, a joint passes through three stages (Fig. 1.11): (1) interzone formation, with condensation of a cell dense region of flattened cells called the interzone; (2) cavitation, the for-

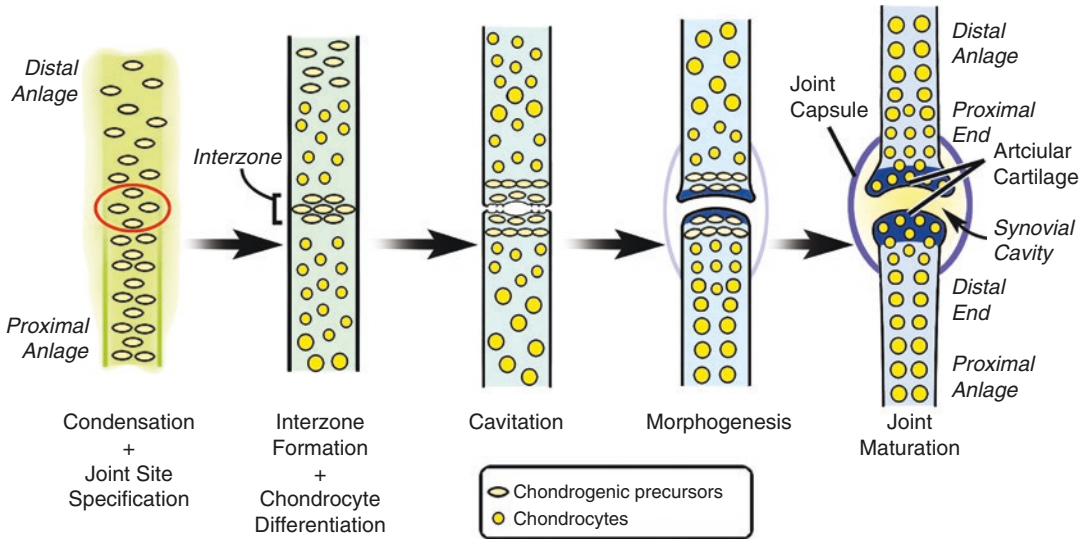

Fig. 1.11 Joint formation. Transformation of a presumptive joint in cartilage anlagen to a joint with synovial cavity and capsule. (Modified from [195]. Courtesy of K.C. Oberg and Loma Linda University)

mation of a gap separating the two skeletal elements; and (3) morphogenesis, the process of forming complementary articular cartilage-lined surfaces to facilitate movement.

The mechanisms that translate Hoxa boundary information into joint domains and interzones are not well characterized. Wnt9a is expressed in the presumptive joint region and upregulates Gdf5 prior to interzone formation [187]. As the interzones condense, however, the expression of Wnt9a and Gdf5 becomes more tightly restricted to interzone cells [188]. Subsequently, Sox11 and Osr1/Osr2 expression within the interzone promotes further upregulation and maintenance of Wnt9a/Gdf5 expression during joint formation [189, 190]. Centrally the interzone begins to cavitate, becomes hypocellular, and accumulates hyaluronan [191, 192]. Although joint-related muscular contractions are not needed for interzone formation, they are essential for proper cavitation to occur [193]. Integrated axis-related patterning pathways and cell movement work together to form complementary cartilage-lined surfaces on the opposing skeletal ends for appropriate articulation [194, 195]. Concurrently, mesoderm surrounding the developing joint condenses, forming fortifying ligaments and the joint capsule [196, 197].

Limb Myogenesis

Formation of the upper limb musculature is an integrated process involving tendons, myocytes, and nerves. Disruption of any one of these structures results in muscle abnormalities [198]. The arrangement of tendons and their sites of bony attachment establish the framework within which muscles will develop (see Fig. 1.10c). The tendon primordia develop from limb mesenchyme. The first indication of tendon formation is the expression of scleraxis (Scx), a tendon-specific transcription factor in precursor tenocytes [199]. Subsequently, the cells express the extracellular matrix protein tenascin [200].

Three dorsoventral pairs of tendon primordia progressively develop within each limb segment [201]. In addition to tendon primordia, muscle connective tissue (MCT) that will encase and direct the developing myocytes forms under the influence of axis-related signals and initially is independent from the influence of migrating myocytes [202, 203]. For example, Wnt7a from the dorsal ectoderm regulates dorsal tendon and MCT formation; mice that lack *En-1*, the transcription factor that limits Wnt7a expression to the dorsal ectoderm, develop a symmetrical bidorsal phenotype, i.e., extensor tendons and muscles for both the dorsal and "ventral" aspects of the limb [69, 72]. However, muscle interaction is an absolute requirement for maintenance of the tendon primordia and the final muscle arrangement; in muscle-deficient limbs, the tendons form but then degenerate [201].

Muscle undergoes progressive and somewhat overlapping phases of development [204]: (1) an embryonic phase with development of primary mononuclear fibers from migrating myoblasts, (2) a fetal/neonatal phase generating secondary multinucleate fibers from migrating myoblasts, and (3) an adult phase that contributes multinucleated fibers derived from satellite cells.

The first marker of limb-related myocyte differentiation during the embryonic phase of myogenesis is the expression of Pax3, a pair-ruled homeodomain transcription factor, in the dorsolateral cells of the dermomyotome in limb-associated somites [205–207]. Subsequently, the Pax3-positive cells will delaminate and migrate into the developing limb bud. *Pax3* knock-out mice show a loss of limb musculature and a loss of cell movements away from the somite [205, 208].

Delamination and migration are also dependent upon scatter factor/hepatocyte growth factor (Sf/Hgf) secreted from the developing limb bud mesenchyme and the corresponding expression of the Sf/Hgf receptor (c-met) in the myocyte precursors [209–212]. Pax3 regulates the expression of *c-met* in myocytes [213], while AER-associated Fgfs via Fgfr4 signaling control *Sf/Hgf* expression and thus the migratory routes of myocytes [212]. Mice deficient in *c-met* or *Hgf*

expression lack migration and show a complete absence of limb musculature [210, 214].

As the myocyte precursors migrate into the limb bud, they split into dorsal and ventral precursors. Lbx1, a homeodomain transcription factor expressed in dorsal myocyte precursors, mediates this segregation. Disruption of *Lbx1* disrupts dorsal muscle migration without significantly affecting the migration of ventral myocytes [215].

AER-related Fgfs regulate the expression of Sf/Hgf within the limb mesoderm, thereby controlling the migration of myocytes as they infiltrate tendon primordia to arrive at their final destination [212]. Within the limb bud, myocyte precursors begin to express *MyoD* and *Myf5*, committing them to a myocyte fate [216]. Activation of these myocyte-specific genes is also thought to depend on axis-related signal molecules, such as Wnt7a and Shh [206, 212]. The myocytes elongate and form primary mononuclear muscle fibers.

Progressive proximal-to-distal differentiation also occurs during myogenesis (see Fig. 1.10c). As myocyte precursors extend into the distal primordial tendons, a second wave of myocyte precursors migrates into the proximal limb. These myocyte precursors express Pax7 in addition to Pax3. Some of these precursors will coalesce around primary myofibers and fuse to form secondary multinucleated myofibers [217]. In addition, a population will remain in a precursor state at the periphery as a satellite cell [218]. Adult multinucleated muscle fibers are derived from satellite cells. It is during secondary or fetal myogenesis that motor endplates form and neuromuscular communication begins.

Limb Innervation

Innervation of the limb follows myocyte migration (see Fig. 1.10d). The axons of both motor and sensory neurons from the limb-associated spinal cord aggregate at the proximal limb boundary, forming several thick fascicles. These fascicles differentiate into the upper, middle, and lower trunks of the brachial plexus [219]. The nerve fascicles enter the limb then subdivide into dorsal and ventral branches. The dorsal branches coalesce to form the posterior cord. The upper and middle regions of the ventral branches join to form the lateral cord and the lower branch continues as medial cord. The cords then divide into the terminal branches of mixed motor and sensory axons. These branches follow a predictable pattern within the limb bud that appears to be controlled by variations in the extracellular matrix [220–222]. The initial entrance and distribution of the terminal branches within the limb do not appear to require signals from the final target tissue. However, for terminal sensory branching, the presence of skin is required [223]. Similarly, for fine targeted branching of motor nerves, differentiating muscle bundles are required [224].

The molecular control of axonal guidance and tissue targeting begins prior to axonal outgrowth during motor neuron differentiation. Shh secreted from the notochord and the floor plate of the spinal cord induces motor neuron and pancreas *homeobox1* (*Mnx1*, previously called *Hb9*), which encodes a transcription factor that transforms the neuroepithelium into motor neurons [225]. Hox transcription factors expressed within the spinal cord organize motor neurons destined for the upper limb into the lateral motor column (LMC), which is also demarcated by the expression of Islet1 and Islet2 (Isl1/Isl2) lim homeodomain transcription factors. The expression of *Raldh2*, and thus the production of RA, within the lateral LMC induces the expression of lim homeodomain 1 (Lhx1) transcription factor and inhibits the expression of Isl1, further subdividing the LMC into medial Isl1-/Isl2-positive neurons that will project into the ventral limb and lateral Lhx1-/Isl2-positive neurons that extend into the dorsal limb [226].

A second phase of complex Hox transcription factor expression coupled with the expression of forkhead box P1 (FoxP1) transcription factor is thought to convey axon targeting information to specific partner muscles within the limb defined by axis-related cues [194]. A complex interplay of ephrins and Eph receptors is involved in the regulation of branching and axonal guidance (see Kao et al., 2012 [227], for a comprehensive

review). Finally, at the target site, Etv4 transcription factors are required to promote the axonal arborization needed for terminal neuromuscular innervation [228].

Dysmorphogenesis and Classification

Congenital upper limb anomaly designations are typically based on appearance. We readily understand the terms such as polydactyly, syndactyly, or radial club hand. However, these terms often fail to inform us of the prognosis, approach to treatment, or the etiology. Many equate congenital upper limb malformations with abnormalities of the skeleton, but disruption of any aspect of limb development can lead to dysmorphology including vascular and neuromuscular differentiation. Classification provides a mechanism to organize dysmorphologies into categories that describe one or more aspects of these anomalies. Ideally, a classification for upper limb anomalies would incorporate the etiologic basis, provide insight into prognosis, and guide treatment [229]. Furthermore, such a system should provide a universal language for discussion across disciplines regarding epidemiology, treatment, and research [230].

A number of classification schemes have been proposed to organize the known spectrum of upper limb anomalies. Probably the earliest recorded classification system was in 1829 by Isidore Saint-Hilaire who initially described anomalies simply as mild or severe [231]. He subsequently focused on what was missing, coining the terms ectromelia (limb absence), phocomelia (missing limb segments), and hemimelia (missing limb parts) [232]. In 1895, Kümmel described upper limb anomalies in terms of defects (deficiencies), adhesions (fusions), or superior numbers (duplications).

Swanson proposed a classification scheme in 1964 [233]. Swanson's scheme was geared to hand surgeons and was considered to be an anatomic and clinical classification that indicated the type of primary embryonic damage [234]. While in the emerging field of clinical genetics, Temtamy had proposed a classification that focused on the genetic basis of malformation [234–236]. A modified version of Swanson's classification, subsequently adopted by the International Federation of Societies for Surgery of the Hand (IFSSH) in 1974, categorized limb anomalies based on failed formation, failed differentiation, duplication, overgrowth, undergrowth, constriction bands, and generalized skeletal anomalies [237]. This same year, Kelikian reviewed a number of the classification schemes that had been proposed and insightfully concluded that our knowledge was still insufficient to formulate a "comprehensive classification" [238].

With time, it was recognized that complex disorders were difficult or impossible to classify within this scheme, prompting a number of authors to suggest modifications [239, 240]. Mounting evidence regarding the etiology of cleft hand prompted the Japanese Society for Surgery of the Hand to add two additional groups to the classification: abnormal induction of digital rays and unclassifiable [241]. However, this modification does not address the need to incorporate genetic etiologic information into other conditions [238].

Increased knowledge of the molecular basis of limb development from clinical genetics and developmental biology prompted a more comprehensive classification system [241]. In 2010, a new classification scheme was proposed that combined anatomic and genetic information [242] (Table 1.1). To facilitate communication, the authors, Drs. Oberg, Manske, and Tonkin, used the general headings "Malformation, Deformation and Dysplasia," terms well established and used by dysmorphologists, clinical geneticists, and developmental biologists. The headings and subheadings indicate not only the altered morphology but also the disrupted molecular pathways identified by clinical genetics. The "OMT" classification scheme has undergone critical evaluation by a group of international hand surgeons (the Congenital Hand Anomalies Study Group, or CHASG) and its capacity/utility to classify upper limb malformations demonstrated [243]. In February of 2014, the

Table 1.1 The updated 2020 IFSSH/OMT classification

I. Malformations
- **A. Entire upper limb: abnormal axis formation (early limb patterning)**
  - **1. Proximodistal axis**
    - (i) Brachymelia
    - (ii) Symbrachydactyly spectrum (with ectodermal elements)
      - (a) Poland syndrome
      - (b) Whole limb excluding Poland syndrome (various levels: humeral to phalangeal)
    - (iii) Transverse deficiency (without ectodermal elements)
      - (a) Amelia
      - (b) Segmental (various levels: humeral to phalangeal)
    - (iv) Intersegmental deficiency (phocomelia)
      - (a) Proximal (humeral – rhizomelic)
      - (b) Distal (forearm – mesomelic)
      - (c) Total (phocomelia)
    - (v) Whole limb duplication/triplication
  - **2. Radioulnar (anterioposterior) axis**
    - (i) Radial longitudinal deficiency
    - (ii) Ulnar longitudinal deficiency
    - (iii) Ulnar dimelia
    - (iv) Radiohumeral synostosis
    - (v) Radioulnar synostosis
    - (vi) Congenital dislocation of the radial head
    - (vii) Forearm hemiphyseal dysplasia, radial (Madelung deformity), or ulnar
  - **3. Dorsoventral axis**
    - (i) Ventral dimelia
    - (ii) Dorsal dimelia
  - **4. Unspecified axis**
    - (i) Shoulder
      - (a) Undescended (Sprengel)
      - (b) Abnormal shoulder muscles
    - (ii) Upper to lower limb transformation
- **B. Handplate: abnormal axis differentiation (late limb patterning/differentiation)**
  - **1. Proximodistal axis**
    - (i) Brachydactyly
    - (ii) Symbrachydactyly (with ectodermal elements)
    - (iii) Transverse deficiency (without ectodermal elements)
    - (iv) Cleft hand (split-hand/foot malformation)
  - **2. Radioulnar (anterioposterior) axis**
    - (i) Radial longitudinal deficiency, hypoplastic thumb
    - (ii) Ulnar longitudinal deficiency, hypoplastic ulnar ray
    - (iii) Radial polydactyly
    - (iv) Triphalangeal thumb
      - (a) Five-finger hand
      - (v) Ulnar dimelia (mirror hand)
      - (vi) Ulnar polydactyly
  - **3. Dorsoventral axis**
    - (i) Dorsal dimelia (palmar nail)
    - (ii) Ventral dimelia (hypoplastic/aplastic nail)
  - **4. Unspecified axis**
    - (i) Soft tissue
      - (a) Cutaneous (simple) syndactyly
    - (ii) Skeletal deficiency
      - (a) Osseous (complex) syndactyly
      - (b) Clinodactyly
      - (c) Kirner's deformity
      - (d) Synostosis/symphalangism
    - (iii) Complex
      - (a) Syndromic syndactyly (e.g., Apert hand)
      - (b) Synpolydactyly
      - (c) Not otherwise specified

II. Deformations
- A. Constriction ring sequence
- B. Not otherwise specified

III. Dysplasias
- **A. Variant growth**
  - **1. Diffuse (whole limb)**
    - (i) Hemihypertrophy
    - (ii) Aberrant flexor/extensor/intrinsic muscle
  - **2. Isolated**
    - (i) Macrodactyly
    - (ii) Aberrant intrinsic muscles of hand
- **B. Tumorous conditions**
  - **1. Vascular**
    - (i) Hemangioma
    - (ii) Malformation
    - (iii) Others
  - **2. Neurological**
    - (i) Neurofibromatosis
    - (ii) Others
  - **3. Connective tissue**
    - (i) Juvenile aponeurotic fibroma
    - (ii) Infantile digital fibroma
    - (iii) Others
  - **4. Skeletal**
    - (i) Osteochondromatosis
    - (ii) Enchondromatosis
    - (iii) Fibrous dysplasia
    - (iv) Epiphyseal abnormalities
    - (v) Pseudoarthrosis
    - (vi) Others
- **C. Congenital contractures**
  - (i) Arthrogryposis multiplex congenita
    - (a) Amyoplasia
    - (b) Distal arthrogryposis
    - (c) Others
  - (ii) Isolated

Table 1.1 (continued)

(a) Camptodactyly
(b) Thumb in palm deformity
(c) Others
IV. Syndromes
A. Specified
1. Acrofacial dysostosis 1 (Nager type) (MIM 154400)
2. Apert (MIM #101200)
3. Al-Awadi/Raas-Rothschild/Schinzel phocomelia (MIM 276820)
4. Baller-Gerold (MIM #218600)
5. Bardet-Biedl (21 types)
6. Beals (MIM 121050)
7. CLOVES (MIM 612918)
8. Carpenter (MIM 201000)
9. Catel-Manzke (MIM 616145)
10. Cornelia de Lange (5 types)
11. Crouzon (MIM 123500)
12. Down (MIM 190685)
13. Ectrodactyly-ectodermal dysplasia-clefting (MIM 129900)
14. Fanconi pancytopenia (MIM 227650)
15. Freeman-Sheldon (MIM 193700)
16. Fuhrmann (MIM 228930)
17. Goltz (focal dermal hypoplasia) (MIM 305600)
18. Gorlin (basal cell nevus syndrome) (MIM 109400)
19. Greig cephalopolysyndactyly (MIM 175700)
20. Hajdu-Cheney (MIM 102500)
21. Hemifacial microsomia (Goldenhar syndrome) (MIM 164210)
22. Holt-Oram (MIM 142900)
23. Lacrimoauriculodentodigital (Levy-Hollister) (MIM 149730)
24. Larsen (MIM 150250)
25. Laurin-Sandrow (MIM 135750)
26. Leri-Weill dyschondrosteosis (MIM 127300)
27. Liebenberg syndrome (MIM #186550)
28. Moebius sequence (MIM 157900)
29. Multiple synostoses (4 types)
30. Nail-patella (MIM 161200)
31. Noonan (2 types)
32. Oculodentodigital dysplasia AD (MIM 164200); AR (MIM 257850)
33. Orofaciodigital (18 types)
34. Otopalatodigital spectrum (filamin A)
35. Pallister-Hall (MIM 146510)
36. Pfeiffer (MIM 101600)
37. Pierre Robin (4 subtypes)
38. Poland (MIM 173800)
39. Proteus (MIM 176920)
40. Roberts (MIM 268300)
41. SC phocomelia (MIM 26900)
42. Rothmund-Thomson (MIM 268400)
43. Rubinstein-Taybi (2 types)
44. Saethre-Chotzen (MIM 101400)
45. Split-hand/foot malformation (7 types)
46. Thrombocytopenia-absent radius (MIM 274000)
47. Townes-Brocks (2 types)
48. Trichorhinophalangeal (3 types)
49. Ulnar-mammary (MIM 181450)
50. VACTERL association (3 types)
B. Others

OMT classification was adopted by the IFSSH as the recommended classification scheme [244].

After several years of use and continuing evaluation, the IFSSH/OMT classification was updated in 2020 to improve classification of multiple anomalies, convey timing of developmental errors, improve terminology, include new entities, and update the classification disorders based on new research insights [245]. Further periodic updates are expected as our understanding of limb formation and the genetic basis of anomalies advances.

Malformations

Malformations are failures of normal development and/or differentiation and are, by far, the most common form of upper limb anomaly [246]. Malformations are subdivided into "entire upper limb" and "handplate" based on basic limb development and evolutionary patterning. Although the three basic axes of development are in play for the handplate as well as the entire limb, the handplate recruits a number of additional molecules/molecular cascades to pattern the highly complex hand. Correspondingly, the handplate has more evolutionary variation and more targets for dysmorphogenesis [91]. This has been corroborated by epidemiological studies of congenital hand anomalies in Sweden and the USA that show 83% and 62% (respectively) of upper limb malformations involve the handplate [246, 247].

Malformations are further subdivided by the primary axis that is disrupted (see Table 1.1). Using the example above, ulnar longitudinal deficiency (ULD), ulnar dimelia, and triphalangeal thumb are all subclassified as disorders of the radioulnar axis. ULD and ulnar dimelia are both disorders of the entire upper limb, while triphalangeal thumb is a disorder limited to the handplate. A category entitled "unspecified axis" is included for entities that do not have a known axis-related nature (e.g., syndactyly) or the suspected axis-related nature is not yet characterized (e.g., clinodactyly).

The etiology of cleft hand also known as split-hand/foot malformations (SHFMs) was a major challenge to previous classification schemes; however, recent studies indicate that SHFMs are linked to disruption of apical ectodermal ridge in its formation or function [248, 249]. This results in variable loss of proximodistal growth in the central handplate. Thus, in the updated IFSSH/OMT classification, these disorders were shifted from unspecified axis (OMT 2014, IB4iiic) to proximodistal axis (OMT 2020, IB1iv) [245].

Deformations

Deformations occur after normal development and differentiation; from an intervention standpoint, there is a better chance that normal structures will still be present. Dysmorphologists also speak of disruption, which is a breakdown of normal tissues, often vascular. For the purposes of congenital upper limb anomalies, both disruption and deformation are typically changes that occur after development and so are collectively included under the heading "Deformation." The classic example is constriction ring sequence (also called amniotic band sequence), which can result in deformed or disrupted tissues. No axis-related subclassification is used because deformations occur after and exogenous to patterned development.

Dysplasias

Dysplasias are abnormalities of development and/or differentiation of isolated tissues common to the limb such as vascular, neural, or skeletal. Dysplasias can disrupt normal development (malformation) and/or cause progressive deformation. Another shift in the 2020 version of the IFSSH/OMT classification was the addition of a congenital contracture subheading that includes arthrogryposis. Classification of arthrogryposis is difficult. Most of these disorders have normal limb patterning, but subsequent contracture formation is due to genetic variations that alter cell function ranging from abnormal cholinergic receptors to deficiencies in peroxisome-mediated lipid metabolism [250, 251]. Thus, the committee felt that "dysplasia" better describes underlying etiologies [245].

Syndromes

Fifty syndromes are listed in the updated IFSSH/OMT classification; however, these are commonly recognized syndromes that have limb anomaly as a component. For example, there are over 500 syndromes that have abnormal development of the thumb as a feature [91]. In the following chapter (Chap. 2), Drs. Laub and Burke will review syndromes that have an upper limb anomaly as a primary feature.

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References

1. O'Rahilly R, Muller F. Developmental stages in human embryos. Washington, DC: Carnegie Institution of Washington; 1987.
2. Tickle C. Embryology. In: KS GA, Sheker LR, editors. The growing hand: diagnosis and management of the upper extremity in children. London: CV Mosby; 2000. p. 25–32.
3. Burke AC, Nelson CE, Morgan BA, Tabin C. Hox genes and the evolution of vertebrate axial morphology. Development. 1995;121:333–46.
4. Moreau C, Caldarelli P, Rocancourt D, Roussel J, Denans N, Pourquie O, et al. Timed collinear activation of hox genes during gastrulation controls the avian forelimb position. Curr Biol. 2019;29(1):35–50.e34.
5. Searls RL, Janners MY. The initiation of limb bud outgrowth in the embryonic chick. Dev Biol. 1971;24(2):198–213.

6. Gros J, Tabin CJ. Vertebrate limb bud formation is initiated by localized epithelial-to-mesenchymal transition. Science. 2014;343(6176):1253–6.
7. Kawakami Y, Capdevila J, Buscher D, Itoh T, Rodriguez Esteban C, Izpisua Belmonte JC. WNT signals control FGF-dependent limb initiation and AER induction in the chick embryo. Cell. 2001;104(6):891–900.
8. Ohuchi H, Nakagawa T, Yamamoto A, Araga A, Ohata T, Ishimaru Y, et al. The mesenchymal factor, FGF10, initiates and maintains the outgrowth of the chick limb bud through interaction with FGF8, an apical ectodermal factor. Development. 1997;124(11):2235–44.
9. Minguillon C, Del Buono J, Logan MP. Tbx5 and Tbx4 are not sufficient to determine limb-specific morphologies but have common roles in initiating limb outgrowth. Dev Cell. 2005;8(1):75–84.
10. Minguillon C, Nishimoto S, Wood S, Vendrell E, Gibson-Brown JJ, Logan MP. Hox genes regulate the onset of Tbx5 expression in the forelimb. Development. 2012;139(17):3180–8.
11. Barrow JR, Thomas KR, Boussadia-Zahui O, Moore R, Kemler R, Capecchi MR, et al. Ectodermal Wnt3/beta-catenin signaling is required for the establishment and maintenance of the apical ectodermal ridge. Genes Dev. 2003;17(3):394–409.
12. Narita T, Nishimatsu S, Wada N, Nohno T. A Wnt3a variant participates in chick apical ectodermal ridge formation: distinct biological activities of Wnt3a splice variants in chick limb development. Dev Growth Differ. 2007;49(6):493–501.
13. Wilkie AO, Patey SJ, Kan SH, van den Ouweland AM, Hamel BC. FGFs, their receptors, and human limb malformations: clinical and molecular correlations. Am J Med Genet. 2002;112(3):266–78.
14. Pizette S, Abate-Shen C, Niswander L. BMP controls proximodistal outgrowth, via induction of the apical ectodermal ridge, and dorsoventral patterning in the vertebrate limb. Development. 2001;128(22):4463–74.
15. Soshnikova N, Zechner D, Huelsken J, Mishina Y, Behringer RR, Taketo MM, et al. Genetic interaction between Wnt/beta-catenin and BMP receptor signaling during formation of the AER and the dorsal-ventral axis in the limb. Genes Dev. 2003;17(16):1963–8.
16. Jin L, Wu J, Bellusci S, Zhang J-S. Fibroblast growth factor 10 and vertebrate limb development. Front Genet. 2019;9(705)
17. Abu-Abed S, Dolle P, Metzger D, Beckett B, Chambon P, Petkovich M. The retinoic acid-metabolizing enzyme, CYP26A1, is essential for normal hindbrain patterning, vertebral identity, and development of posterior structures. Genes Dev. 2001;15(2):226–40.
18. Hogan BL, Thaller C, Eichele G. Evidence that Hensen's node is a site of retinoic acid synthesis. Nature. 1992;359(6392):237–41.
19. Niederreither K, McCaffery P, Drager UC, Chambon P, Dolle P. Restricted expression and retinoic acid-induced downregulation of the retinaldehyde dehydrogenase type 2 (RALDH-2) gene during mouse development. Mech Dev. 1997;62(1):67–78.
20. Cunningham TJ, Zhao X, Sandell LL, Evans SM, Trainor PA, Duester G. Antagonism between retinoic acid and fibroblast growth factor signaling during limb development. Cell Rep. 2013;3(5):1503–11.
21. Zhao X, Sirbu IO, Mic FA, Molotkova N, Molotkov A, Kumar S, et al. Retinoic acid promotes limb induction through effects on body axis extension but is unnecessary for limb patterning. Curr Biol. 2009;19(12):1050–7.
22. Kessel M, Gruss P. Homeotic transformations of murine vertebrae and concomitant alteration of Hox codes induced by retinoic acid. Cell. 1991;67(1):89–104.
23. Deschamps J. Ancestral and recently recruited global control of the Hox genes in development. Curr Opin Genet Dev. 2007;17(5):422–7.
24. Wolpert L. Positional information and the spatial pattern of cellular differentiation. J Theor Biol. 1969;25(1):1–47.
25. Fallon JF, Kelley RO. Ultrastructural analysis of the apical ectodermal ridge during vertebrate limb morphogenesis. II. Gap junctions as distinctive ridge structures common to birds and mammals. J Embryol Exp Morphol. 1977;41(1):223–32.
26. Summerbell D, Lewis JH. Time, place and positional value in the chick limb-bud. J Embryol Exp Morphol. 1975;33(3):621–43.
27. Chiang C, Litingtung Y, Harris MP, Simandl BK, Li Y, Beachy PA, et al. Manifestation of the limb prepattern: limb development in the absence of sonic hedgehog function. Dev Biol. 2001;236(2):421–35.
28. Ros MA, Dahn RD, Fernandez-Teran M, Rashka K, Caruccio NC, Hasso SM, et al. The chick oligozeugodactyly (ozd) mutant lacks sonic hedgehog function in the limb. Development. 2003;130(3):527–37.
29. MacCabe JA, Errick J, Saunders JW Jr. Ectodermal control of the dorsoventral axis in the leg bud of the chick embryo. Dev Biol. 1974;39(1):69–82.
30. Lewandoski M, Sun X, Martin GR. Fgf8 signalling from the AER is essential for normal limb development. Nat Genet. 2000;26(4):460–3.
31. Fernandez-Teran M, Ros MA. The Apical Ectodermal Ridge: morphological aspects and signaling pathways. Int J Dev Biol. 2008;52(7):857–71.
32. Niswander L, Tickle C, Vogel A, Booth I, Martin GR. FGF-4 replaces the apical ectodermal ridge and directs outgrowth and patterning of the limb. Cell. 1993;75(3):579–87.
33. Fallon JF, Lopez A, Ros MA, Savage MP, Olwin BB, Simandl BK. FGF-2: apical ectodermal ridge growth signal for chick limb development. Science. 1994;264(5155):104–7.
34. Mariani FV, Ahn CP, Martin GR. Genetic evidence that FGFs have an instructive role in limb proximal-distal patterning. Nature. 2008;453(7193):401–5.
35. Sun X, Lewandoski M, Meyers EN, Liu YH, Maxson RE Jr, Martin GR. Conditional inactivation of Fgf4

reveals complexity of signalling during limb bud development. Nat Genet. 2000;25(1):83–6.
36. Sun X, Mariani FV, Martin GR. Functions of FGF signalling from the apical ectodermal ridge in limb development. Nature. 2002;418(6897):501–8.
37. Boulet AM, Moon AM, Arenkiel BR, Capecchi MR. The roles of Fgf4 and Fgf8 in limb bud initiation and outgrowth. Dev Biol. 2004;273(2):361–72.
38. Summerbell D, Lewis JH, Wolpert L. Positional information in chick limb morphogenesis. Nature. 1973;244(5417):492–6.
39. Summerbell D, Wolpert L. Precision of development in chick limb morphogenesis. Nature. 1973;244(5413):228–30.
40. Dudley AT, Ros MA, Tabin CJ. A re-examination of proximodistal patterning during vertebrate limb development. Nature. 2002;418(6897):539–44.
41. Tabin C, Wolpert L. Rethinking the proximodistal axis of the vertebrate limb in the molecular era. Genes Dev. 2007;21(12):1433–42.
42. Rosello-Diez A, Arques CG, Delgado I, Giovinazzo G, Torres M. Diffusible signals and epigenetic timing cooperate in late proximo-distal limb patterning. Development. 2014;141(7):1534–43.
43. Rosello-Diez A, Ros MA, Torres M. Diffusible signals, not autonomous mechanisms, determine the main proximodistal limb subdivision. Science. 2011;332(6033):1086–8.
44. Rosello-Diez A, Torres M. Regulative patterning in limb bud transplants is induced by distalizing activity of apical ectodermal ridge signals on host limb cells. Dev Dyn. 2011;240(5):1203–11.
45. Yashiro K, Zhao X, Uehara M, Yamashita K, Nishijima M, Nishino J, et al. Regulation of retinoic acid distribution is required for proximodistal patterning and outgrowth of the developing mouse limb. Dev Cell. 2004;6(3):411–22.
46. Yakushiji-Kaminatsui N, Kondo T, Hironaka KI, Sharif J, Endo TA, Nakayama M, et al. Variant PRC1 competes with retinoic acid-related signals to repress Meis2 in the mouse distal forelimb bud. Development. 2018;145(19)
47. Knezevic V, De Santo R, Schughart K, Huffstadt U, Chiang C, Mahon KA, et al. Hoxd-12 differentially affects preaxial and postaxial chondrogenic branches in the limb and regulates sonic hedgehog in a positive feedback loop. Development. 1997;124(22):4523–36.
48. Saunders JW Jr, Gasseling MT. Ectodermal-mesenchymal interactions in the origin of limb symmetry. In: Flesichmajer R, Billingham RE, editors. Epithelial-mesenchymal interactions. Baltimore: William & Wilkins; 1968. p. 78–97.
49. Tickle C, Summerbell D, Wolpert L. Positional signalling and specification of digits in chick limb morphogenesis. Nature. 1975;254(5497):199–202.
50. Tickle C. Limb regeneration. Am Sci. 1981;69(6):639–46.
51. Tickle C, Lee J, Eichele G. A quantitative analysis of the effect of all-trans-retinoic acid on the pattern of chick wing development. Dev Biol. 1985;109(1):82–95.
52. Tickle C, Crawley A, Farrar J. Retinoic acid application to chick wing buds leads to a dose-dependent reorganization of the apical ectodermal ridge that is mediated by the mesenchyme. Development. 1989;106(4):691–705.
53. Tickle C. Retinoic acid and chick limb bud development. Dev Suppl. 1991;1:113–21.
54. Wanek N, Gardiner DM, Muneoka K, Bryant SV. Conversion by retinoic acid of anterior cells into ZPA cells in the chick wing bud. Nature. 1991;350(6313):81–3.
55. Riddle RD, Johnson RL, Laufer E, Tabin C. Sonic hedgehog mediates the polarizing activity of the ZPA. Cell. 1993;75(7):1401–16.
56. Kraus P, Fraidenraich D, Loomis CA. Some distal limb structures develop in mice lacking sonic hedgehog signaling. Mech Dev. 2001;100(1):45–58.
57. Xu B, Wellik DM. Axial Hox9 activity establishes the posterior field in the developing forelimb. Proc Natl Acad Sci USA. 2011;108(12):4888–91.
58. Li D, Sakuma R, Vakili NA, Mo R, Puviindran V, Deimling S, et al. Formation of proximal and anterior limb skeleton requires early function of Irx3 and Irx5 and is negatively regulated by Shh signaling. Dev Cell. 2014;29(2):233–40.
59. Zeller R, Lopez-Rios J, Zuniga A. Vertebrate limb bud development: moving towards integrative analysis of organogenesis. Nat Rev Genet. 2009;10(12):845–58.
60. Charitè J, McFadden DG, Olson EN. The bHLH transcription factor dHAND controls sonic hedgehog expression and establishment of the zone of polarizing activity during limb development. Development. 2000;127(11):2461–70.
61. Galli A, Robay D, Osterwalder M, Bao X, Benazet JD, Tariq M, et al. Distinct roles of Hand2 in initiating polarity and posterior Shh expression during the onset of mouse limb bud development. PLoS Genet. 2010;6(4):e1000901.
62. Zakany J, Kmita M, Duboule D. A dual role for Hox genes in limb anterior-posterior asymmetry. Science. 2004;304(5677):1669–72.
63. Schimmang T, Lemaistre M, Vortkamp A, Ruther U. Expression of the zinc finger gene Gli3 is affected in the morphogenetic mouse mutant extra-toes (Xt). Development. 1992;116(3):799–804.
64. Hui CC, Joyner AL. A mouse model of greig cephalopolysyndactyly syndrome: the extra-toesJ mutation contains an intragenic deletion of the Gli3 gene. Nat Genet. 1993;3(3):241–6.
65. Litingtung Y, Dahn RD, Li Y, Fallon JF, Chiang C. Shh and Gli3 are dispensable for limb skeleton formation but regulate digit number and identity. Nature. 2002;418(6901):979–83.

66. te Welscher P, Zuniga A, Kuijper S, Drenth T, Goedemans HJ, Meijlink F, et al. Progression of vertebrate limb development through SHH-mediated counteraction of GLI3. Science. 2002;298(5594):827–30.
67. McGlinn E, van Bueren KL, Fiorenza S, Mo R, Poh AM, Forrest A, et al. Pax9 and Jagged1 act downstream of Gli3 in vertebrate limb development. Mech Dev. 2005;122(11):1218–33.
68. Parr BA, McMahon AP. Dorsalizing signal Wnt-7a required for normal polarity of D-V and A-P axes of mouse limb. Nature. 1995;374(6520):350–3.
69. Loomis CA, Harris E, Michaud J, Wurst W, Hanks M, Joyner AL. The mouse Engrailed-1 gene and ventral limb patterning. Nature. 1996;382(6589):360–3.
70. Logan C, Hornbruch A, Campbell I, Lumsden A. The role of Engrailed in establishing the dorsoventral axis of the chick limb. Development. 1997;124(12):2317–24.
71. Cygan JA, Johnson RL, McMahon AP. Novel regulatory interactions revealed by studies of murine limb pattern in Wnt-7a and En-1 mutants. Development. 1997;124(24):5021–32.
72. Loomis CA, Kimmel RA, Tong CX, Michaud J, Joyner AL. Analysis of the genetic pathway leading to formation of ectopic apical ectodermal ridges in mouse Engrailed-1 mutant limbs. Development. 1998;125(6):1137–48.
73. Riddle RD, Ensini M, Nelson C, Tsuchida T, Jessell TM, Tabin C. Induction of the LIM homeobox gene Lmx1 by WNT7a establishes dorsoventral pattern in the vertebrate limb. Cell. 1995;83(4):631–40.
74. Vogel A, Rodriguez C, Warnken W, Izpisua Belmonte JC. Dorsal cell fate specified by chick Lmx1 during vertebrate limb development. Nature. 1995;378(6558):716–20.
75. Haro E, Watson BA, Feenstra JM, Tegeler L, Pira CU, Mohan S, et al. Lmx1b-targeted cis-regulatory modules involved in limb dorsalization. Development. 2017;144(11):2009–20.
76. Zuniga A, Haramis AP, McMahon AP, Zeller R. Signal relay by BMP antagonism controls the SHH/FGF4 feedback loop in vertebrate limb buds. Nature. 1999;401(6753):598–602.
77. Michos O, Panman L, Vintersten K, Beier K, Zeller R, Zuniga A. Gremlin-mediated BMP antagonism induces the epithelial-mesenchymal feedback signaling controlling metanephric kidney and limb organogenesis. Development. 2004;131(14):3401–10.
78. Bandyopadhyay A, Tsuji K, Cox K, Harfe BD, Rosen V, Tabin CJ. Genetic analysis of the roles of BMP2, BMP4, and BMP7 in limb patterning and skeletogenesis. PLoS Genet. 2006;2(12):e216.
79. Benazet JD, Bischofberger M, Tiecke E, Goncalves A, Martin JF, Zuniga A, et al. A self-regulatory system of interlinked signaling feedback loops controls mouse limb patterning. Science. 2009;323(5917):1050–3.
80. Watson BA, Feenstra JM, Van Arsdale JM, Rai-Bhatti KS, Kim DJH, Coggins AS, et al. LHX2 mediates the FGF-to-SHH regulatory loop during limb development. J Dev Biol. 2018;6(2):13. 01-19
81. Verheyden JM, Sun X. An Fgf/Gremlin inhibitory feedback loop triggers termination of limb bud outgrowth. Nature. 2008;454(7204):638–41.
82. Pickering J, Rich CA, Stainton H, Aceituno C, Chinnaiya K, Saiz-Lopez P, Ros MA, Towers M. An intrinsic cell cycle timer terminates limb bud outgrowth. Elife. 2018;7
83. Yang Y, Niswander L. Interaction between the signaling molecules WNT7a and SHH during vertebrate limb development: dorsal signals regulate anteroposterior patterning. Cell. 1995;80(6):939–47.
84. Fernandez-Teran M, Ros MA, Mariani FV. Evidence that the limb bud ectoderm is required for survival of the underlying mesoderm. Dev Biol. 2013;381(2):11.
85. Petit F, Sears KE, Ahituv N. Limb development: a paradigm of gene regulation. Nat Rev Genet. 2017;18(4):245–58.
86. Williamson I, Kane L, Devenney PS, Flyamer IM, Anderson E, Kilanowski F, et al. Developmentally regulated Shh expression is robust to TAD perturbations. Development. 2019:146(19).
87. Lettice LA, Horikoshi T, Heaney SJ, van Baren MJ, van der Linde HC, Breedveld GJ, et al. Disruption of a long-range cis-acting regulator for Shh causes preaxial polydactyly. Proc Natl Acad Sci U S A. 2002;99(11):7548–53.
88. Sagai T, Hosoya M, Mizushina Y, Tamura M, Shiroishi T. Elimination of a long-range cis-regulatory module causes complete loss of limb-specific Shh expression and truncation of the mouse limb. Development. 2005;132(4):797–803.
89. Williamson I, Lettice LA, Hill RE, Bickmore WA. Shh and ZRS enhancer colocalisation is specific to the zone of polarising activity. Development. 2016;143(16):2994–3001.
90. Potuijt JWP, Galjaard RH, van der Spek PJ, van Nieuwenhoven CA, Ahituv N, Oberg KC, et al. A multidisciplinary review of triphalangeal thumb. J Hand Surg Eur Vol. 2019;44(1):59–68.
91. Oberg KC. Review of the molecular development of the thumb: digit primera. Clin Orthop Relat Res. 2014;472(4):1101–5.
92. Marinic M, Aktas T, Ruf S, Spitz F. An integrated holo-enhancer unit defines tissue and gene specificity of the Fgf8 regulatory landscape. Dev Cell. 2013;24(5):530–42.
93. Woltering JM, Duboule D. The origin of digits: expression patterns versus regulatory mechanisms. Dev Cell. 2010;18(4):526–32.
94. Yokouchi Y, Sasaki H, Kuroiwa A. Homeobox gene expression correlated with the bifurcation process of limb cartilage development. Nature. 1991;353(6343):443–5.

95. Nelson CE, Morgan BA, Burke AC, Laufer E, DiMambro E, Murtaugh LC, et al. Analysis of Hox gene expression in the chick limb bud. Development. 1996;122(5):1449–66.
96. Kmita M, Fraudeau N, Herault Y, Duboule D. Serial deletions and duplications suggest a mechanism for the collinearity of Hoxd genes in limbs. Nature. 2002;420(6912):145–50.
97. Dreyer SD, Naruse T, Morello R, Zabel B, Winterpacht A, Johnson RL, et al. Lmx1b expression during joint and tendon formation: localization and evaluation of potential downstream targets. Gene Expr Patterns. 2004;4(4):397–405.
98. Zeller R: It takes time to make a pinky: unexpected insights into how SHH patterns vertebrate digits. Sci STKE 2004, 2004(259):pe53.
99. Harfe BD, Scherz PJ, Nissim S, Tian H, McMahon AP, Tabin CJ. Evidence for an expansion-based temporal Shh gradient in specifying vertebrate digit identities. Cell. 2004;118(4):517–28.
100. Zhu J, Nakamura E, Nguyen MT, Bao X, Akiyama H, Mackem S. Uncoupling Sonic hedgehog control of pattern and expansion of the developing limb bud. Dev Cell. 2008;14(4):624–32.
101. Yang Y, Drossopoulou G, Chuang PT, Duprez D, Marti E, Bumcrot D, et al. Relationship between dose, distance and time in sonic hedgehog-mediated regulation of anteroposterior polarity in the chick limb. Development. 1997;124(21):4393–404.
102. Towers M, Mahood R, Yin Y, Tickle C. Integration of growth and specification in chick wing digit-patterning. Nature. 2008;452(7189):882–6.
103. Sheth R, Marcon L, Bastida MF, Junco M, Quintana L, Dahn R, et al. Hox genes regulate digit patterning by controlling the wavelength of a Turing-type mechanism. Science. 2012;338(6113):1476–80.
104. Turing AM. The chemical basis of morphogenesis. Phil Trans R Soc Lond B. 1952;237:37–72.
105. Raspopovic J, Marcon L, Russo L, Sharpe J. Modeling digits. Digit patterning is controlled by a Bmp-Sox9-Wnt Turing network modulated by morphogen gradients. Science. 2014;345(6196):566–70.
106. Newman SA, Glimm T, Bhat R. The vertebrate limb: an evolving complex of self-organizing systems. Prog Biophys Mol Biol. 2018;137:12–24.
107. Suzuki T, Hasso SM, Fallon JF. Unique SMAD1/5/8 activity at the phalanx-forming region determines digit identity. Proc Natl Acad Sci U S A. 2008;105(11):4185–90.
108. Montero JA, Lorda-Diez CI, Ganan Y, Macias D, Hurle JM. Activin/TGFbeta and BMP crosstalk determines digit chondrogenesis. Dev Biol. 2008;321(2):343–56.
109. Dahn RD, Fallon JF. Interdigital regulation of digit identity and homeotic transformation by modulated BMP signaling. Science. 2000;289(5478):438–41.
110. Chen Y, Knezevic V, Ervin V, Hutson R, Ward Y, Mackem S. Direct interaction with Hoxd proteins reverses Gli3-repressor function to promote digit formation downstream of Shh. Development. 2004;131(10):2339–47.
111. Wang B, Fallon JF, Beachy PA. Hedgehog-regulated processing of Gli3 produces an anterior/posterior repressor gradient in the developing vertebrate limb. Cell. 2000;100(4):423–34.
112. Drossopoulou G, Lewis KE, Sanz-Ezquerro JJ, Nikbakht N, McMahon AP, Hofmann C, et al. A model for anteroposterior patterning of the vertebrate limb based on sequential long- and short-range Shh signalling and Bmp signalling. Development. 2000;127(7):1337–48.
113. Rowe DA, Cairns JM, Fallon JF. Spatial and temporal patterns of cell death in limb bud mesoderm after apical ectodermal ridge removal. Dev Biol. 1982;93(1):83–91.
114. Sanz-Ezquerro JJ, Tickle C. Fgf signaling controls the number of phalanges and tip formation in developing digits. Curr Biol. 2003;13(20):1830–6.
115. Winkel A, Stricker S, Tylzanowski P, Seiffart V, Mundlos S, Gross G, et al. Wnt-ligand-dependent interaction of TAK1 (TGF-beta-activated kinase-1) with the receptor tyrosine kinase Ror2 modulates canonical Wnt-signalling. Cell Signal. 2008;20(11):2134–44.
116. Witte F, Chan D, Economides AN, Mundlos S, Stricker S. Receptor tyrosine kinase-like orphan receptor 2 (ROR2) and Indian hedgehog regulate digit outgrowth mediated by the phalanx-forming region. Proc Natl Acad Sci USA. 2010;107(32):14211–6.
117. Koshiba-Takeuchi K, Takeuchi JK, Arruda EP, Kathiriya IS, Mo R, Hui CC, Srivastava D, Bruneau BG. Cooperative and antagonistic interactions between Sall4 and Tbx5 pattern the mouse limb and heart. Nat Genet. 2006;38(2):175–83.
118. Bastida MF, Perez-Gomez R, Trofka A, Zhu J, Rada-Iglesias A, Sheth R, et al. The formation of the thumb requires direct modulation of Gli3 transcription by Hoxa13. Proc Natl Acad Sci U S A. 2020;117(2):1090–6.
119. Montavon T, Le Garrec JF, Kerszberg M, Duboule D. Modeling Hox gene regulation in digits: reverse collinearity and the molecular origin of thumbness. Genes Dev. 2008;22(3):346–59.
120. Vargas AO, Fallon JF. Birds have dinosaur wings: the molecular evidence. J Exp Zool B Mol Dev Evol. 2005;304(1):86–90.
121. Vargas AO, Kohlsdorf T, Fallon JF, Vandenbrooks J, Wagner GP. The evolution of HoxD-11 expression in the bird wing: insights from Alligator mississippiensis. PLoS One. 2008;3(10):e3325.
122. Villavicencio-Lorini P, Kuss P, Friedrich J, Haupt J, Farooq M, Turkmen S, et al. Homeobox genes d11-d13 and a13 control mouse autopod cortical bone and joint formation. J Clin Invest. 2010;120(6):1994–2004.
123. Hasson P, DeLaurier A, Bennett M, Grigorieva E, Naiche LA, Papaioannou VE, et al. Tbx4 and tbx5 acting in connective tissue are required for

limb muscle and tendon patterning. Dev Cell. 2010;18(1):148–56.
124. Casanova JC, Badia-Careaga C, Uribe V, Sanz-Ezquerro JJ. Bambi and Sp8 expression mark digit tips and their absence shows that chick wing digits 2 and 3 are truncated. PLoS One. 2012;7(12):e52781.
125. Casanova JC, Sanz-Ezquerro JJ. Digit morphogenesis: is the tip different? Dev Growth Differ. 2007;49(6):479–91.
126. Kawakami Y, Esteban CR, Matsui T, Rodriguez-Leon J, Kato S, Izpisua Belmonte JC. Sp8 and Sp9, two closely related buttonhead-like transcription factors, regulate Fgf8 expression and limb outgrowth in vertebrate embryos. Development. 2004;131(19):4763–74.
127. Haro E, Delgado I, Junco M, Yamada Y, Mansouri A, Oberg KC, et al. Sp6 and Sp8 transcription factors control AER formation and dorsal-ventral patterning in limb development. PLoS Genet. 2014;10(8):e1004468.
128. Allan CH, Fleckman P, Fernandes RJ, Hager B, James J, Wisecarver Z, et al. Tissue response and Msx1 expression after human fetal digit tip amputation in vitro. Wound Repair Regen. 2006;14(4):398–404.
129. Han M, Yang X, Farrington JE, Muneoka K. Digit regeneration is regulated by Msx1 and BMP4 in fetal mice. Development. 2003;130(21):5123–32.
130. Yoon BS, Pogue R, Ovchinnikov DA, Yoshii I, Mishina Y, Behringer RR, et al. BMPs regulate multiple aspects of growth-plate chondrogenesis through opposing actions on FGF pathways. Development. 2006;133(23):4667–78.
131. Murgai A, Altmeyer S, Wiegand S, Tylzanowski P, Stricker S. Cooperation of BMP and IHH signaling in interdigital cell fate determination. PLoS One. 2018;13(5):e0197535.
132. Cunningham TJ, Chatzi C, Sandell LL, Trainor PA, Duester G. Rdh10 mutants deficient in limb field retinoic acid signaling exhibit normal limb patterning but display interdigital webbing. Dev Dyn. 2011;240(5):1142–50.
133. Rodriguez-Leon J, Merino R, Macias D, Ganan Y, Santesteban E, Hurle JM. Retinoic acid regulates programmed cell death through BMP signalling. Nat Cell Biol. 1999;1(2):125–6.
134. Weatherbee SD, Behringer RR, Rasweiler JJ, Niswander LA. Interdigital webbing retention in bat wings illustrates genetic changes underlying amniote limb diversification. Proc Natl Acad Sci USA. 2006;103(41):15103–7.
135. Choi K. Hemangioblast development and regulation. Biochem Cell Biol. 1998;76(6):947–56.
136. Craig MP, Sumanas S. ETS transcription factors in embryonic vascular development. Angiogenesis. 2016;19(3):275–85.
137. Koyano-Nakagawa N, Garry DJ. Etv2 as an essential regulator of mesodermal lineage development. Cardiovasc Res. 2017;113(11):1294–306.
138. Lee D, Park C, Lee H, Lugus JJ, Kim SH, Arentson E, et al. ER71 acts downstream of BMP, Notch, and Wnt signaling in blood and vessel progenitor specification. Cell Stem Cell. 2008;2(5):497–507.
139. Park C, Afrikanova I, Chung YS, Zhang WJ, Arentson E, Fong Gh G, et al. A hierarchical order of factors in the generation of FLK1- and SCL-expressing hematopoietic and endothelial progenitors from embryonic stem cells. Development. 2004;131(11):2749–62.
140. Shalaby F, Rossant J, Yamaguchi TP, Gertsenstein M, Wu XF, Breitman ML, et al. Failure of blood-island formation and vasculogenesis in Flk-1-deficient mice. Nature. 1995;376(6535):62–6.
141. Shalaby F, Ho J, Stanford WL, Fischer KD, Schuh AC, Schwartz L, et al. A requirement for Flk1 in primitive and definitive hematopoiesis and vasculogenesis. Cell. 1997;89(6):981–90.
142. Zimna A, Kurpisz M. Hypoxia-inducible factor-1 in physiological and pathophysiological angiogenesis: applications and therapies. Biomed Res Int. 2015;2015:549412.
143. Drake CJ. Embryonic and adult vasculogenesis. Birth Defects Res C Embryo Today. 2003;69(1):73–82.
144. Moser M, Patterson C. Bone morphogenetic proteins and vascular differentiation: BMPing up vasculogenesis. Thromb Haemost. 2005;94(4):713–8.
145. He L, Papoutsi M, Huang R, Tomarev SI, Christ B, Kurz H, et al. Three different fates of cells migrating from somites into the limb bud. Anat Embryol. 2003;207(1):29–34.
146. Caplan AI. The vasculature and limb development. Cell Differ. 1985;16(1):1–11.
147. Vargesson N. Vascularization of the developing chick limb bud: role of the TGFbeta signalling pathway. J Anat. 2003;202(1):93–103.
148. Deckers MM, van Bezooijen RL, van der Horst G, Hoogendam J, van Der Bent C, Papapoulos SE, et al. Bone morphogenetic proteins stimulate angiogenesis through osteoblast-derived vascular endothelial growth factor A. Endocrinology. 2002;143(4):1545–53.
149. Hellstrom M, Phng LK, Hofmann JJ, Wallgard E, Coultas L, Lindblom P, et al. Dll4 signalling through Notch1 regulates formation of tip cells during angiogenesis. Nature. 2007;445(7129):776–80.
150. Siekmann AF, Lawson ND. Notch signalling limits angiogenic cell behaviour in developing zebrafish arteries. Nature. 2007;445(7129):781–4.
151. Jones CA, Li DY. Common cues regulate neural and vascular patterning. Curr Opin Genet Dev. 2007;17(4):332–6.
152. Thurston G. Role of angiopoietins and tie receptor tyrosine kinases in angiogenesis and lymphangiogenesis. Cell Tissue Res. 2003;314(1):61–8.
153. Krebs LT, Xue Y, Norton CR, Shutter JR, Maguire M, Sundberg JP, et al. Notch signaling is essential

for vascular morphogenesis in mice. Genes Dev. 2000;14(11):1343–52.
154. Tamura K, Amano T, Satoh T, Saito D, Yonei-Tamura S, Yajima H. Expression of rigf, a member of avian VEGF family, correlates with vascular patterning in the developing chick limb bud. Mech Dev. 2003;120(2):199–209.
155. Betsholtz C, Lindblom P, Gerhardt H. Role of pericytes in vascular morphogenesis. EXS. 2005;94:115–25.
156. Wolf K, Hu H, Isaji T, Dardik A. Molecular identity of arteries, veins, and lymphatics. J Vasc Surg. 2019;69(1):253–62.
157. Pawlikowski B, Wragge J, Siegenthaler JA. Retinoic acid signaling in vascular development. Genesis. 2019;57(7–8):e23287.
158. Bohnsack BL, Lai L, Dolle P, Hirschi KK. Signaling hierarchy downstream of retinoic acid that independently regulates vascular remodeling and endothelial cell proliferation. Genes Dev. 2004;18(11):1345–58.
159. Ribes V, Otto DM, Dickmann L, Schmidt K, Schuhbaur B, Henderson C, et al. Rescue of cytochrome P450 oxidoreductase (Por) mouse mutants reveals functions in vasculogenesis, brain and limb patterning linked to retinoic acid homeostasis. Dev Biol. 2007;303(1):66–81.
160. Ribes V, Fraulob V, Petkovich M, Dolle P. The oxidizing enzyme CYP26a1 tightly regulates the availability of retinoic acid in the gastrulating mouse embryo to ensure proper head development and vasculogenesis. Dev Dyn. 2007;236(3):644–53.
161. Rodriguez-Niedenfuhr M, Burton GJ, Deu J, Sanudo JR. Development of the arterial pattern in the upper limb of staged human embryos: normal development and anatomic variations. J Anat. 2001;199(Pt 4):407–17.
162. Mrazkova O. Ontogenesis of arterial trunks in the human fore-arm. Folia Morphol (Praha). 1973;21(2):193–6.
163. Marin-Llera JC, Garciadiego-Cazares D, Chimal-Monroy J. Understanding the cellular and molecular mechanisms that control early cell fate decisions during appendicular skeletogenesis. Front Genet. 2019;10:977.
164. Kawakami Y, Rodriguez-Leon J, Belmonte JC. The role of TGFbetas and Sox9 during limb chondrogenesis. Curr Opin Cell Biol. 2006;18(6):723–9.
165. Amarilio R, Viukov SV, Sharir A, Eshkar-Oren I, Johnson RS, Zelzer E. HIF1alpha regulation of Sox9 is necessary to maintain differentiation of hypoxic prechondrogenic cells during early skeletogenesis. Development. 2007;134(21):3917–28.
166. Lefebvre V, Li P, de Crombrugghe B. A new long form of Sox5 (L-Sox5), Sox6 and Sox9 are coexpressed in chondrogenesis and cooperatively activate the type II collagen gene. EMBO J. 1998;17(19):5718–33.
167. Karsenty G. Transcriptional control of skeletogenesis. Annu Rev Genom Hum Genet. 2008;9:183–96.
168. Bhattaram P, Penzo-Mendez A, Kato K, Bandyopadhyay K, Gadi A, Taketo MM, et al. SOXC proteins amplify canonical WNT signaling to secure nonchondrocytic fates in skeletogenesis. J Cell Biol. 2014;207(5):657–71.
169. Diaz-Hernandez ME, Bustamante M, Galvan-Hernandez CI, Chimal-Monroy J. Irx1 and Irx2 are coordinately expressed and regulated by retinoic acid, TGFbeta and FGF signaling during chick hindlimb development. PLoS One. 2013;8(3):e58549.
170. Zou H, Wieser R, Massague J, Niswander L. Distinct roles of type I bone morphogenetic protein receptors in the formation and differentiation of cartilage. Genes Dev. 1997;11(17):2191–203.
171. Pizette S, Niswander L. BMPs are required at two steps of limb chondrogenesis: formation of prechondrogenic condensations and their differentiation into chondrocytes. Dev Biol. 2000;219(2):237–49.
172. Yoon BS, Ovchinnikov DA, Yoshii I, Mishina Y, Behringer RR, Lyons KM. Bmpr1a and Bmpr1b have overlapping functions and are essential for chondrogenesis in vivo. Proc Natl Acad Sci USA. 2005;102(14):5062–7.
173. Bandyopadhyay A, Yadav PS, Prashar P. BMP signaling in development and diseases: a pharmacological perspective. Biochem Pharmacol. 2013;85(7):857–64.
174. Weston AD, Rosen V, Chandraratna RA, Underhill TM. Regulation of skeletal progenitor differentiation by the BMP and retinoid signaling pathways. J Cell Biol. 2000;148(4):679–90.
175. Weston AD, Chandraratna RA, Torchia J, Underhill TM. Requirement for RAR-mediated gene repression in skeletal progenitor differentiation. J Cell Biol. 2002;158(1):39–51.
176. Dranse HJ, Sampaio AV, Petkovich M, Underhill TM. Genetic deletion of Cyp26b1 negatively impacts limb skeletogenesis by inhibiting chondrogenesis. J Cell Sci. 2011;124(Pt 16):2723–34.
177. Hoffman LM, Garcha K, Karamboulas K, Cowan MF, Drysdale LM, Horton WA, et al. BMP action in skeletogenesis involves attenuation of retinoid signaling. J Cell Biol. 2006;174(1):101–13.
178. Gray DJ, Gardner E, O'Rahilly R. The prenatal development of the skeleton and joints of the human hand. Am J Anat. 1957;101(2):169–223.
179. Shubin NH, Alberch P. A morphogenetic approach to the origin and basic organization of the tetrapod limb. In: Evolutionary biology. New York: Plenum Press; 1986. p. 319–87.
180. Hinchliffe JR, Johnson DR. The development of the vertebrate limb. Oxford: Clarendon Press; 1980.
181. Kim IS, Otto F, Zabel B, Mundlos S. Regulation of chondrocyte differentiation by Cbfa1. Mech Dev. 1999;80(2):159–70.
182. Nakashima K, Zhou X, Kunkel G, Zhang Z, Deng JM, Behringer RR, de Crombrugghe B. The novel zinc finger-containing transcription factor osterix is

required for osteoblast differentiation and bone formation. Cell. 2002;108(1):17–29.
183. Yang X, Matsuda K, Bialek P, Jacquot S, Masuoka HC, Schinke T, et al. ATF4 is a substrate of RSK2 and an essential regulator of osteoblast biology; implication for Coffin-Lowry Syndrome. Cell. 2004;117(3):387–98.
184. Mackie EJ, Ahmed YA, Tatarczuch L, Chen KS, Mirams M. Endochondral ossification: how cartilage is converted into bone in the developing skeleton. Int J Biochem Cell Biol. 2008;40(1):46–62.
185. Noback CR, Robertson GG. Sequences of appearance of ossification centers in the human skeleton during the first five prenatal months. Am J Anat. 1951;89(1):1–28.
186. Stuart HC, Pyle SI, Cornoni J, Reed RB. Onsets, completions and spans of ossification in the 29 bonegrowth centers of the hand and wrist. Pediatrics. 1962;29:237–49.
187. Hartmann C, Tabin CJ. Wnt-14 plays a pivotal role in inducing synovial joint formation in the developing appendicular skeleton. Cell. 2001;104(3):341–51.
188. Decker RS, Koyama E, Pacifici M. Genesis and morphogenesis of limb synovial joints and articular cartilage. Matrix Biol. 2014;
189. Kan A, Ikeda T, Fukai A, Nakagawa T, Nakamura K, Chung UI, et al. SOX11 contributes to the regulation of GDF5 in joint maintenance. BMC Dev Biol. 2013;13:4.
190. Gao Y, Lan Y, Liu H, Jiang R. The zinc finger transcription factors Osr1 and Osr2 control synovial joint formation. Dev Biol. 2011;352(1):83–91.
191. Dalgleish AE. Development of the limbs of the mouse: PhD Thesis, Stanford University; Stanford, CA. 1964.
192. Craig FM, Bayliss MT, Bentley G, Archer CW. A role for hyaluronan in joint development. J Anat. 1990;171(4):17–23.
193. Nowlan NC, Sharpe J, Roddy KA, Prendergast PJ, Murphy P. Mechanobiology of embryonic skeletal development: insights from animal models. Birth Defects Res C Embryo Today. 2010;90(3):203–13.
194. Khan IM, Redman SN, Williams R, Dowthwaite GP, Oldfield SF, Archer CW. The development of synovial joints. Curr Top Dev Biol. 2007;79:1–36.
195. Pacifici M, Koyama E, Iwamoto M. Mechanisms of synovial joint and articular cartilage formation: recent advances, but many lingering mysteries. Birth Defects Res C Embryo Today. 2005;75(3):237–48.
196. Tozer S, Duprez D. Tendon and ligament: development, repair and disease. Birth Defects Res C Embryo Today. 2005;75(3):226–36.
197. Mitrovic D. Development of the diarthrodial joints in the rat embryo. Am J Anat. 1978;151(4):475–85.
198. Sharma K, Izpisua Belmonte JC. Development of the limb neuromuscular system. Curr Opin Cell Biol. 2001;13(2):204–10.
199. Schweitzer R, Chyung JH, Murtaugh LC, Brent AE, Rosen V, Olson EN, et al. Analysis of the tendon cell fate using Scleraxis, a specific marker for tendons and ligaments. Development. 2001;128(19):3855–66.
200. Ros MA, Rivero FB, Hinchliffe JR, Hurle JM. Immunohistological and ultrastructural study of the developing tendons of the avian foot. Anat Embryol. 1995;192(6):483–96.
201. Kardon G. Muscle and tendon morphogenesis in the avian hind limb. Development. 1998;125(20):4019–32.
202. Edom-Vovard F, Duprez D. Signals regulating tendon formation during chick embryonic development. Dev Dyn. 2004;229(3):449–57.
203. Sefton EM, Kardon G. Connecting muscle development, birth defects, and evolution: an essential role for muscle connective tissue. Curr Top Dev Biol. 2019;132:137–76.
204. Murphy M, Kardon G. Origin of vertebrate limb muscle: the role of progenitor and myoblast populations. Curr Top Dev Biol. 2011;96:1–32.
205. Williams BA, Ordahl CP. Pax-3 expression in segmental mesoderm marks early stages in myogenic cell specification. Development. 1994;120(4):785–96.
206. Buckingham M, Bajard L, Chang T, Daubas P, Hadchouel J, Meilhac S, Montarras D, Rocancourt D, Relaix F. The formation of skeletal muscle: from somite to limb. J Anat. 2003;202(1):59–68.
207. Sze LY, Lee KK, Webb SE, Li Z, Paulin D. Migration of myogenic cells from the somites to the fore-limb buds of developing mouse embryos. Dev Dyn. 1995;203(3):324–36.
208. Bober E, Franz T, Arnold HH, Gruss P, Tremblay P. Pax-3 is required for the development of limb muscles: a possible role for the migration of dermomyotomal muscle progenitor cells. Development. 1994;120(3):603–12.
209. Dietrich S, Abou-Rebyeh F, Brohmann H, Bladt F, Sonnenberg-Riethmacher E, Yamaai T, et al. The role of SF/HGF and c-Met in the development of skeletal muscle. Development. 1999;126(8):1621–9.
210. Bladt F, Riethmacher D, Isenmann S, Aguzzi A, Birchmeier C. Essential role for the c-met receptor in the migration of myogenic precursor cells into the limb bud. Nature. 1995;376(6543):768–71.
211. Brand-Saberi B, Muller TS, Wilting J, Christ B, Birchmeier C. Scatter factor/hepatocyte growth factor (SF/HGF) induces emigration of myogenic cells at interlimb level in vivo. Dev Biol. 1996;179(1):303–8.
212. Scaal M, Bonafede A, Dathe V, Sachs M, Cann G, Christ B, et al. SF/HGF is a mediator between limb patterning and muscle development. Development. 1999;126(21):4885–93.
213. Epstein JA, Shapiro DN, Cheng J, Lam PY, Maas RL. Pax3 modulates expression of the c-Met receptor during limb muscle development. Proc Natl Acad Sci U S A. 1996;93(9):4213–8.

214. Schmidt C, Bladt F, Goedecke S, Brinkmann V, Zschiesche W, Sharpe M, et al. Scatter factor/hepatocyte growth factor is essential for liver development. Nature. 1995;373(6516):699–702.
215. Schafer K, Braun T. Early specification of limb muscle precursor cells by the homeobox gene Lbx1h. Nat Genet. 1999;23(2):213–6.
216. Tajbakhsh S, Buckingham ME. Mouse limb muscle is determined in the absence of the earliest myogenic factor myf-5. Proc Natl Acad Sci U S A. 1994;91(2):747–51.
217. Ontell M, Kozeka K. The organogenesis of murine striated muscle: a cytoarchitectural study. Am J Anat. 1984;171(2):133–48.
218. Otto A, Collins-Hooper H, Patel K. The origin, molecular regulation and therapeutic potential of myogenic stem cell populations. J Anat. 2009;215(5):477–97.
219. Dieu T, Newgreen D. Chicken wings and the brachial plexus. Neurol Res. 2007;29(3):225–30.
220. Wehrle-Haller B, Koch M, Baumgartner S, Spring J, Chiquet M. Nerve-dependent and -independent tenascin expression in the developing chick limb bud. Development. 1991;112(2):627–37.
221. Swanson GJ, Lewis J. Sensory nerve routes in chick wing buds deprived of motor innervation. J Embryol Exp Morphol. 1986;95:37–52.
222. Swanson GJ. Paths taken sensory nerve fibres in aneural chick wing buds. J Embryol Exp Morphol. 1985;86:109–24.
223. Martin P, Khan A, Lewis J. Cutaneous nerves of the embryonic chick wing do not develop in regions denuded of ectoderm. Development. 1989;106(2):335–46.
224. Lewis J, Chevallier A, Kieny M, Wolpert L. Muscle nerve branches do not develop in chick wings devoid of muscle. J Embryol Exp Morphol. 1981;64:211–32.
225. Polleux F, Ince-Dunn G, Ghosh A. Transcriptional regulation of vertebrate axon guidance and synapse formation. Nat Rev Neurosci. 2007;8(5):331–40.
226. Dasen JS, Jessell TM. Hox networks and the origins of motor neuron diversity. Curr Top Dev Biol. 2009;88:169–200.
227. Kao TJ, Law C, Kania A. Eph and ephrin signaling: lessons learned from spinal motor neurons. Semin Cell Dev Biol. 2012;23(1):83–91.
228. Dasen JS. Transcriptional networks in the early development of sensory-motor circuits. Curr Top Dev Biol. 2009;87:119–48.
229. Manske PR, Oberg KC. Classification and developmental biology of congenital anomalies of the hand and upper extremity. J Bone Joint Surg Am. 2009;91(Suppl 4):3–18.
230. Tonkin MA, Oberg KC. Congenital hand I - embryology, classification, and principles. In: Chang J, Neligan PC, editors. Plastic surgery, Hand and upper extremity, vol. 6. 3rd ed. Philadelphia: Elsevier; 2012. p. 526–47.
231. Saint-Hilaire IG. Propositions sur la monstruosit'e. Paris: Imp. Didot le Jeune; 1829.
232. Saint-Hilaire IG. Histoire g'en'erale et particuli `ere des anomalies de l'organisation chez l'homme et les animaux. Paris: J.B. Baillière; 1932.
233. Swanson AB. A classification for congenital malformations of the hand. Acad Med Bull N J. 1964;10:166–9.
234. Lösch GM, Buck-Gramcko D, Cihak R, Sharader M, Seichert V. An attempt to classify the malformations of the hand based on morphogenetic criteria. Chirurgia Plastica. 1984;8(1):18.
235. Temtamy SA. Genetic factors in hand malformations. Baltimore: Johns Hopkins University; 1966.
236. Temtamy SA, McKusick VA. The genetics of hand malformations. Birth Defects Orig Artic Ser. 1978;14(3):i-619.
237. Kay H. A proposed international terminology for the classification of congenital limb deficiencies. ICIB/JACPOC. 1974;13(7):1–16.
238. Kelikian H. Classifications. In: Kelikian H, editor. Congenital deformities of the hand and forearm. Philadelphia: WB Saunders; 1974. p. 51–88.
239. Knight SL, Kay SPJ. Classification of congenital anomalies. In: Gupta A, Kay SPJ, Scheker LR, editors. The growing hand. London: Harcourt; 2000. p. 125–35.
240. Tonkin MA. Description of congenital hand anomalies: a personal view. J Hand Surg Br. 2006;31(5):489–97.
241. Ogino T. Congenital hand committee of the JSSH: modified IFSSH classification. J Japan Soc Surg Hand. 2000;17:353–65.
242. Oberg KC, Feenstra JM, Manske PR, Tonkin MA. Developmental biology and classification of congenital anomalies of the hand and upper extremity. J Hand Surg Am. 2010;35(12):2066–76.
243. Tonkin MA, Tolerton SK, Quick TJ, Harvey I, Lawson RD, Smith NC, et al. Classification of congenital anomalies of the hand and upper limb: development and assessment of a new system. J Hand Surg Am. 2013;38(9):1845–53.
244. Ezaki M, Baek GH, Horii E, Hovius SE. IFSSH scientific committee on congenital conditions: classification of congenital hand and upper limb anomalies. IFSSH Ezine. 2014;4(2):14–6.
245. Goldfarb CA, Wall LB, Ezaki M, Oberg KC. Oberg-Manske-Tonkin (OMT) Classification of Congenital Upper Extremities: Update for 2020. J Hand Surg Am. 2020;45(6):542–7.
246. Ekblom AG, Laurell T, Arner M. Epidemiology of congenital upper limb anomalies in Stockholm, Sweden, 1997 to 2007: application of the Oberg, Manske, and Tonkin classification. J Hand Surg Am. 2014;39(2):237–48.
247. Goldfarb CA, Wall LB, Bohn DC, Moen P, Van Heest AE: Epidemiology of congenital upper limb anomalies in a midwest United States population: an assessment using the Oberg, Manske, and Tonkin

classification. J Hand Surg Am 2015, 40(1):127–32. e121–2.
248. Kantaputra PN, Carlson BM. Genetic regulatory pathways of split-hand/foot malformation. Clin Genet. 2019;95(1):132–9.
249. Sowinska-Seidler A, Socha M, Jamsheer A. Split-hand/foot malformation – molecular cause and implications in genetic counseling. J Appl Genet. 2014;55(1):105–15.
250. Itzkovitz B, Jiralerspong S, Nimmo G, Loscalzo M, Horovitz DD, Snowden A, et al. Functional characterization of novel mutations in GNPAT and AGPS, causing rhizomelic chondrodysplasia punctata (RCDP) types 2 and 3. Hum Mutat. 2012;33(1):189–97.
251. Morgan NV, Brueton LA, Cox P, Greally MT, Tolmie J, Pasha S, et al. Mutations in the embryonal subunit of the acetylcholine receptor (CHRNG) cause lethal and Escobar variants of multiple pterygium syndrome. Am J Hum Genet. 2006;79(2):390–5.

2 Incidence and Prevalence of Congenital Anomalies of the Upper Limb

Donald R. Laub Jr.

Incidence

The best epidemiological studies of incidence of congenital anomalies are total population studies; there are four total population studies of congenital anomalies of the upper extremity (CAUE) in the literature (Table 2.1). A 5-year birth registry study of Edinburgh, Scotland, by Rogala et al. found the prevalence of babies born with any limb anomalies to be 30 out of 10,000 live births and the incidence of upper limb anomalies to be 22.5 out of 10,000 live births [1]. Of those with upper limb anomalies, 35% had another non-upper limb anomaly. They used an older classification, that of Temtamy and McKusick [2], so direct comparisons to more recent studies are difficult. One striking finding in this study is the complete lack of isolated simple syndactyly, which in other studies was found to be relatively common.

An 11-year total population study of Western Australia found the prevalence of babies born with upper limb anomalies to be 19.76 in 10,000 live births [3]. Forty-six percent of those affected had another non-hand congenital anomaly. Fifty-one percent had bilateral hand anomalies, and 17% had multiple different hand anomalies. The most common anomalies were failures of differentiation (35%), duplications (33%), and failures of formation (15%). Congenital upper extremity anomalies were more common in boys; preterm, post-term, and multiple births; and older mothers. No significant differences in prevalence or frequency of anomalies were found between whites and nonwhites, left and right sides, and in babies that survived and those who died shortly after birth.

Similarly, an 11-year total population study of the Stockholm region of Sweden found a recorded incidence of congenital anomalies of the upper limb of 21.5 per 10,000 live births [4]. Fifty-four

Table 2.1 Incidence and classification of congenital anomalies of the upper extremity (CAUE) in total population studies

Study	Ekblom et al. [4]	Giele et al. [3]	Rogala et al. [1]
Country	Sweden	Australia	Scotland
Years of survey	1997–2007	1980–1990	1964–1968
Incidence (per 10,000 live births)	21.50	19.76	16.00
Non-hand anomaly present (%)	23	46	15[a]
Failure of formation (%)	18	15	35
Duplication (%)	26	33	38[a]
Overgrowth (%)	2	1	35[a]
Undergrowth (%)	3	10	1[a]
Constriction ring (%)	1	3	2[a]
Generalized (%)	2	3	2[a]

[a]Author's interpretation: classification system differs

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percent of the children with congenital anomalies of the upper limb were boys. The anomalies affected the right side only in 30%, the left side only in 33%, and both sides in 37%. Non-hand anomalies were recorded in 23% of the children with congenital anomalies of the upper limb, most commonly in the lower limbs. In 17% of the affected children, there was a known occurrence among relatives. Failure of differentiation was the most common category (47%), followed by duplication (26%), failure of formation (18%), undergrowth (3%), generalized abnormalities and syndromes (2.4%), overgrowth (1.7%), and constriction ring syndrome (1.5%).

There are total population studies of limb deficiency anomalies; for example, a 9-year total population study of the national incidence of upper limb deficiencies in Finland found an incidence of congenital deficiency anomalies of the upper limb of 5.26 per 10,000 live births [5]. These studies approximate the "failure of formation" category of complete CAUE population studies (Table 2.2).

Incidence figures derived by extrapolation from surveys of patients presenting for treatment show slightly lower incidence: an estimated 16 to 18 per 10,000 births [9–11]. It is thought that these population studies may underestimate incidence, as the milder deformities may never present for treatment. A comparison of a population-based study and clinic registry of Swedish children with CAUE showed an underestimation of incidence by 6% in the clinic registry and a low degree of correlation of classification of anomalies [12].

Other studies focus on certain higher incidence anomalies, such as syndactyly. Swarup et al. studied infants born between 1997 and 2014 in New York State and found 3306 newborns with a syndactyly diagnosis [13]. This is an overall incidence of 0.074% or 7 cases per 10,000 live births. The majority of these patients underwent surgical correction before age 2.

The IFSSH classification is a useful tool for classifying most CAUE and enables comparison between studies, but is based on theories of embryological failure and is subject to some differences of interpretation. Ambiguities in the categorization of anomalies may then lead to differences of incidence of certain classifications [14]. For instance, the IFSSH classification could classify polydactyly with complex syndactylies as duplication, but for clinical purposes, it fits better into the category of failure of differentiation. Miura et al. [15] and Ogino [16, 17] suggested that a common teratological mechanism causes cleft hand, syndactyly, and polydactyly and that they should be put into a new category: failure of induction of digital rays. Classifying congenital absence of digits is also ambiguous; the distinctions between brachysyndactyly, symbrachydactyly (atypical cleft hand), and transverse arrest are not clearly defined.

In the Stockholm study, thumb hypoplasia was categorized as failure of formation, longitudinal arrest, and radial ray deficiency, whereas in the study from Western Australia, thumb hypoplasia was categorized as undergrowth. The Stockholm study showed a much lower frequency of undergrowth as a result. There was also a surprisingly large disparity between the categories of transverse arrest and symbrachydactyly regarding associated non-hand anomalies. Other differences in relative frequencies are also likely caused by other differences of interpretation of classification strategies.

Table 2.2 Incidence of upper limb deficiency anomalies in total population studies

Study	Koskimies et al. [5]	Giele et al. [3]	Kallen et al. [6]	Rogala et al. [1]	Aro et al. [7]	Froster and Baird [8]
Country	Finland	Australia	Sweden	Scotland	Finland	Canada
Years of survey	1993–2005	1980–1990	1965–1979	1964–1968	1964–1077	1952–1984
Incidence (per 10,000 live births)	5.25	5.12	4.00	6.70	4.00	3.40

Epidemiologic studies are important for healthcare planning, detecting changes in incidence over time, and comparing differences among regions. These two total population studies of CAUE agree on total incidence figures. These population studies are slightly higher than the estimated 0.16–0.18% incidence for CAUE in surveys of patients presenting for treatment (Table 2.3) [9, 10, 18–20]. It is assumed that this is due to the fact that milder deformities may not present for treatment.

These studies do, however, reveal the difficulties in comparing studies owing to different classification strategies and weaknesses within the IFSSH classification. For example, two studies of CAUE in Edinburgh, UK [2, 10], and two studies from Japan [18, 19] show markedly different relative frequency of incidence of duplication; presumably such a finding in ethnically similar populations is due to differences in classification (see Table 2.3).

Goldfarb et al. reported a total of 4,883,072 live births in New York State between 1992 and 2010 [21]. The overall prevalence of congenital upper extremity anomalies was 27.2 cases per 10,000 live births. Polydactyly was most common with 12,418 cases and a prevalence rate of 23.4 per 10,000 live births. The next most common anomalies included syndactyly with 627 cases affecting the hands (1498 total) and reduction defects (1111 cases). Specific syndromes were quite rare and were noted in a total of 215 live births. The prevalence of anomalies was higher in New York City compared with New York State populations at 33.0 and 21.9 per 10,000 live births, respectively.

Goldfarb and another group studied live births in three hospitals in two large metropolitan areas in the Midwest United States over a 1-year interval. They reported 641 individuals with 653 congenital upper extremity anomalies. They classified these using Oberg, Manske, and Tonkin (OMT) classification. They reported 480 extremities (74%) with a limb malformation including 184 involving the entire limb. Arthrogryposis was the most common of these (53 extremities). Anomalies affecting only the hand plate accounted for 62% (296) of the malformations. Of these, radial polydactyly (15%) was the most common specific anomaly, followed by symbrachydactyly (13%) and cleft hand (11%). There were 87 extremities with deformations and 58 of these were trigger digits. A total of 109 children had a syndrome or association, constriction ring sequence being the most common. They felt the OMT to be straightforward to use and that most anomalies could be easily assigned [22].

Ekblom et al. published a follow-up to their 2010 study in which they reclassified the same 562 individuals according to the OMT classification. In this study, the same 562 individuals clas-

Table 2.3 Comparison of classification of relative frequency of CAUE in population studies and large case series

Study	Ekblom et al. [4]	Giele et al. [3]	Flatt [9]	Ogino et al. [19]	Cheng et al. [20]	Lamb et al. [10]	Rogala et al. [2]	Yamaguchi et al. [18]
Country	Sweden	Australia	USA	Japan	China	UK	UK	Japan
Years of compilation	1997–2007	1980–1990	1960–1994	1968–1984	1976–1986	1976–1978	1964–1968	1961–1972
Failure of formation (%)	21.50	15	15	11	11	18	28	16
Failure of differentiation (%)	23	32	41	52	30	41	21	28
Duplication (%)	18	38	15	19	40	20	40	26
Overgrowth (%)	26	1	1	1	1	1	–	1
Undergrowth (%)	2	8	9	9	2	14	8	14
Constriction ring (%)	3	3	2	5	5	4	3	1
Generalized (%)	1	3	4	3	4	–	–	–
Unclassified (%)	2	–	13	1	3	–	–	14

sified as having 585 anomalies according to the IFSSH classification had 577 CAUE according to the OMT classification. In this classification, the largest main category was malformations (429 cases), followed by deformations (124 cases), dysplasia (10 cases), and syndromes (14 cases). They felt that although there were some minor difficulties within the OMT classification, this classification was more useful and accurate than the IFSSH system [23].

References

1. Rogala EJ, Wynne-Davies R, Littlejohn A, Gormley J. Congenital limb anomalies: frequency and aetiological factors. Data from the Edinburgh Register of the Newborn (1964-68). J Med Genet. 1974;11:221–33.
2. Temtamy SA, McKusick VA. The genetics of hand malformations. Birth Defects Orig Artic Ser. 1978;14(3):i–xviii, 1–619.
3. Giele H, Giele C, Bower C, Allison M. The incidence and epidemiology of congenital upper limb anomalies: a total population study. J Hand Surg Am. 2001;26(4):628–34.
4. Ekblom AG, Laurell T, Arner M. Epidemiology of congenital upper limb anomalies in 562 children born in 1997 to 2007: a total population study from Stockholm, Sweden. J Hand Surg Am. 2010;35(11):1742–54.
5. Koskimies E, Lindfors N, Gissler M, Peltonen J, Nietosvaara Y. Congenital upper limb deficiencies and associated malformations in Finland: a population-based study. J Hand Surg Am. 2011;36(6):1058–65.
6. Kallen B, Rahmani T, Winberg J. Infants with congenital limb reduction registered with the Swedish Register of Congenital Malformations. Teratology. 1984;29:73–85.
7. Aro T, Heinonen OP, Saxen L. Incidence and secular trends of congenital limb defects in Finland. Int J Epdemiol. 1982;3:239–44.
8. Froster U, Baird P. Upper limb deficiencies and associated malformations: a population-based study. Am J Med Genet. 1992;44:767–81.
9. Flatt AE. Classification and Incidence. In: The care of congenital hand anomalies. 2nd ed. St. Louis: Quality Medical Publishers; 1994. p. 47–63.
10. Lamb DW, Wynne-Davies R, Soto L. An estimate of the population frequency of congenital malformations of the upper limb. J Hand Surg Am. 1982;7(6):557–62.
11. Conway H, Bowe J. Congenital deformities of the hands. Plast Reconstr Surg. 1956;18:286–90.
12. Hermansson L, Bodin L, Wranne L. Upper Limb deficiencies in Swedish children—a comparison between a population-based and clinic-based register. Early Hum Dev. 2001;63:131–44.
13. Swarup I, Zhang Y, Do H, Daluiski A. Epidemiology of syndactyly in New York State. World J Orthop. 2019;10(11):387–93.
14. Tonkin MA. Description of hand anomalies: a personal view. J Hand Surg Br. 2006;31B:489–97.
15. Miura T, Nakamura R, Horii E. The position of symbrachydactyly in the classification of congenital hand anomalies. J Hand Surg Br. 1994;19B:350–4.
16. Ogino T. Clinical and experimental studies on the teratogenic mechanisms of the cleft hand, polydactyly and syndactyly. J Jap Orthop Assoc. 1979;53:1753–60.
17. Ogino T. Teratogenic relationship between polydactyly, syndactyly and cleft hand. J Hand Surg Br. 1990;15B:201–9.
18. Yamaguchi S. Incidence of various congenital anomalies of the hand from 1961 to 1972. Japanese Society for Surgery of the Hand, Fukuoka, Japan, 1973, cited in: Flatt AE: The care of congenital hand anomalies. 2nd ed. St. Louis: Quality Medical Publishers; 1994. p. 62.
19. Ogino T, Minami A, Fukuda K, Kato H. Congenital anomalies of the upper limb among the Japanese in Sapporo. J Hand Surg Br. 1986;11B:364–71.
20. Cheng JCY, Chow SK, Leung PC. Classification of 578 cases of congenital upper limb anomalies with the IFSSH system—a 10 years' experience. J Hand Surg Am. 1987;12A(6):1055–60.
21. Goldfarb CA, Shaw N, Steffen JA, Wall LB. The prevalence of congenital hand and upper extremity anomalies based upon the New York Congenital Malformations Registry. J Pediatr Orthop. 2017 Mar;37(2):144–8.
22. Goldfarb CA, Wall LB, Bohn DC, Moen P, Van Heest AE. Epidemiology of congenital upper limb anomalies in a midwest United States population: an assessment using the Oberg, Manske, and Tonkin classification. J Hand Surg Am. 2015;40(1):127–32. e1–2.
23. Ekblom AG, Laurell T, Arner M. Epidemiology of congenital upper limb anomalies in Stockholm, Sweden, 1997 to 2007: application of the Oberg, Manske, and Tonkin classification. J Hand Surg Am. 2014;39(2):237–48.

Genetics of Associated Syndromes

3

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The genetics of hand formation have already been reviewed (Chap. 1). The genetic pathways were originally elucidated through chick and mouse studies. Genetic studies of human malformations and malformation syndromes have provided further insight. Congenital hand malformations can be categorized using a number of different criteria. A common classification scheme uses the broad designations of polydactyly, syndactyly, brachydactyly, oligodactyly, and reduction defects. Hand malformations can occur in isolation or as a part of a larger pattern of malformation. Although there are over a hundred recognized syndromes with hand anomalies as a part of their expression, this review will concentrate on only those syndromes for which the hand malformation is a cardinal or defining feature.

I. Syndromes with polydactyly
II. Syndromes with syndactyly
III. Syndromes with brachydactyly
IV. Syndromes with oligodactyly
V. Syndromes with reduction defects

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Syndromes with Polydactyly

Polydactyly was classified in 1978 by Temtamy and McKusick [1] into the following categories:

- Postaxial type A – Postaxial extra digits that are well developed
- Postaxial type B – Pedunculated postminimus
- Preaxial type I – Duplication of thumbs/great toes
- Preaxial type II – Triphalangeal thumbs/duplication of great toes
- Preaxial type III – Absent thumbs, one or two extra preaxial digits
- Preaxial type IV – Broad thumbs, preaxial polysyndactyly, postaxial postminimus

In 1998, Castilla reported on the congenital hand malformations using a study of Latin American Collaborative Study of Congenital Malformations [2]. He reviewed 5927 consecutively born polydactyly cases. Castilla divided the polydactylies into postaxial, preaxial, and rare, a group in which he included mesoaxial and combinations of digits. These groups were then further subdivided into isolated or associated, depending upon whether there were other anomalies present. The associated category was then further subdivided into combined, if the other anomaly was a limb anomaly; syndromic, if the polydactyly occurred in a combination of anomalies representing a syndrome; and MCA, or

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multiple congenital anomalies, if the anomalies did not fit a recognizable pattern or syndrome.

From Castilla's study, several patterns emerged. Postaxial is the most common type of polydactyly and the most likely to be isolated. Although multiple chromosomal locations have been inferred for isolated forms of postaxial polydactyly, only a few genes have clearly been identified. One of those genes, GLI3, belongs to a family of genes involved in cellular signaling and patterning through the sonic hedgehog (SHH) developmental pathway. GLI3 is involved in syndromic forms of polydactyly that are mentioned further in this chapter, but can also cause isolated postaxial as well as preaxial polydactyly [3].

The rare polydactylies, that is, not clearly only postaxial or only preaxial, are the most likely to be associated with an underlying syndrome. Trisomy 13, Meckel syndrome, and Down syndrome accounted for 75% of the syndromic polydactyly cases in this study. In both Meckel and trisomy 13 syndromes, postaxial polydactyly is a cardinal feature of the syndrome. For Down syndrome, although preaxial polydactyly can be seen in Down syndrome with a higher frequency than in the general population, it would not be considered a cardinal feature of Down syndrome. Syndromes in which polydactyly is a cardinal feature can subdivided using the classification of postaxial, preaxial, mesoaxial, and combined and further subdivided by the other common findings or by a common aspect of development.

Syndromes with Postaxial Polydactyly: Craniofacial Anomalies as a Primary Feature

Polydactyly is a cardinal feature for a group of syndromes in which the major or defining features are craniofacial abnormalities (Table 3.1). These include the various types of oral-facial-digital (OFD) syndrome. Various reviewers have described the different types of OFD syndromes on their various oral, facial, and digital abnormalities, and many are now known to be genetically distinct. The primary findings of the OFD syndromes are polydactyly and a combination of oral anomalies, most prominently abnormalities of the tongue and frenula.

Postaxial Polydactyly as a Feature in Ciliopathies

Ciliopathies are a group of conditions in which the genes code for proteins that are important in the cilium-centrosome complex (CCC). The function of the CCC is to sense a wide variety of intracellular signals that affect polarity, proliferation, differentiation, and tissue maintenance. Many of the syndromes in which postaxial polydactyly is a cardinal feature belong to a subset of ciliopathies known as the single-gene ciliopathies [4] and are in Table 3.2.

The single-gene ciliopathies with postaxial polydactyly include a subset of ciliopathies that are characterized by the profound effect on the

Table 3.1 Primarily craniofacial syndromes associated with postaxial polydactyly

Syndrome	Other cardinal features	Inheritance/ OMIM Gene/locus
Oral-facial-digital II, Mohr (OFD II)	Preaxial polysyndactyly of the feet, cleft tongue, midline partial cleft lip, hypertrophic frenula, hamartomas of the tongue, conductive deafness	AR/252100
Oral-facial-digital III (OFD III)	See-saw winking of eyelids, oral frenulas, hamartomas of the tongue, supernumerary teeth, intellectual disability	AR/258850
Oral-facial-digital V (OFD V)	Hypertelorism, midline cleft of the upper lip, lobulated tongue, intellectual disability	AR/174300 DDX59/1q32.1
Otopalatodigital, type II	Hypertelorism, micrognathia, cleft palate, overlapping fingers, dense bones	XLR/304120 FLNA/Xq28

Table 3.2 Ciliopathy syndromes associated with postaxial polydactyly

Syndrome	Other cardinal features	Inheritance/ OMIM Gene/locus
Acrocallosal	Hypoplastic or absent corpus callosum, other brain abnormalities, preaxial polydactyly/syndactyly of the feet	AR/200990 KIF7/15q26.1
Bardet-Biedl, with more than 20 genetically distinct types	Obesity, intellectual disability, retinal dystrophy, renal anomalies, male hypogonadotropic hypogonadism, complex female genitourinary malformations	AR Multiple genes
Ellis-van Creveld, types 1 and 2	Atrial septal defect, short ribs, acromesomelic limb shortening, oral frenula	AR/225500 EVC/4p16 EVC2/4p16
Asphyxiating thoracic dystrophy, type 1 (Jeune type)	Short ribs, brachydactyly, short stature, renal failure, hepatic and pancreatic fibrosis, retinal degeneration	AR/208500 ATD1
Asphyxiating thoracic dystrophy 2 (ATD2)	Narrow thorax, brachydactyly, short stature, shortened and bowed femora	AR/611263 IFT80/3q25.33
McKusick-Kaufman	Mesoaxial polydactyly, congenital heart disease, and hydrometrocolpos in females and genital malformations in males (most commonly hypospadias, cryptorchidism, and chordee)	AR/236700 MKKS/20p12.2
Meckel syndrome (Meckel-Gruber), more than 10 genetically distinct types	Encephalocele, cystic kidneys, microphthalmia, cleft lip//palate, hepatic fibrosis	AR Multiple genes
Oral-facial-digital, type I (OFD I)	Syndactyly and asymmetric brachydactyly of hands with occasional pre- and postaxial polydactyly of hands, preaxial polydactyly of feet, midline cleft lip, cleft tongue, hamartomas of the tongue, hyperplastic frenula, intellectual disability, polycystic kidneys	XLR/311200 OFD1/Xp22.2
Short rib polydactyly syndromes	All have short ribs Other features vary but include gastrointestinal, urogenital, cardiac, and craniofacial abnormalities	AR Multiple genes

skeleton. These include the perinatal lethal short-rib polydactyly syndromes, asphyxiating thoracic dystrophy, Ellis-van Creveld syndrome, and a group with cranioectodermal phenotypes. This group of skeletal ciliopathies, all of which follow autosomal recessive inheritance patterns, are associated with at least 26 known genes [5]. The severity ranges from the short rib polydactylies, characterized by very small thoracic cages, lung hypoplasia, and often, early infant death. Ellis-van Creveld syndrome and Jeune thoracic dystrophy also include short ribs as a defining feature, but have other distinctive features that separate them from the short rib polydactyly group. The configuration of the ribs is different in these last two conditions as well.

Ciliopathies also include Bardet-Biedl syndrome and Meckel-Gruber syndrome. Both of these syndromes can be caused by one of multiple genes, but all of the genes share the property that they encode proteins important in the CCC [4].

Bardet-Biedl syndrome is a multisystem disorder in which the primary features are retinal degeneration, cystic kidney disease or urinary tract malformation, intellectual disability, diabetes mellitus, obesity, infertility, and postaxial polydactyly. The delineation of the genetics of Bardet-Biedl syndrome helped establish ciliopathies as an important disease entity when it was shown that many of the proteins formed by genes responsible for BBS were expressed in the ciliated sensory neurons of the nematode *C. elegans* [5]. The polarization of cells required for the formation of the tubules in the kidney represents the action of these ciliary proteins that are affected by BBS gene mutations [4].

Both McKusick-Kaufman syndrome and Bardet-Biedl syndrome 6 (BBS6) are caused by mutations in the MKKS gene. McKusick-

Kaufman syndrome is an autosomal recessive, multisystem condition with polydactyly, heart defects, and genital abnormalities and is most common in the Old Order Amish community. MKKS codes for a protein important in centrosomal function, possibly acting as a chaperonin. Silencing of the transcript of that gene leads to multinucleate and multicentrosomal cells with cytokinesis defects [6].

Meckel-Gruber syndrome is a recessively inherited condition in which the cardinal features include central nervous system malformations, particularly occipital encephalocele, Arnold-Chiari malformation, absence of midline structures such as the corpus callosum and septum pellucidum, and cerebellar malformations. Other major findings include cystic changes in the kidneys and liver. The genes that cause Meckel-Gruber syndrome code for proteins that localize to the centrosome, to the pericentriolar region, or to the cilium itself.

Oral-facial-digital syndrome type 1 (OFD1) is an X-linked disorder in which the gene product has been shown to localize in the renal epithelial cells in the polarized region. Expression of OFD1 is necessary for primary cilia formation and left-right axis specification [4, 7], making OFD1 a ciliopathy syndrome as well. The hand findings in OFD1 are variable and primarily involve asymmetric shortening of the digits in the hands with variable syndactyly and preaxial polydactyly of the feet. However, postaxial and preaxial polydactyly of the hands has also been reported.

Other Syndromes with Polydactyly of Varying Types

Table 3.3 lists some of the many other syndromes associated with polydactyly. Grebe chondrodysplasia is a dwarfing condition in which all of the long bones are severely shortened, particularly

Table 3.3 Other selected syndromes associated with polydactyly

Syndrome	Type	Other cardinal features	Inheritance/ OMIM Gene/locus
Carpenter syndrome	Postaxial	Brachydactyly with clinodactyly and syndactyly, broad/bifid thumbs, brachycephaly, craniosynostosis, intellectual disability	AR/201000 RAB23/6p11.2
Chondrodysplasia, Grebe type	Postaxial	Hypoplastic digits, severe shortening of long bones	AR/200700 CDMP1/ GDF5/20q11.2
Greig cephalopolysyndactyly	Preaxial/ postaxial	Preaxial polydactyly of feet, syndactyly, craniosynostosis, macrocephaly with frontal bossing, absence of corpus callosum	AD/175700 GLI3/7p14.1
Laurin-Sandrow	Preaxial/ postaxial Mirror	Mirror polysyndactyly of hands and feet, ulnar and fibular dimelia, dysplasia or absence of the radius and tibia, cleft nares	AD/135750 LMBR1/7q36.3
Pallister-Hall	Postaxial/ mesoaxial	Hypothalamic hamartoblastoma, hypopituitarism, imperforate anus, abnormal or absent epiglottis, early death	AD/146510 GLI3/7p14.1
Simpson-Golabi-Behmel	Postaxial	Brachydactyly, syndactyly, overgrowth, coarse facial features, intellectual disability	XL/312870 GPC3/Xq26.2
Smith-Lemli-Opitz	Postaxial	2–3 syndactyly of toes, microcephaly, intellectual disability, hypospadias, cryptorchidism	AR/270400 DHCR7/11q13.4
Townes-Brocks	Preaxial	Distal deviation of thumbs, hypoplastic thumbs, microcephaly, ear anomalies and hearing loss, anal and intestinal atresias, genital anomalies, renal anomalies and kidney disease	AD/107480 SALL1/16q21.1
Ulnar-mammary	U	Postaxial polydactyly, apocrine abnormalities, hypopigmentation and hypoplasia of areola, nipple and breast, genital anomalies in males, delayed puberty	AD/181450 TBX3/12q24.21

the distal portions, and is associated with postaxial polydactyly of the hands. Grebe chondrodysplasia is caused by mutations in the growth differentiation factor 5 (GDF5) gene, also known as the cartilage-derived morphogenetic protein 1 (CDMP1) gene. This gene has been found to be responsible for other types of chondrodysplasias including acromesomelic dysplasia, Hunter-Thompson type, Du Pan syndrome (fibular hypoplasia and complex brachydactyly), multiple synostosis syndrome 2, as well as isolated heritable hand malformations including brachydactyly types A1, A2, and C and proximal symphalangism type 1B (OMIM gene 601,146).

Greig cephalopolysyndactyly is a multiple malformation syndrome that is usually ascertained through the limb abnormalities, but includes craniofacial findings such as macrocephaly with an unusual head shape. In Greig, the hand and foot abnormalities are quite variable and include a combination of polydactyly and syndactyly. The polydactyly can be postaxial, preaxial, mesoaxial, or a mixture of all three and can vary from limb to limb in the same individual. Greig is caused by mutations in the Gli-Kruppel family member 3 (GLI3) gene on 7p13. GLI3 is a gene in the zinc finger gene family and is also the gene responsible for Pallister-Hall syndrome, a syndrome in which the polydactyly can be postaxial or mesoaxial, and other cardinal features include hypothalamic hamartoma, pituitary dysfunction, and visceral malformations. Mutations in GLI3 are also found in some of the isolated heritable forms of polydactyly, including postaxial polydactyly types A1 and B and preaxial polydactyly type IV [3, 8, 9].

Syndromes with Syndactyly

Syndactyly is harder to accurately study as mild cutaneous syndactyly is often not reported as a congenital anomaly. Significant cutaneous syndactyly and bony syndactyly are associated with a number of underlying syndromes. Complete syndactyly of the third and fourth digits of the hands, also called zygodactyly, can be seen in fetuses with triploidy (karyotype with three copies of every chromosome) but can also occur as an isolated finding.

Syndactyly can be found as a defining feature in a group of syndromes with craniosynostosis as a major feature, often called acrocephalosyndactylies (Table 3.4). Syndactyly of all the fingers into a mitten-like extremity occurs in Apert syndrome, an MCA syndrome in which there is significant craniosynostosis involving multiple sutures.

Syndactyly is also seen in a number of other syndromes. It is a defining characteristic in only some of these, which are listed in Table 3.5.

Table 3.4 Craniosynostosis syndromes associated with syndactyly

Syndrome	Digits involved on the hand	Other cardinal features	Inheritance/ OMIM Gene/locus
Apert	1–5; can be osseous or cutaneous, often resulting in a "mitten" hand	Midface hypoplasia, cleft palate, hypertelorism, hyperhidrosis, variety of brain malformations, fusion of cervical vertebrae, intellectual disability, hearing loss	AD/101200 FGFR2/10q26.13
Carpenter syndrome	2–5	Postaxial polydactyly, brachydactyly with clinodactyly, broad/bifid thumbs, brachycephaly, intellectual disability	AR/201000 RAB23/6p11.2
Pfeiffer	2–3	Syndactyly of toes, broad and medially deviated distal phalanges of thumb and great toe, brachymesophalangy hypertelorism, brachycephaly	AD/101600+ FGFR1/8p11.23 FGFR2/10q26.13
Saethre-Chotzen	2–3	3–4 syndactyly of toes, brachydactyly and clinodactyly, ossification defects and hyperostosis of skull, short clavicles, facial asymmetry	AD/101400+ TWIST/7p21.1 FGFR2/10q26.13

Table 3.5 Other syndromes associated with syndactyly as a defining or significant feature

Syndrome	Digits involved	Other cardinal features	Inheritance/ OMIM Gene/locus
Focal dermal hypoplasia (Goltz)	Primarily 3–4 but can include others	Ectrodactyly, oligodactyly, dermal hypoplasia, microphthalmia, other eye abnormalities, facial asymmetry, cleft palate	XL/305600 PORCN/Xp11.23
Fraser	2–4	Cryptophthalmos, syndactyly, and abnormalities of the respiratory and urogenital tract	AR/219000+ FRAS1/4q21.21 FREM2/13q13.3 GRIP1/12q14.3
Greig cephalopolysyndactyly	1–5, variable	Preaxial polydactyly of feet, syndactyly of toes, macrocephaly with frontal bossing, absence of corpus callosum	AD/175700 GLI3/7p14.1
Laurin-Sandrow	1–5	Mirror polysyndactyly of hands and feet, ulnar and fibular dimelia, dysplasia or absence of the radius and tibia, cleft nares	AD/135750 LMBR1/14q13
Oculodentodigital (ODD)	4–5	Syndactyly of third and fourth toes, microcephaly, intellectual disability, hearing loss, brain abnormalities, microphthalmia, cleft lip/palate, microdontia, enamel hypoplasia, hyperostosis of skull and vertebrae, palmoplantar keratoderma	AD/164200 GJA1/6p22.31
Oral-facial-digital II, Mohr (OFD II)	1–5	Preaxial polysyndactyly of the feet, cleft tongue, midline partial cleft lip, hypertrophic frenula, hamartomas of the tongue, conductive deafness	AR/252100
Pallister-hall	4–5	Postaxial/mesoaxial polydactyly, hypothalamic hamartoblastoma, hypopituitarism, imperforate anus, abnormal or absent epiglottis, early death	AD/146510 GLI3/7p14.1
Poland	Unilateral brachydactyly, syndactyly, oligodactyly	Aplasia of the pectoralis major, cardiac defects, rib anomalies, can be seen with Moebius	AD or sporadic/173800 Unknown

Syndromes with Brachydactyly

Isolated Brachydactyly

Brachydactyly of the hands or shortened digits can be due to absent, underdeveloped, or abnormally shaped phalanges (brachyphalangy), or metacarpals (brachymetacarpia), or a combination of these. Brachydactyly can involve all of the digits or only some of the digits. Bell classified isolated brachydactyly in 1951 [1, 10] into Types A through E with subtypes.

Type A: Brachymesophalangy
- Type A-1: Brachymesophalangy II–V; brachyphalangy I
- Type A-2: Brachymesophalangy II
- Type A-3: Brachymesophalangy V

Type B
- Aplasia terminal phalanges, II–V
- Hypoplasia middle phalanges, II–V
- Broad distal phalanges, I

Type C
- Brachymesophalangy II, III, V
- Hypersegmentation, proximal phalanges, II, III

Type D
- Short, broad thumb distal phalanx

Type E
- Brachymetacarpia
- Brachymetatarsia

Brachydactyly can occur as an isolated finding, usually as a dominant trait. The genetics of

isolated brachydactyly is summarized in Table 3.6.

Brachydactyly is a common finding in more than 50 different skeletal dysplasias, but rarely is the defining characteristic. Skeletal dysplasias are reviewed in Chap. 27 and will not be reviewed here.

There are single reports of families in which brachydactyly occurs as a dominant trait with one or two other features, but the genetics of these conditions is not well defined. These single-family reports will not be included in this review. Numerous multiple malformation syndromes have brachydactyly as a prominent or cardinal feature. Some of the more common of these are listed in Table 3.7.

Cornelia de Lange, or Brachman de Lange, syndrome is a multiple malformation syndrome

Table 3.6 Genetics of isolated brachydactyly

Classification	Description	Genetics OMIM
Type A1	Brachymesophalangy II–V; brachyphalangy I	AD/112500 IHH/2q35 BDA1B/5p13.3-p13.2
Type A2	Brachymesophalangy II	AD/112600 BMPR1B/4q22.3 BMP2/20p12.3 GDF5/20q11.22
Type A3	Brachymesophalangy V	AD/112700
Type B	Aplasia terminal phalanges, II–V, hypoplasia middle phalanges, II-V, broad distal phalanges, I, symphalangism, syndactyly	AD/113000 ROR2/9q22.31
Type C	Hypersegmentation of proximal and middle phalanges, II, III, brachymesophalangy II and III, ulnar deviation II and III	AD/113100 GDF5/20q11.22
Type D	Stub thumb; short, broad thumb distal phalanx	AD/113200 HOXD13/2q31.1
Type E	Brachymetacarpia, variable	AD/113300 HOXD13/2q31.1
Sugarman	Brachydactyly with major proximal phalangeal shortening, duplicated first metacarpals	AR/272150
Temtamy type (Type A4, not classified by Bell)	Brachymesophalangy II and V	AD/112800

Table 3.7 Syndromes with brachydactyly as a major feature

Syndrome	Hand features	Other cardinal features	Inheritance/OMIM Gene/locus
Aarskog	Brachydactyly of all fingers with clinodactyly of fifth, unusual positioning of fingers on extension	Short stature, hypertelorism, shawl scrotum	XL/305400 FGD1/Xp11.21
Acrodysostosis	Brachyphalangia and brachymetacarpia	Brachymetatarsia Brachymelic short stature, saddle nose, intellectual disability	AD/101800 PRKARIA/17q24.2 PDE4D, 5q11.2–12.1
Adams-Oliver	Digits may be short or have terminal transverse defects	Cutis aplasia, terminal transverse defects of limbs, intellectual disability in recessive form	AD/100300+ ARHGAP31/3q13.33 RBPJ/4p15.2 NOTCH1/9q34.3 DLL4/15q15.1 AR/614219 DOCK6/19p13.2
Albright hereditary osteodystrophy	Short distal phalanx of thumb, brachymetacarpia (4 and 5)	Short stature, intellectual disability, obesity, round face, resistance to PTH, TSH, and GHRH, hypogonadism	AD/103580 GNAS1/20q13.2

(continued)

Table 3.7 (continued)

Syndrome	Hand features	Other cardinal features	Inheritance/OMIM Gene/locus
Brachydactyly-ectrodactyly-fibular aplasia (Genuardi)	Brachydactyly, ectrodactyly	Fibular aplasia or hypoplasia	AD/113310
Brachydactyly-hallux varus-thumb abduction (Christian)	Brachymetacarpia (1), broad abducted thumbs	Hallux varus	AD/112450
Brachydactyly-hypertension	Brachyphalangy, brachymetacarpia	Hypertension	AD/112410 PDE3A/12p12.2
Carpenter syndrome	Brachydactyly with clinodactyly, postaxial polydactyly, broad/bifid thumbs, syndactyly (2–5)	Brachycephaly, craniosynostosis, intellectual disability	AR/201000 RAB23/6p11.2
Coffin-Lowry	Brachydactyly with tapering fingers, tufted drumstick appearance to distal phalanges on x-ray, small fingernails	Short stature, short bifid sternum with pectus deformities, coarse facial features, hypertelorism, scoliosis, hypodontia, rectal/uterine prolapse	XL/303600 RPS6KA3/Xp22.12
Coffin-Siris	Hypoplasia of fifth fingers (particularly distal phalanx), absence of fifth fingernail	Hypoplastic or absent toenails, short stature, sparse scalp hair, intellectual disability, coarse facial features, wide mouth with full lips, feeding difficulties, frequent infections	AR/135900 ARID1B/6q25.3
Cohen	Brachymetacarpia, narrow hands	Short stature, obesity, prominent upper central incisors, intellectual disability	AR/216550 VPS13B/8q22.2
Cornelia de Lange	Brachymetacarpia (1), clinodactyly (5), oligodactyly, ulnar deficiency	Short stature, microcephaly, intellectual disability, characteristic face with arched eyebrows, synophrys, downturned mouth and upturned nose, hirsutism, variable phenotype	AD/122470+ NIPBL/5p13.2 RAD21/8q24.11 SMC3/10q25.2 XL/300040+ SMC1A/Xp11.22 HDAC8/Xq13.1
Cranioectodermal dysplasia	Brachydactyly, single transverse palmar creases, clinodactyly (5) short, broad distal phalanges	Short stature, sagittal craniosynostosis, skeletal dysplasia, fine, sparse hair, lax skin, dental abnormalities, liver and kidney failure	AR/218330+ IFT122/3q21.3-q22.1 WDR35/2p24.1 IFT43/14q24.3 WDR19/4p14
DOOR	Hypoplastic or absent distal phalanges, triphalangeal thumbs	Sensorineural deafness, onychodystrophy, osteodystrophy, intellectual disability, seizures, visual impairment, microcephaly	AR/220500 TBC1D24/16p13.3
Floating harbor	Brachydactyly, clinodactyly (5), broad thumbs	Short stature, severe speech and language delay, deep-set eyes, bulbous nose, behavioral problems	AD/136140 SRCAP/16p11.2
Hand-foot-genital	Short, proximally placed thumbs, brachydactyly (5), ulnar deviation (2), clinodactyly (5), hypoplastic middle phalanges, delayed ossification of carpals, short first metacarpals, pseudoepiphyses	Absent/short halluces with medial deviation, brachydactyly, delayed ossification of tarsals, short first metatarsal, hypoplastic distal and middle phalanges of feet, genital defects (internal – female, external – male),	AD/140000 HOXA13/7p15.2

Table 3.7 (continued)

Syndrome	Hand features	Other cardinal features	Inheritance/OMIM Gene/locus
Holt-Oram	Spectrum of upper limb defects, primarily involving the radial ray but can include the ulna, humerus and the shoulder girdle; brachydactyly, oligodactyly, syndactyly	Cardiac defects include ventricular septal defect, atrial septal defect, and others	AD/142900 TBX5/12q24.1
Kabuki	Brachydactyly, short middle phalanges, short metacarpals (4 and 5), clinodactyly (5), prominent fingertip pads	Distinctive facial features with long palpebral fissures and lateral ectropion, ptosis, cleft palate, cardiac defects, hyperextensible joints, intellectual disability	AD/147920 KMT2D/12q13.12 XL/300867 KDM6A/Xp11.3
Moebius	Brachydactyly, oligodactyly	Sixth and seventh nerve palsy, absent pectoral muscles, Klippel-Feil anomaly	AD/157900 Linked to several loci
Pfeiffer	Brachymesophalangy, syndactyly, broad and medially deviated distal phalanx of thumb	Syndactyly of toes, broad and medially deviated distal phalanges of great toe, craniosynostosis, hypertelorism, brachycephaly	AD/101600 FGFR1/8p11.23 FGFR2/10q26.13
Poland	Unilateral brachydactyly, syndactyly, oligodactyly	Aplasia of the pectoralis major, cardiac defects, rib anomalies, can be seen with Moebius	AD or sporadic/173800 Unknown
Robinow	Brachydactyly, brachymetacarpia, bifid terminal phalanges, clinodactyly (5), hypoplastic/absent thumbs	Short stature, hypertelorism, costovertebral abnormalities, "fetal face"	AD/180700+ WNT5A/3p14.3 DVL1/1p36.33 DVL3/3q27.1 AR/268130+ ROR2/9q22.31 NXN/17p13.3
Rubinstein-Taybi	Brachydactyly, broad thumbs with radial deviation, clinodactyly (5)	Broad great toes, short stature, intellectual disability, microcephaly, downslanting palpebral fissures, narrow palate, beaked nose, grimacing smile	AD/180849+ CREBBP/16p13.3 Deletion 16p13.3 EP300/22q13.2
Saethre-Chotzen	Brachydactyly, clinodactyly, 2–3 syndactyly	3–4 syndactyly of toes, craniosynostosis, ossification defects and hyperostosis of skull, short clavicles, facial asymmetry	AD/101400 TWIST/7p21 FGFR2/10q26.13
Schinzel-Giedion	Brachydactyly, brachymetacarpia (1), hypoplastic distal phalanges	Severe pes planus, short stature, intellectual disability, seizures, sclerotic skull and long bones, skeletal abnormalities, renal and genital anomalies	AD/269150 SETBP1/18q12.3
Smith-Magenis	Brachydactyly, broad hands	Brachycephaly, broad, flat midface, intellectual disability, sleep disturbance, characteristic behavior	AD/182290 RAI1/17p11.2 Deletion 17p11.2
Townes-Brocks	Distal deviation of thumbs, hypoplastic thumbs, preaxial polydactyly	Microcephaly, ear anomalies and hearing loss, anal and intestinal atresias, genital anomalies, renal anomalies and kidney disease	AD/107480+ SALL1/16q21.1 DACT1/14q23.1
Turner	Brachymetacarpia (4 and 5)	Short stature, webbed neck, ovarian failure, horseshoe kidney, coarctation of the aorta	Monosomy X

that was first described in severely affected cases in which there was moderate to severe intellectual disability and severely affected upper limbs with oligodactyly and ulnar deficiency. Short stature and microcephaly were often severe. The facial appearance was also striking, with high arched eyebrows and synophrys, a small upturned nose, and a long philtrum with thin lips and a crescent-shaped mouth with downturned edges. Most cases were sporadic. When the first gene was identified, NIPBL, the phenotype was found to be much more variable in affected individuals. In particular the upper limb defects ranged from the classical findings of ulnar ray deficiency to individuals with small hands and individuals with brachydactyly. Following that, four other genes were identified that caused the same phenotype, with either autosomal dominant or X-linked inheritance.

Syndromes with Oligodactyly/ Reduction Defects

The final category of syndromes with hand defects involves a group of syndromes in which the hands have reduction defects, resulting in either oligodactyly or adactyly (Table 3.8). Reduction defects are usually divided into those with radial ray defects and those with ulnar ray defects, and then a third category for conditions in which either or both rays might be involved. The reduction defects may just involve the digits, leading to oligodactyly, or may involve whole parts of the hand and/or upper extremity. They can be classified by the part of the hand structure that is involved.

Hand malformations are an important feature of many multiple malformation syndromes, and

Table 3.8 Syndromes with oligodactyly or adactyly

Syndrome	Segment involved: radial (R), ulnar (U), middle (M), all (A)	Other cardinal features	Inheritance/OMIM Gene/locus
Adams-Oliver	R, M, U	Brachydactyly, cutis aplasia, intellectual disability in recessive form	AD/100300+ ARHGAP31/3q13.33 RBPJ/4p15.2 NOTCH1/9q34.3 DLL4/15q15.1 AR/614219 DOCK6/19p13.2
Brachydactyly-ectrodactyly-fibular aplasia (Genuardi)	M	Brachydactyly, fibular aplasia or hypoplasia	AD/113310
CHILD	M, U		XL/308050 NSDHL/Xq28
Cornelia de Lange	U, M	Short stature, microcephaly, intellectual disability, characteristic face with arched eyebrows, synophrys, downturned mouth and upturned nose, hirsutism, variable phenotype	AD/122470+ NIPBL/5p13.2 RAD21/8q24.11 SMC3/10q25.2 XL/300040+ SMC1A/Xp11.22 HDAC8/Xq13.1
Ectrodactyly-ectodermal dysplasia-clefting	M	Ectrodactyly of the feet, cleft lip/palate, light-colored and sparse hair, anodontia or oligodontia, tear duct anomalies, urinary tract abnormalities	AD/ 604,292 TP63/3q28

Table 3.8 (continued)

Syndrome	Segment involved: radial (R), ulnar (U), middle (M), all (A)	Other cardinal features	Inheritance/OMIM Gene/locus
Fanconi anemia	R	Short stature, intellectual disability, renal anomalies, genital abnormalities, microcephaly, café au lait spots, deafness, cardiac defects, chromosomal breakage	AR/227650+ PHF9/2p16.1 FANCD2/3p25.3 FANCE/6p21.31 XRCC9/9p13.3 FANCC/9q22.32 FANCF/11p14.3 BRCA2/13q13.1 XRCC2/7q36.1 FANCI/15q26.1 SLX4/16p13.3 ERCC4/16p13.12 PALB2/16p12.2 FANCA/16q24.3 RAD51C/17q22 BRIP1/17q23.2 FANCB/Xp22.2 RAD51/15.1 BRCA1/17q21.31 RFWD3/16q23.1 MAD2L2/1p36.22 UBE2T/1q32.1
Hand-foot-genital	R	Brachydactyly, clinodactyly (5) and ulnar deviation (2), abnormalities of the toes and metatarsals, primarily the great toe, brachydactyly of toes, genital defects (internal – female, external – male),	AD/140000 HOXA13/7p15.2
Holt-Oram	R	Brachydactyly, syndactyly, occasional involvement of shoulder girdle, cardiac defects include ventricular septal defect, atrial septal defect, and others	AD/142900 TBX5/12q24.1
Nager	R	Malar hypoplasia, downslanting palpebral fissures, partial absence of lower eyelashes, high nasal bridge, micrognathia, cleft palate, abnormal ears, radioulnar synostosis	AD/154400 SF3B4/1q21.2
Poland	Unilateral R	Unilateral aplasia of the pectoralis major with ipsilateral brachydactyly and syndactyly, cardiac defects, rib anomalies, can be seen with Moebius	AD or sporadic/173800 Unknown
Postaxial acrofacial dysostosis (POADS) – also known as Miller	U	Malar hypoplasia, downslanting palpebral fissures, eyelid coloboma, micrognathia, cleft lip/palate, abnormal ears, accessory nipples	AR/263750 DHODH/16q22.2
Roberts	U	Phocomelia, prenatal onset growth deficiency, microcephaly, ear, eye, heart and urogenital anomalies, intellectual disability	AR/268300 ESCO2/8p21.1
Robinow	R	Brachydactyly, short stature, hypertelorism, costovertebral abnormalities, “fetal face”	AD/180700+ WNT5A/3p14.3 DVL1/1p36.33 DVL3/3q27.1 AR/268130+ ROR2/9q22.31 NXN/17p13.3

(continued)

Table 3.8 (continued)

Syndrome	Segment involved: radial (R), ulnar (U), middle (M), all (A)	Other cardinal features	Inheritance/OMIM Gene/locus
Ulnar-mammary	U	Postaxial polydactyly, apocrine abnormalities, hypopigmentation and hypoplasia of areola, nipple and breast, genital anomalies in males, delayed puberty	AD/181450 TBX3/12q24.21
VACTERL	R	Vertebral defects, anal atresia, cardiac defects, renal defects, ear defects, tracheoesophageal atresia	

the genes involved give clues to the morphogenesis of the limbs as well as many other areas of development.

References

1. Temtamy SA, McKusick VA. The genetics of hand malformations. Birth Defects Orig Artic Ser. 1978;14(3):i–xviii, 1–619.
2. Castilla EE, Lugarinho R, da Graca Dutra M, Salgado LJ. Associated anomalies in individuals with polydactyly. Am J Med Genet. 1998;80(5):459–65.
3. Radhakrishna U, Bornholdt D, Scott HS, Patel UC, Rossier C, Engel H, et al. The Phenotypic Spectrum of GLI3 Morphopathies Includes Autosomal Dominant Preaxial Polydactyly Type-IV and Postaxial Polydactyly Type-A/B; No Phenotype Prediction from the Position of GLI3 Mutation. Am J Hum Genet. 1999;65:645–55.
4. Hildebrandt F, Benzing T, Katsanis N. Ciliopathies. N Engl J Med. 2011;364(16):1533–43.
5. Reiter JF, Leroux MR. Genes and molecular pathways underpinning ciliopathies. Nat Rev Mol Cell Biol. 2017;18(9):533–47.
6. Kim JC, Ou YY, Badano JL, Esmail MA, Leitch CC, Fiedrich E, et al. MKKS/BBS6, a divergent chaperonin-like protein linked to the obesity disorder Bardet-Biedl syndrome, is a novel centrosomal component required for cytokinesis. J Cell Sci. 2005;118(Pt 5):1007–20.
7. Romio L, Wright V, Price K, Winyard PJ, Donnai D, Porteous ME, et al. OFD1, the gene mutated in oral-facial-digital syndrome type 1, is expressed in the metanephros and in human embryonic renal mesenchymal cells. J Am Soc Nephrol. 2003;14(3):680–9.
8. Biesecker LG. What you can learn from one gene: GLI3. J Med Genet. 2006;43(6):465–9.
9. Johnston JJ, Sapp JC, Turner JT, Amor D, Aftimos S, Aleck KA, et al. Molecular analysis expands the spectrum of phenotypes associated with GLI3 mutations. Hum Mutation. 2010;31(10):1142–54.
10. Temtamy SA. Classification of hand malformations as isolated defects: an overview. J Genet Hum. 1982;30(4):281–90.

4 Anesthesia Concerns in Congenital Anomalies of the Upper Extremity

Rebecca Evans, Ann F. T. Lawrence, and Emily L. Stebbins

Introduction

Anesthesia for children utilizes a team of specialists to aid the child and family through the perioperative period. Even the healthiest of children can benefit from being cared for by a pediatric anesthesiology team, a nursing team familiar with caring for children, child life specialists to ease transitions through the hospital, and a supportive family. Additional team members may be required for children with complex medical, behavioral, or social situations. Coordinating care requires time, patience, and communication.

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Preoperative Management

Prior to the Day of Surgery

Unlike adult patients, pediatric patients require few, if any, preoperative tests prior to the day of the procedure. All patients should be evaluated by a pediatrician prior to presenting to the operating room to avoid cancellations secondary to acute illness and to ensure chronic illnesses, such as asthma, are optimized. However, some patients with congenital anomalies of the upper extremities have co-existing congenital sequelae, which may be part of a syndrome. These patients may require a more extensive workup including cardiac imaging, laboratory blood draws, and acquiring previous anesthesia and intubation records. Below is a table of common syndromes and congenital anomalies associated with congenital anomalies of the upper extremity which may require a more extensive preoperative workup (Table 4.1).

Neurotoxicity and Anesthesia

In December of 2016, the Food and Drug Administration released a warning for inhaled anesthetics, benzodiazepines, etomidate, ketamine, pentobarbital, propofol, and methohexital, stating: "…repeated or lengthy (>3 hr) use of general anesthetic and sedation drugs during

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Table 4.1 Common syndromes and congenital anomalies associated with congenital anomalies of the upper extremity

	Anesthetic concern	Preoperative workup
Amniotic band syndrome	Possible difficult airway if craniofacial involvement; possible cardiac or pulmonary restriction if scoliosis is present; often born preterm or low birth weight	Obtain previous intubation records, possible preoperative IV; cardiac and pulmonary evaluation if scoliosis is present
Apert syndrome	Possible difficult airway due to cervical spine fusion, hydrocephalus, obstructive sleep apnea, choanal atresia, fusion of tracheal rings, and craniofacial abnormalities; congenital heart disease; cognitive delay	Obtain previous intubation records, possible preoperative IV; cardiac evaluation; discussion with child life to provide a supportive environment in the setting of cognitive delay
Arthrogryposis	Possible difficult airway secondary to micrognathia, tracheal stenosis, possible cleft palate, and a rigid neck; scoliosis; structural abnormalities of the kidney; congenital heart disease; difficult IV placement	Obtain previous intubation records, possible preoperative IV; cardiac and pulmonary evaluation if scoliosis is present; history of unusual reactions to medications secondary to altered kidney function
Epidermolysis bullosa	Possible difficult airway secondary to chronic oral scarring, mouth contraction, tongue fixation, limited mouth opening, and laryngeal obstruction; anemia, electrolyte imbalances, renal failure, malnutrition, difficult IV placement, difficult monitor placement, difficulty securing IV and endotracheal tube due to affected skin	Obtain previous intubation records, possible preoperative IV; preoperative laboratory evaluation including complete blood count and electrolytes
Holt-Oram syndrome	Congenital cardiac disease	Cardiac evaluation
Poland syndrome	Congenital chest wall deformity	Chest x-ray
VACTERL	Congenital cardiac disease; tracheoesophageal fistula; renal disease	Cardiac evaluation; anesthetic record from tracheoesophageal fistula or anal atresia repair; renal ultrasound, possible laboratory electrolytes

surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children's brains" [1]. Multiple medical associations including the Society for Pediatric Anesthesia, the American Society of Anesthesiologists, and SmartTots responded to this warning by referring to current studies that there is no direct evidence that anesthesia is unsafe for children [2]. However, some parents prefer delaying elective procedures until their child is older.

The initial concern regarding the exposure of anesthetics to children began in 2001 in an article first describing the cellular impacts of fetal alcohol syndrome. Researchers discovered that ethanol altered cellular synaptogenesis and apoptosis through blockade of NMDA receptors and GABA receptor activation, two common mechanisms of actions by anesthetic medications [3]. Further studies using animal models revealed similar findings to the exposure of ethanol; however, the duration of anesthetic exposure and quantity of anesthetic medications administered was much greater than commonly used in children [4–8]. Retrospective cohort studies began examining the incidence of learning disabilities in children with early exposure to anesthesia and found a single exposure had no impact; however, three or more exposures elevated the risk of having a learning disability [9–12]. More recently, the GAS study, the first randomized control trial evaluating neurotoxicity in children after exposure to anesthesia, randomized infants receiving a hernia repair to either general anesthesia or spinal anesthesia. No difference in cognitive or behavioral function has been identified with follow-up at 2 or 5 years of age [13, 14].

Ongoing research continues with new articles published monthly to further understand the impact of anesthetics on the developing brain. Parents requesting information regarding the risks and benefits of anesthesia for their child should have this conversation with their anesthesiologist either during a preoperative visit or on the day of the procedure. Up-to-date resources for parents including video and written literature may be found at smarttots.org.

Benefits of Pediatric Anesthesia Board Certification

In 2013, pediatric anesthesiology became a board-certified specialty for the first time. In order to obtain board certification, a pediatric anesthesiologist must attend a 1-year fellowship at a board-accredited program and pass a written exam. The fellowship program must meet certification criteria regarding the number of children cared for during each developmental stage, as well as participation in a minimum number of clinically complex cases. Physicians previously practicing pediatric anesthesiology were grandfathered into board certification upon meeting specific patient care criteria and passing a written exam.

In January of 2017, the American College of Surgeons released a verification of surgery program to ensure pediatric surgical patients have access to high-quality care. As part of the program to achieve level 1 or 2 certification, hospitals are required to adhere to specific guidelines regarding the anesthetic care of children. Current recommendations include: a board-certified pediatric anesthesiologist *must* serve all pediatric patients aged 2 years or younger and *should* serve all pediatric patients aged 5 years or younger or with an ASA status of 3 or higher. A pediatric anesthesiologist must also be available to arrive at the bedside within 60 minutes or less, 24 hours a day and 7 days a week, for add-on emergent cases [15]. The expertise acquired through fellowship training of a pediatric anesthesiologist and the volume of pediatric patients cared for by an individual have been shown to improve patient morbidity and mortality, particularly with the youngest patient populations [16–19]. These guidelines were constructed based on the research data of the frequency of cardiac arrests in infants, noting a decreased rate of complications with anesthetic care performed by a fellowship-trained pediatric anesthesiologist, in children aged 2 years old and younger.

Common Reasons for Cancelling Surgical Cases

Preoperative Fasting Guidelines

The American Society of Anesthesiologists updates practice guidelines regularly to assist practitioners and patients in making medical decisions about healthcare. In 2017, the American Society of Anesthesiologists released an updated version of preoperative fasting guidelines and the use of pharmacological agents to reduce the risk of pulmonary aspiration in healthy individuals undergoing elective surgery [20]. Below is a table outlining the current recommendations (Table 4.2). Patients who do not adhere to these guidelines for elective surgery place themselves at an increased and unnecessary risk for pulmonary aspiration. Patients are informed of these guidelines during a pre-anesthesia visit or phone call and are informed their procedure will need to be rescheduled if they do not adhere to the guidelines. In many institutions, patients are still asked to fast after midnight. However, in the pediatric population, clear fluids should be given as close to the recommended fasting time as possible. This can reduce the risk of dehydration, hypoglycemia, and difficulty in placing an IV [21].

Table 4.2 The American Society of Anesthesiologists Preoperative Fasting Guidelines, updated 2017

	Minimum fasting period (hours)
Clear liquids	2
Breast milk	4
Infant formula	6
Nonhuman milk	6
Light meal (toast and clear liquids)	6
Fried food, fatty food, and meat	8

Upper Respiratory Tract Infections

Another common cause of cancellation of elective surgery is the presence of an upper respiratory tract infection. Children on average have 6–8 upper respiratory tract infections per year. When the child is in the midst of an upper respiratory tract infection or has recently recovered from an upper respiratory tract infection, the child is at an increased risk for airway complications, such as laryngospasm, bronchospasm, or hypoxia during anesthetic care. Children who present with a fever, productive cough, decrease in activity level, or decrease in oral intake will likely be rescheduled for 4–6 weeks from the current surgical date to give the child time to recover from their illness. If a child had an upper respiratory tract infection within the past month but currently is asymptomatic, the child may still be at an elevated risk for airway complications [22].

Table 4.3 Risks factors associated with preoperative anxiety

Child related	Parent related	Environment related
Age (1–5 y/o)	High trait and state anxiety	Sensory overload
Poor previous experience with medical procedures/ illness	Parents who use avoidance coping mechanisms	Conflicting messages
Shy/inhibited temperament	Divorced parents	
Lack of developmental maturity/social adaptability	Parents who have undergone multiple medical procedures	
High cognitive levels	Mothers	
Not enrolled in daycare	Parents of children <1 y/o	
	Parents of children with repeated hospital admissions	

Perioperative Anxiety

Children presenting for repair of a congenital anomaly of the upper extremity may be at a higher risk for preoperative anxiety due to the young age at the time of procedure and multiple medical visits leading up to the surgical procedure [23]. Estimates reveal 40–60% of children develop significant fear and anxiety before surgery. Many children and families list the separation from parents and induction of anesthesia as the most stressful time during the surgical experience [24, 25]. Research has identified child, parent, and environmentally related risk factors for children having preoperative anxiety (Table 4.3) [26].

Assisting families with anxiety during the preoperative period involves a variety of strategies.

Behavioral interventions to help alleviate anxiety include a preoperative interview, preoperative preparation programs, and parental presence during induction of anesthesia. Preoperative interviews are most commonly performed by nursing staff in the preoperative area to help familiarize themselves with a patient's condition as well as to provide information to families. Throughout the interview, the family can expect to receive information about what to expect from arrival to the hospital up to the initiation of the surgical procedure. This helps define expectations for the experience the family will undergo on the day of surgery.

Some hospitals offer a pre-admission or presurgical tour designed for children of all ages and families to learn more about the surgical experience [27, 28]. These tours may be done in person or reviewed as a video. Tours can take the family through a standard surgical experience by walking a patient through the preoperative area, operating room, post-anesthesia care unit, and the inpatient unit, to familiarize the family with the flow and process of a typical surgical day.

Child Life

Child life specialists also play a critical role in providing support for families and children during their hospital experience. They are certified healthcare workers who have completed a minimum of a bachelor's degree in child life or child development, an internship of 480–600 hours at an accredited program, and passed a standardized examination [29]. Their role in the healthcare team includes providing an environment that

encourages therapeutic play, aiding in the psychological preparation for coming to the hospital, providing coping strategies to help the patient manage pain, and providing support to parents and siblings of the patient. The child life specialist does this by providing developmentally appropriate information to the patient, encouraging the patient to express emotions and ask questions about the process, and developing a relationship with the patient and their family.

Research has revealed that inclusion of a child life specialist to the healthcare team greatly impacts the child's experience. Studies have found children to have less emotional distress, better overall coping with their hospital stay, a better understanding of procedures, and a more positive adjustment to the hospital in the recovery period. Parents also report higher satisfaction when a child life specialist is involved in the care of their children [29].

Some tactics child life specialist use to help reduce anxiety in the hospital setting include distraction with music or video and have recently included the use of virtual reality devices. Virtual reality devices may serve as the main "anesthetic" for children undergoing short imaging procedures, laboratory blood draws, or other brief medical procedures. These tools can also be used to aid anxiety during separation from a parent or anxiety during induction of general anesthesia [30]. Including a child life specialist to the various stages of surgical care can greatly improve the patient and family experience.

Provider Training

There are also training programs physicians and other healthcare providers can partake in to identify and modify their behavior to better suit the pediatric population. One program is the Provider-Tailored Intervention for Perioperative Stress (P-TIPS). Through this study, the researcher identified behaviors of healthcare providers that helped children cope in the hospital setting, such as distraction, nonprocedural talk, and humor. They also identified provider behaviors that were distressing to children, which included reassurance, apology, empathy, criticism, and allowing the child too much control over the medical procedure. Providers were offered a brief (less than 2 hours) seminar on child development and how to improve patient interactions as well as a video analysis of their live interactions with patients [31]. Through behavioral modification, providers may also positively contribute to reducing perioperative anxiety.

Parental Presence During Induction

Controversy remains regarding the benefits to the child if accompanied by a parent during the induction of anesthesia. Calm children with calm parents benefit the most from parental presence during induction. Parental presence during induction may also negate the need for premedication and avoid difficulty with separating the child from the parent. Parental presence during induction has been correlated with greater parent satisfaction with the anesthetic experience. However, an anxious parent, who criticizes, provides excessive reassurance, or commands can provide greater distress to the child [32–34].

Anxiolytic Medications

Another option to help reduce a child's anxiety is through the administration of medications in the preoperative area before bringing the patient to the operating room or prior to intravenous (IV) placement if preoperative IV access is preferred over mask induction. The most commonly used pharmacological intervention is oral midazolam. Oral midazolam is dosed based on the child's weight, with children receiving 0.5 mg/kg up to a maximum of 20 mg. Most children are less anxious approximately 10–15 minutes after administration, though some children may have a paradoxical reaction, making the child more anxious [35]. A fentanyl lollipop may be an alternative option to oral midazolam. A dose of 15–20 mcg/kg showed a reduction in anxiety and increased sedation for children in the preoperative period. However, children were more likely to have nausea in the recovery room if administered a fentanyl lollipop [36]. Intranasal medications are also an option. Fentanyl (1.5 mcg/kg), dexmedetomidine (3 mcg/kg), and midazolam (0.2 mg/kg) may all be administered intrana-

sally. This may be a preferred method for a child who is unwilling or unable to tolerate oral medications [37–39]. Another alternative is administration of intramuscular ketamine. Dosing for this medication is 2–4 mg/kg, producing results in approximately 3–5 minutes, upon which time the child should be transported to the operating room [40].

Each of the strategies discussed above can greatly improve the surgical experience for a family. However, these strategies take time, patience, and skilled staff to implement. Scheduling an appropriate amount of time for a child during the preoperative period allows the family to better adapt to the hospital setting and reduces delays between operative cases.

Intraoperative Care

There are a number of hurdles the anesthesiologist must overcome in the care of a child with congenital anomalies of the upper extremity. Many of these challenges are associated with the age of the child undergoing the procedure, the duration of the procedure, and the degree of discomfort associated with the procedure.

Intravenous Access

Many children brought to the operating room will undergo a general anesthetic with mask induction and placement of an intravenous catheter following induction. Given the nature of the procedure where one or two extremities will be prepped into the surgical field, the number of intravenous access sites is diminished. In addition, some children with congenital anomalies of the upper extremity may have previously had an intravenous catheter for care while in the neonatal intensive care unit or for operative repair for another congenital anomaly, further limiting viable access options. Some tools such as vein visualization technology and ultrasound and having the patient continue clear liquids up to 2 hours prior to the procedure to maintain hydration may aid the anesthesiologist in intravenous access placement [41, 42]. However, a prolonged intravenous placement time may be inevitable.

Glucose Management

Children 6 months old and younger are at an increased risk for hypoglycemia during the intraoperative period. Due to the immaturity of their liver at this stage in their life, these children are unable to produce glucose stores through gluconeogenesis, placing them at risk for hypoglycemia if their glucose stores are not replenished intraoperatively [43]. Glucose management can be easily obtained by monitoring blood glucose levels on an hourly basis and supplementing the child with dextrose-containing fluids as deemed necessary.

Fluid Management

Fluid management should also be closely watched during a prolonged procedure. Maintenance fluids may be administered following the 4-2-1 rule (4 mL/kg for the first 10 kg of the child's weight, 2 mL/kg for the next 10 kg of the child's weight, and 1 mL/kg for each kg above 20 kg) [44, 45]. A balanced solution such as lactated Ringer's solution or Plasma-Lyte will help maintain homeostasis of electrolytes throughout longer procedures [46]. Additional boluses in increments of 20 mL/kg may be administered to account for preoperative fasting, blood loss, and evaporation in the surgical field if the patient is hypotensive [47].

Thermoregulation

There are four mechanisms for heat loss in the operating room environment: (1) conduction, (2) evaporation, (3) radiation, and (4) convection. Using tools to help reduce these forms of heat loss is critical in children, who have a larger body surface area than adults. Some tactics include

forced air warmers, increasing the ambient room temperature, administering heated fluids, using radiant heat lamps, and covering the head with a warm blanket or hat [48, 49].

Thermoregulation is particularly important from a physiologic standpoint during the intraoperative period. Studies based from the trauma literature reveal a reduction in coagulopathies when patients are kept warm, allowing coagulation factors to work optimally in their normal temperature range [50]. In addition, studies have revealed that patients who are kept normothermic have a reduction in post-surgical infection and improved wound healing [51]. Metabolism can be negatively impacted by hypothermia, resulting in prolonged pharmacological half-lives [49].

Children 6 months old and younger are at an increased risk for hypothermia during the intraoperative period. This patient population is at highest risk for hypothermia during the intraoperative period due to the lack of subcutaneous tissue, disproportionately large head, and a lack of ability to shiver [48].

Tourniquet

Tourniquet application to improve visualization of the operative field and reduce blood loss may be used in children [52]. As with adult patients, placing padding beneath the tourniquet can help minimize damage to the skin [53]. Although the main goal of the tourniquet is to optimize the surgical field while minimizing the risk for nerve damage secondary to the compression from the tourniquet, this can be a challenging balance in children. Literature regarding the tourniquet pressure to be used for pediatric patients varies, with recommendations from 75 mmHg above the awake systolic pressure to twice the systolic pressure [54]. Other studies recommended inflating the tourniquet in 25 mmHg increments until arterial flow has stopped [52]. The duration of tourniquet time before increased risk of nerve damage is also questionable in children, with recommendations to limit tourniquet time to less than 2 hours [52, 54].

Maintenance of Anesthesia

Most anesthetics for repair of congenital upper extremity anomalies include the use of general anesthesia as the mainstay anesthetic. General anesthesia may be successfully achieved through a variety of modalities, whether based on inhaled anesthetics, total intravenous anesthetics, or a balanced combination of the two. However, some reports include using regional anesthesia as an adjunct or the sole anesthetic for upper extremity procedures, to reduce the systemic use of medications for a localized procedure [55]. No sole method of anesthesia is proven superior to another, though one combination may be superior over another based upon a risk-benefit analysis for a particular patient.

Regional Anesthesia

The use of regional anesthesia as an adjunct to general anesthesia or as a sole anesthetic is being incorporated into more anesthetic plans as a tool to reduce the administration of opioid pain medications, reduce the intensity of general anesthesia during a surgical procedure, and allow more children to recover at home as opposed to in the hospital setting. In addition, peripheral nerve blocks provide a sympathectomy to the upper extremity, increasing the blood flow and temperature to the skin at the wound site to aid in healing. Peripheral nerve blocks also provide muscle relaxation to the surgical site, improving manipulation of the extremity for surgical repair [56, 57].

The Pediatric Regional Anesthesia Network, a collaboration of 21 institutions founded in 2007, has further delved into the safety of regional anesthesia in children by gathering data of the practice, risks, and incidence of complications in pediatric regional anesthesia [58]. Numerous observational studies of upper extremity peripheral nerve blocks have been published in Europe, the United States, and other countries around the world [59]. The majority of upper extremity nerve blocks are placed after a child is under general anesthesia, a practice that is as safe as plac-

ing an upper extremity block in an awake adult [60]. However, some institutions report success with the use of sedation or monitored anesthesia care for the placement of blocks [55].

Field Blocks

The simplest use of regional anesthesia is a field block typically performed by the surgeon after the child is placed under general anesthesia. This is a quickly performed block that provides localized pain relief to a particular surgical site. However, the majority of these blocks last between 2 and 6 hours, depending upon the local anesthetic used, which may or may not provide adequate pain control for the patient in the postoperative period. In more painful or longer duration surgical procedures, a peripheral nerve block along the brachial plexus may be more beneficial for the patient. It is important to consider the total dose of local anesthetic that can be used based on the child's weight in each case (Table 4.4).

Nerve Blocks

A variety of locations along the brachial plexus can provide regional anesthesia to any location on the upper extremity. The location of block placement depends upon the surgical location, the intention of a single-shot versus a catheter placement, and the safety of the location to be blocked. Single-shot nerve blocks have a duration of analgesia for approximately 18–24 hours, while catheter nerve blocks can provide analgesia for days.

Historically, axillary blocks were the most commonly performed upper extremity regional anesthetic due to the ease of placement prior to ultrasound-guided blocks. Axillary blocks provide analgesia to the elbow, forearm, and hand through anesthetizing the radial, median, and ulnar nerves. The provider must be mindful to also block the musculocutaneous nerve, outside of the neurovascular sheath, if surgical repair includes the lateral forearm [56, 57, 61]. The use of ultrasound guided needle placement aids in ensuring the distribution of local anesthetic around the entire axillary sheath, reduces the risk of hematoma secondary to injury of the axillary artery, reduces the risk of intravascular injection, and reduces the risk of nerve injury. Placement of a continuous catheter in this location can be fraught with difficulties secondary to catheter migration due to the mobility of the arm at this location and concerns for sterility secondary to the warm, dark environment of the axilla [56].

With the integration of ultrasound-guided peripheral nerve blocks in children, additional sites of the brachial plexus have been utilized to provide more precise analgesia at the surgical site. Interscalene blocks provide analgesia to the shoulder and proximal humerus. Common consequences associated with this block include hemidiaphragmatic paralysis, Horner's syndrome, and recurrent laryngeal nerve block, which should be described to the patient and family prior to the procedure. More serious complications include vertebral artery injection, intrathecal injection, and pneumothorax [56, 57, 60, 62]. Visualization of the needle at all times during placement of the block is critical.

Supraclavicular blocks provide analgesia from the upper arm past the elbow and are often a very successful block due to the bundling of the trunks and divisions of the brachial plexus at this location. This block has been used successfully as the sole anesthetic for closed reduction of arm fractures at one institution [63]. Concerns with this block include an elevated risk of pneumothorax due to the close proximity of the needle placement with the first rib, just medial to the lungs [56, 57, 63, 64].

Infraclavicular nerve blocks have also been successfully described in children. This block also provides analgesia to the upper arm and elbow, similar to the supraclavicular nerve block, though the block is placed at the level of the cords of the brachial plexus. This approach provides

Table 4.4 Maximum local anesthetic dose, field blocks

	Without epinephrine (mg/kg)	With epinephrine (1:200,000) (mg/kg)	Duration of action (with epinephrine)
Lidocaine	4–5	7	0.5–2 hours (2–4 hours)
Bupivacaine	2.5	3	2–4 hours (3–6 hours)
Ropivacaine	3	4	2–4 hours (3–6 hours)

Table 4.5 Peripheral nerve blocks dosage recommendations for single-shot and continuous infusions

	Coverage of block	Single-shot block (mL/kg 0.2% ropivacaine)	Continuous infusion (0.2% ropivacaine mL/hour)
Interscalene	Shoulder, proximal humerus	0.2–0.4	6–10
Supraclavicular	Upper arm, elbow	0.2–0.3	4–10
Infraclavicular	Upper arm, elbow	0.2–0.3	4–10
Axillary	Elbow, forearm, hand	0.1–0.2	6–8

superior sensory and motor blockade to the axillary block, requires one injection location versus two or more with the axillary block, and also allows regional anesthesia to be performed on children whom arm abduction is not possible [65]. In addition, the risk of respiratory side effects, as seen with interscalene blocks, are not present. As with the supraclavicular block, pneumothorax is a potential complication with placement of the needle near the lungs, which is greatly mitigated with the use of ultrasound guidance [56, 57, 65, 66].

Single-Shot Versus Catheter Peripheral Nerve Blocks

The decision to perform a single-shot nerve block versus leave a continuous catheter depends upon the anticipated recovery period. A continuous nerve catheter may be more beneficial to the patient for procedures where blood vessel dilation from the sympathectomy of the nerve block is desired, where surgical pain is intense or predicted to endure greater than 12–16 hours, or where significant bony work accompanies soft tissue work. Catheters placed in the interscalene, supraclavicular, or infraclavicular location may have a reduced incidence of migration and risk of infection than those placed in the axillary location. The incidence of infection occurring with peripheral nerve catheters greatly increases after 5 days, with recommendations to remove catheters on postoperative day 5. Children do not need to remain hospitalized with a nerve catheter in place, which may allow earlier patient discharge. Patient's discharged home with a nerve catheter should be contacted at least every 24 hours to ensure the nerve catheter is functioning well, answer any questions, and provide information regarding the next steps in management [67, 68]. Dosing for single-shot and continuous catheter infusions is listed in Table 4.5**.**

Local Anesthetic Toxicity

As with any medication used in medical care, there are risks associated with the use of local anesthetics, particularly regarding the administration of too much local anesthetic for a given child's weight. Certain local anesthetics, such as ropivacaine, have a lower cardiac toxicity than bupivacaine, lowering the risk of complications from local anesthetic systemic toxicity [69]. However, ropivacaine is currently more expensive than bupivacaine, which may be prohibitive in some anesthetic practices. Table 4.4 reveals the maximum local anesthetic administration. Keep in mind that the use of multiple local anesthetics is additive toward the maximum local anesthetic administration.

All personnel performing peripheral nerve blocks should be familiar with the treatment of local anesthetic systemic toxicity. Local anesthetics mechanism of action is to block sodium channels, which include central nervous system and cardiovascular sodium channels when systemic levels rise to become toxic. Symptoms such as seizures, tachyarrhythmias, and cardiovascular collapse may be masked under general anesthesia [70]. If local anesthetic systemic toxicity is suspected, following the guidelines from the Society of Pediatric Anesthesia checklist for crisis events will aid with management. Initial management includes stopping the seizure, securing the airway if not already secured, administration of lipid emulsion therapy as both a bolus (1.5 mL/kg) and continuous infusion (0.25 mL/kg/min), cardiopulmonary resuscitation if indicated, and small doses of epinephrine (1 mcg/kg) [71].

Postoperative Management

Assessment of Postoperative Pain

Assessing a child's pain may be difficult for the clinician as well as the parent depending upon the child's developmental stage. Numerous age-appropriate scales have been validated to assess a child's pain. One assessment tool that may be used for children less than 1 year of age is the Neonatal Infant Pain Scale (NIPS) (Table 4.6) [72]. For children older than 1 year but who cannot communicate their pain may use the Face, Legs, Activity, Cry, and Consolability Revised Scale (FLACC-R) (Table 4.7) [73]. Children 4–8 years old may be able to use the Faces Pain Scale Revised to communicate their level of pain (Fig. 4.1). Lastly, children 8 years old or older may use the Numeric Rating Scale (Fig. 4.2) [74]. These scales are designed to be used by clinicians, nurses, and families to facilitate pain management. Other scales are also available to assess a pediatric patient's pain and may be better suited for an individual patient.

Table 4.6 Neonatal Infant Pain Scale (NIPS)

	0	1	2
Facial expression	Relaxed muscles	Grimace	
Cry	No cry	Whimper	Vigorous
Breathing pattern	Relaxed	Change in breathing	
Arms	Relaxed	Restrained	
Legs	Relaxed	Restrained	
State of arousal	Asleep/ awake	Fussy	

Adapted from [72]
Score 0–2 = no pain, 3–4 = moderate pain, >4 = severe pain

Codeine and Tramadol

Beginning in 2011, the World Health Organization, the US Food and Drug Administration, and the European Medicines Agency removed codeine and tramadol from its list of essential medications for children [75]. The use of codeine in the postoperative period was linked to death and respiratory depression among children less than 12 years of age due to the variable, genetic-based metabolism of codeine to morphine by the CYP2D6 enzyme. Clinicians are encouraged to use alternative, pure opioids such as morphine, oxycodone, or hydromorphone to reduce the risk of drug accumulation due to variation in metabolism.

Multimodal Analgesia

Not all postoperative pain requires treatment with opioid medications. If the child rates their pain toward the lower end of the pain spectrum, tools such as ice, heat, or distraction may be a reasonable place to start. Not all surgical procedures will be amendable to heat or ice application and should only be performed when discussed with the surgeon. However, distractions through activity, reading a book, watching a movie, or playing a game are all possible ways to help a child cope with pain.

Table 4.7 Face, Legs, Activity, Cry, and Consolability Revised Scale

	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, uninterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position, relaxed	Uneasy, restless, tense	Kicking, legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting, back and forth, tense	Arched, rigid, or jerking
Cry	No cry	Moans or whimpers, occasional complaint	Crying steadily, screams, sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or being talked to, distractible	Difficult to console or comfort

Reprinted with permission from Malviya et al. [73]
Score between 0 (no pain) and 10 (severe pain)

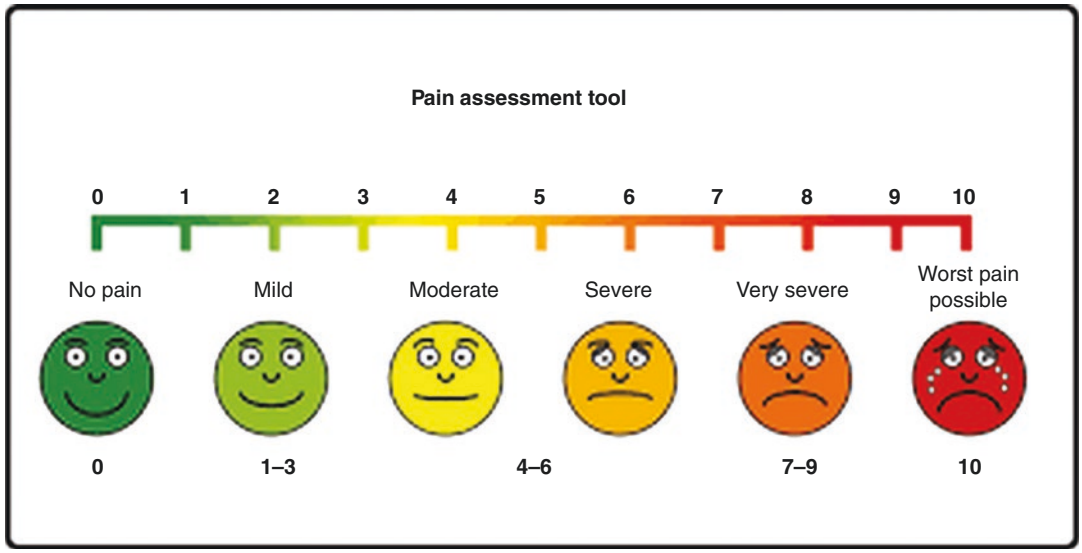

Fig. 4.1 Faces Pain Scale

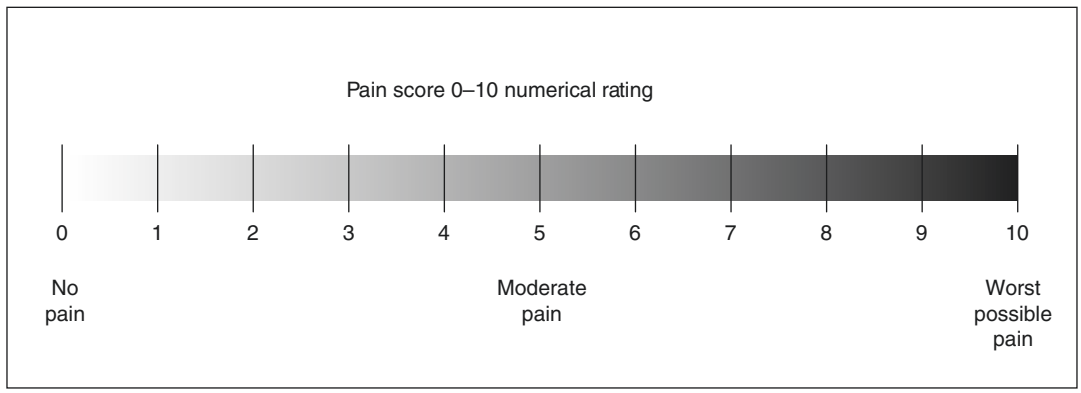

Fig. 4.2 Numeric rating scale

For children with moderate to severe pain, medical interventions are generally recommended. By using multimodal analgesia in the perioperative period, many children may be discharged from the hospital without the need for opioid pain medications [76, 77]. Some alternatives to opioids which may be used alone, in combination with one another, or in combination with opioids include non-steroidal anti-inflammatory drugs, acetaminophen, local anesthetics, N-methyl-D-aspartate antagonists (such as ketamine), α-2 adrenergic agonists (such as clonidine or dexmedetomidine), and voltage-gated calcium channel α2δ proteins (such as gabapentin or pregabalin). By inhibiting pain signals from a variety of sources with the use of multimodal analgesia, the child may experience fewer or no side effects from opioids and may reduce the duration and quantity of opioid medications necessary in the recovery period. As with any medication, side effects such as sedation, dysphoria, or an allergic reaction may occur, with the most common reactions and recommended dosing listed in Table 4.8.

Table 4.8 Multimodal analgesia medications for the perioperative period

	Type of drug	Dosing	Precautions
Acetaminophen	COX 3 inhibitor, activation descending serotonergic pathway	10–15 mg/kg PO, IV, or PR, every 6 hours	Liver failure
Ibuprofen	NSAID	10–15 mg/kg PO, every 6 hours	Renal failure, gastrointestinal bleed
Ketorolac	NSAID	0.5 mg/kg IV, every 6 hours	Renal failure, gastrointestinal bleed
Meloxicam	NSAID	0.125 mg/kg, once per day	Renal failure, gastrointestinal bleed
Dexmedetomidine	α-2 adrenergic agonists	0.5–1 mcg/kg IV, intraoperatively	Bradycardia, hypotension, sedation
Clonidine	α-2 adrenergic agonists	4–5 mcg/kg PO, 1–2 mcg/kg IV intraoperatively	Bradycardia, hypotension, sedation
Ketamine	NMDA antagonist	0.5–1 mg/kg IV, intraoperatively	Dysphoria
Gabapentin	Voltage-gated calcium channel α2δ proteins	5 mg/kg PO, every 8 hours	Sedation, headaches
Pregabalin	Voltage-gated calcium channel α2δ proteins	2–3 mg/kg PO, every 8–12 hours	Vision problems, moodiness

Conclusion

Caring for a child with congenital anomalies of the upper extremity throughout the perioperative period involves the collaboration of numerous healthcare providers for the child and family. Tactics to facilitate care throughout all phases of the perioperative period can provide an environment where the child can safely undergo a procedure and return home in an expedient manner. Pediatric anesthesiologists provide expertise in helping safely guide a family through the perioperative period.

References

1. Food and Drug Administration. FDA drug safety communication: FDA review results in new warnings about using general anesthetics and sedation drugs in young children and pregnant women. 2016 Dec. fda.gov/media/101937/download.
2. SmartTots. Consensus statement on the use of anesthetic and sedative drugs in infants and toddlers. 2015 Oct. pedsanesthesia.org/wp-content/uploads/2017/11/ConsensusStatement.pdf.
3. Olney JW, Wozniak DF, Jevtovic-Todorovic V, Ikonomidou C. Glutamate signaling and the fetal alcohol syndrome. Ment Retard Dev Disabil Res Rev. 2001;7(4):267–75.
4. Brambrink AM, Evers AS, Avidan MS, Farber NB, Smith DJ, Zhang X, et al. Isoflurane-induced neuroapoptosis in the neonatal rhesus macaque brain. Anesthesiology. 2010;112(4):834–41.
5. Zou X, Patterson TA, Divine RL, Sadovova N, Zhang X, Hanig JP, et al. Prolonged exposure to ketamine increases neurodegeneration in the developing monkey brain. Int J Dev Neurosci. 2009;27(7):727–31.
6. Slikker W Jr, Zou X, Hotchkiss CE, Divine RL, Sadovova N, Twaddle NC, et al. Ketamine-induced neuronal cell death in the perinatal rhesus monkey. Toxicol Sci. 2007;98(1):145–58.
7. Ikonomidou C, Bosch F, Miksa M, Bittigau P, Vöckler J, Dikranian K, et al. Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. Science. 1999;283(5398):70–4.
8. Jevtovic-Todorovic V, Hartman RE, Izumi Y, Benshoff ND, Dikranian K, Zorumski CF, et al. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. J Neurosci. 2003;23(3):876–82.
9. Wilder RT, Flick RP, Sprung J, Katusic SK, Barbaresi WJ, Mickelson C, et al. Early exposure to anesthesia and learning disabilities in a population-based birth cohort. Anesthesiology. 2009;110(4):796–804.
10. Flick RP, Katusic SK, Colligan RC, Wilder RT, Voigt RG, Olson MD, et al. Cognitive and behavioral outcomes after early exposure to anesthesia and surgery. Pediatrics. 2011. peds-2011.
11. Ing C, DiMaggio C, Whitehouse A, Hegarty MK, Brady J, von Ungern-Sternberg BS, et al. Long-term differences in language and cognitive function after childhood exposure to anesthesia. Pediatrics. 2012. peds-2011.

12. Bartels M, Althoff RR, Boomsma DI. Anesthesia and cognitive performance in children: no evidence for a causal relationship. Twin Res Hum Genet. 2009;12(3):246–53.
13. Davidson AJ, Disma N, de Graaff JC, Withington DE, Dorris L, Bell G, et al. Neurodevelopmental outcome at 2 years of age after general anaesthesia or awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. Lancet. 2016;387(10015):239–50.
14. McCann ME, de Graaff JC, Dorris L, Disma N, Withington D, Bell G, et al. Neurodevelopmental outcome at 5 years of age after general anaesthesia or awake-regional anaesthesia in infancy (GAS): an international, multicentre, randomised controlled equivalence trial. Lancet. 2019;393(10172):664–77.
15. American College of Surgeons. Optimal resources for children's surgical care v.1. 2015. facs.org/-/media/files/quality-programs/csv/acs-cav_standartdmanual.ashx.
16. Auroy Y, Ecoffey C, Messiah A, Rouvier B. Relationship between complications of pediatric anesthesia and volume of pediatric anesthetics [letter]. Anesth Analg. 1997;84:234–5.
17. Campling EA, Devlin HB, Lunn JN. The report of the national confidential enquiry into perioperative deaths. London: NCEPOD; 1989.
18. Keenan RL, Shapiro JH, Dawson K. Frequency of anesthetic cardiac arrest in infants: effect of pediatric anesthesiologists. J Clin Anesth. 1991;3:433–6.
19. Crone RK. Frequency of anesthetic cardiac arrest in infants: effect of pediatric anesthesiologists [editorial]. J Clin Anesth. 1991;3:431–2.
20. American Society of Anesthesiologists Practice Parameter. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application of healthy patients undergoing elective procedures: an updated report by the American Society of Anesthesiologists Task Force on preoperative fasting and the use of pharmacological agents to reduce the risk of pulmonary aspiration. Anesthesiology. 2017;126(3):376–93.
21. Dennhardt N, Beck C, Huber D, Sander B, Boehne M, Boethig D, et al. Optimized preoperative fasting times decrease ketone body concentration and stabilize mean arterial blood pressure during induction of anesthesia in children younger than 36 months: a prospective observational cohort study. Paediatr Anaesth. 2016;26(8):838–43.
22. Tait AR, Malviya S. Anesthesia for the child with an upper respiratory tract infection: still a dilemma? Anesth Analg. 2005;100(1):59–65.
23. Watson S. The principles of management of congenital anomalies of the upper limb. Arch Dis Child. 2000;83(1):10–7.
24. Banchs R, Lerman J. Preoperative anxiety management, emergence delirium, and postoperative behavior. Anesthesiol Clin. 2014;32(1):1–23.
25. Kain ZN, Mayes LC, Caldwell-Andrews AA, Karas DE, McClain BC. Preoperative anxiety, postoperative pain, and behavioral recovery in young children undergoing surgery. Pediatrics. 2006;118(2):651–8.
26. Kain ZN, Mayes LC, O'Connor TZ, Cicchetti DV. Preoperative anxiety in children: predictors and outcomes. Arch Pediatr Adolesc Med. 1996;150(12):1238–45.
27. O'Byrne K, Peterson L, Saldana L. Survey of pediatric hospitals' preparation programs: evidence of the impact of health psychology research. Health Psychol. 1997;16:147–54.
28. Saile H, Burgmeier R, Schmidt LR. A meta-analysis of studies on psychological preparation of children facing medical procedures. Psychol Health. 1988;2:107–32.
29. American Academy of Pediatrics. Child life services. Pediatrics. 2014;133(5):e1471–8.
30. Eijlers R, Utens EMWJ, Staals LM, de Nijs PFA, Berhmans JM, Wijnen RMH, et al. Systematic review and meta-analysis of virtual reality in pediatrics: effects on pain and anxiety. Anesth Analg. 2019;129(5):1344–53.
31. Martin SR, MacLaren Chorney J, Tan ET, Fortier MA, Blount RL, Wald SH, et al. Changing healthcare providers' behavior during pediatric inductions with an empirically-based intervention. Anesthesiology. 2011;115(1):18–27.
32. Kain Z, Mayes L, Wang S, Caramico LA, Hofstadter MB. Parental presence during induction of anesthesia vs. sedative premedication: which intervention is more effective? Anesthesiology. 1998;89(5):1147–56.
33. Gauderer MW, Lorig JL, Eastwood DW. Is there a place for parents in the operating room? J Pediatr Surg. 1989;24(7):705–6.
34. Messeri A, Caprilli S, Busoni P. Anaesthesia induction in children: a psychological evaluation of the efficiency of parents' presence. Paediatr Anaesth. 2004;14(7):551–6.
35. Kain ZN, Mayes LC, Bell C, Weisman S, Hofstadter MB, Rimar S. Premedication in the United States: a status report. Anesth Anal. 1997;84:427–32.
36. Feld LH, Champeau MW, van Steennis CA, Scott JC. Preanesthetic medication in children: a comparison of oral transmucosal fentanyl citrate versus placebo. Anesthesiology. 1989;71(3):374–7.
37. Fuks AB, Kaufman E, Ram D, Hovav S, Shapira J. Assessment of two doses of intranasal midazolam for sedation of young pediatric dental patients. Pediatr Dent. 1994;16(4):301–5.
38. Behrle N, Birisci E, Dalabih A. Intranasal dexmedetomidine as a sedative for pediatric procedural sedation. J Pediatric Pharmacol Ther. 2017;22(1):4–8.
39. Chatrath V, Kumar R, Thakur M. Intranasal fentanyl, midazolam, and dexmedetomidine as premedication in pediatric patients. Anesth Essays Res. 2018;12(3):748–53.

40. Graudins A, Meek R, Egerton-Warburton D, Oakley E, Seith R. The PICHFORK (Pain in Children Fentanyl or Ketamine) Trial: a randomized controlled trial comparing intranasal ketamine and fentanyl for relief of moderate to severe pain in children with limb injuries. Ann Emerg Med. 2015;65(3):248–54.
41. Hodge D, Fleisher G. Pediatric catheter flow rates. Am J Emerg Med. 1985;3(5):403.
42. Maxwell LG, Yaster M. Perioperative management issues in pediatric patients. Anaesthesiol Clin North Am. 2000;18:601–32.
43. Deshpande S, Platt MW. The investigation and management of neonatal hypoglycemia. Semin Fetal Neonatal Med. 2005;10(4):351–61.
44. Feld LG, Neuspiel DR, Foster BA, Leu MG, Garber MD, Austin K, et al. Clinical practice guideline: maintenance intravenous fluids in children. Pediatrics. 2018;142(6):e20183083.
45. Holliday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. Pediatrics. 1957;19(5):823–32.
46. Rizoli S. PlasmaLyte. J Trauma. 2011;70(5 Suppl):S17–8.
47. Meyers RS. Pediatric fluid and electrolyte therapy. J Pediatric Pharmacol Ther. 2009;14(4):204–11.
48. Gregory GA, Brett C. Neonatology for anesthesiologists. In: Davis PJ, Cladis FP, Motoyama EK, editors. Smith's anesthesia for infants and children. Philadelphia: Elsevier; 2011. p. 512–53.
49. Diaz M, Becker D. Thermoregulation: physiological and clinical consideration during sedation and general anesthesia. Anesth Prog. 2010;51(1):25–33.
50. Polerman KH. Hypothermia and coagulation. Crit Care. 2012;16(Suppl 2):A20.
51. Bull A, Wilson J, Worth LJ, Stuart RL, Gillespie E, Waxman B, et al. A bundle of care to reduce colorectal surgical infections: an Australian experience. J Hosp Infect. 2011;78(4):297–301.
52. Tredwell SJ, Wilmink M, Inkpen K, McEwen JA. Pediatric tourniquets: analysis of cuff and limb interface, current practice, and guidelines for use. J Pediatr Orthop. 2001;21:671–6.
53. Kutty S, McElwain JP. Padding under tourniquets in tourniquet controlled surgery: Bruner's ten rules revisited. Injury. 2002;33:75.
54. Sharma JP, Salhorta R. Tourniquets in orthopedic surgery. Indian J Orthop. 2012;46(4):377–83.
55. Amiri HR, Espandar R. Upper extremity surgery in younger children under ultrasound-guided supraclavicular brachial plexus block: a case series. J Child Orthop. 2010;4:315–9.
56. Shah RD, Suresh S. Applications of regional anaesthesia in paediatrics. Br J Anaesth. 2013;111(51):i114–24.
57. Bosenberg A. Upper and lower limb blocks in children. Updates Anaesth. 2015;30(1):99–111.
58. Polaner DM, Taenzer AH, Walker BJ, Bosenberg A, Krane EJ, Suresh S, et al. Pediatric regional anesthesia network (PRAN): a multi-institutional study of the use and incidence of complications of pediatric regional anesthesia. Anesth Analg. 2012;115(6):1353–64.
59. Ecoffey C. Safety in pediatric regional anesthesia. Pediatr Anesth. 2012;22:25–30.
60. Taenzer A, Walker BJ, Bosenberg AT, Krane EJ, Martin LD, Polaner DM, et al. Interscalene brachial plexus blocks under general anesthesia in children: is this safe practice? Reg Anesth Pain Med. 2014;39(6):502–5.
61. Fisher WJ, Bingham RM, Hall R. Axillary brachial plexus block for perioperative analgesia in 250 children. Pediatr Anesth. 1999;9(5):435–8.
62. Van Geffen JG, Tielens L, Gielen M. Ultrasound-guided interscalene brachial plexus block in a child with femur fibula ulna syndrome. Pediatr Anesth. 2006;16(3):330–2.
63. Pande R, Pande M, Bhadani U, Pandey CK, Bhattacharya A. Supraclavicular brachial plexus block as a sole anaesthetic technique in children: an analysis of 200 cases. Anaesthesia. 2000;55(8):798–802.
64. De Jose MB, Banus E, Egea MN, Serrano S, Perello M, Mabrok M. Ultrasound-guided supraclavicular versus infraclavicular brachial plexus blocks in children. Pediatr Anesth. 2008;18(9):838–44.
65. Dadure C, Raux O, Troncin R, Rochette A, Capdevia X. Continuous infraclavicular brachial plexus block for acute pain management in children. Anesth Analg. 2003;97(3):691–3.
66. Marhofer P, Sitzwohl C, Greher M, Kapral S. Ultrasound guidance for infraclavicular brachial plexus anaesthesia in children. Anaesthesia. 2004;59(7):642–6.
67. Walker BJ, Long JB, De Oliveira GS, Szmuk P, Setiawan C, Polaner DM, Suresh S. Peripheral nerve catheters in children: an analysis of safety and practice patterns from the pediatric regional anesthesia network (PRAN). Br J Anaesth. 2015;115(3):457–62.
68. Gurnaney H, Kraemer FW, Maxwell L, Muhly WT, Schleelein L, Ganesh A. Ambulatory continuous peripheral nerve blocks in children and adolescents: a longitudinal 8-year single center study. Anesth Analg. 2014;118(3):621–7.
69. Graf BM, Abraham I, Eberbach N, Kunst G, Stowe DF, et al. Differences in cardiotoxicity of bupivacaine and ropivacaine are the result of physiochemical and stereoselective properties. Anesthesiology. 2002;96(6):1427–34.
70. El-Boghdadly K, Pawa A, Chin KJ. Local anesthetic systemic toxicity: current perspectives. Local Reg Anesth. 2018;11:35–44.
71. Society of Pediatric Anesthesia. Pedi crisis critical events checklist. Revision 2020 Jan. http://www.pedsanesthesia.org/wpcontent/uploads/2018/03/SPACriticalEventsChecklists.pdf.
72. Lawrence J, Alcock D, McGrath P, Kay J, MacMurray SB, Dulberg C. The development of a tool to assess neonatal pain. Neonatal Netw. 1993;2(6):59–66.

73. Malviya S, Voepel-Lewis T, Burke C, Merkel S, Tait AR. The revised FLACC observational pain tool: improved reliability and validity for pain assessment in children with cognitive impairment. Pediatr Anesth. 2006;16(3):258–65.
74. Wong C, Lau E, Campbell F. Pain management in children: part 1 – assessment tools and a brief review of nonpharmacological and pharmacological options. Can Pharm J (Ott). 2012;145(5):222–5.
75. Tobias JD, Green TP, Cote CJ. Codeine: time to say "no". Pediatrics. 2016;138(4):e20162396.
76. Yaster M. Multimodal analgesia in children. Eur J Anaesthesiol. 2010;27(10):851–7.
77. Suresh S, Birmingham PK, Kozlowski RJ. Pediatric pain management. Anesthesiol Clin. 2012;30(1):101–17.

5 Physical Medicine and Rehabilitation Management of Children with Congenital Anomalies of the Upper Extremity

Scott E. Benjamin

Physical medicine and rehabilitation, otherwise known as physiatry, is the medical specialty most specifically interested in increasing functional independence. The goal of treatment is to assist the patient with adapting to and overcoming physical or cognitive impairments that limit function, to the extent actually possible. The physiatrist as a member of a multidisciplinary team is a key provider working toward these goals.

Physiatry works with physical therapists, occupational therapists, prosthetist/orthotists, surgeons (orthopedic, plastic, neuro), families, case management, social work, psychology, speech and language pathologists, assistive technology, etc. to get people as functionally independent as possible. In the context of upper limb deformities, the physiatrist most closely works with the surgeons involved in any reconstruction, the occupational therapists, and the prosthetists and, of course, the children and families. Intervention needs appropriate timing of medical, rehabilitation, and educational services.

Habilitation of the child with upper limb deformity must take into account multiple factors, such as the type of deformity—longitudinal, transverse, proximal, or distal. Consideration is taken of systemic or other deformities in certain syndromes. The team must consider the patients' goals, the families' goals and preconceptions, the practicality of the particular intervention, and the potential of the individual patient.

In the realm of prosthetics, as microchip computer technology and biomedical engineering continue to develop at a significant pace, the possibility for more advanced successful rehabilitation interventions with sophisticated equipment continues to grow. However, this must be weighed against the cost and insurance coverage for such technology. While there might be more technically advanced equipment available, the medical provider must question whether this truly provides a higher level of independence and ability, and whether the patient's insurance policy will cover this more expensive option. In the field of orthotics and prosthetics, insurance authorization for durable medical equipment is becoming more and more difficult to obtain. Healthcare professionals need to be able to document medical necessity of their care, and the specifics of this documentation are very important. On multiple occasions, this writer has had to re-document and argue for what would seem to be an obvious medical need.

Also, there needs to be an awareness of the fact that just because there is an available intervention, that intervention may not lead to an actual improvement in function and may simply be rejected by the patient or family.

In the case of the pediatric patient in particular, parental "buy in" to the treatment plan is

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imperative. Significant education, counseling, and emotional support may be needed. Dealing with a child with a chronic medical condition, physical impairment, or deformity can cause significant stress in the family, feelings of self-blame, shame, and helplessness for the parents and shame, frustration, and embarrassment for the child.

Rehabilitation psychology, child psychology, and parental counseling are all important concepts to remember when dealing with the upper limb deformity population.

Thus, many players and considerations are all important in the management of the upper limb-deficient patient. Depending on the specific institution, the physiatrist may be the team leader responsible for coordinating care and educating the patient and family. Other providers, including therapists, surgeons, teachers, counselors, and prosthetists all work together to provide care.

Exam of the Upper Limb-Deficient Child

Standard pediatric history is obtained, including pregnancy, birth, and developmental history. Cause for limb deficiency; surgical history; concomitant medical history, e.g., vision, hearing, and learning disabilities and cognitive abilities; hobbies; and interests are all important considerations. Social history is obtained in regard to family support, living situation, family expectations, preconceptions, etc. One should discuss the family's reaction to acceptance of limb loss, and try to get a sense of the child's innate ability to adapt and accept.

General and focused exam of the child with limb deficiency is performed, noting length, passive range of motion, active movement and strength, sensation, proprioception, scarring, and tissue redundancy. Functional use of the limb in its current condition should be carefully assessed. Coordination, motor planning, tolerance to examination, ability to follow directions, and behavior are all-important aspects, as well.

Common Upper Limb Deficiencies and Management Considerations

Upper limb deficiency incidence is about 4.1–16 per 10,000, according to the National Center for Health Statistics. Most of the time these are considered spontaneous events without a hereditary component, and the cause is usually unknown. However, first-trimester drug exposures, amniotic band, and some syndromes are known associations. There are five syndromes associated with upper limb deficiencies, particularly absence of the radius. These include TAR syndrome (thrombocytopenia with absence of the radius), Fanconi's syndrome (anemia and leucopenia with absence of radius), Holt-Oram syndrome (atrial septal defects and/tetralogy of Fallot), Baller-Gerold syndrome (craniosynostosis), and VACTERL syndrome (vertebral, anal, cardiac, tracheoesophageal atresia, renal, and limb defects) (see Chap. 8).

The literature indicates that most children and types of upper extremity deficiencies are fitted for prosthesis at some point, but Kuyper et al. found that this did not necessarily lead to better functional outcome and suggested that some types of upper extremity deficiencies will ultimately lead to prosthetic rejection [1]. Thus, again, understanding the practical realities of prosthetic prescription is as important as the availability of such technology. For example, patients with linear defects tend not to receive prosthetics.

Prosthetic prescription is thought to be most appropriately introduced earlier rather than later to aid in acceptance. Parental and sibling response to the prosthetic management is important in early acceptance. First introduction of a prosthetic is around the time of independent sitting. The first prosthesis is passive, used mostly as an introduction and for aid in positional challenges while in the sitting position. Then subsequently active prostheses are introduced.

Of patients with various upper limb deficiencies, some are more likely to have successful functional outcomes with prosthetics, and others

more function with surgical interventions without prosthetics, discussed elsewhere in this book.

A major part of management of the patient with upper limb deficiency is simply deciding on the appropriateness of prosthetic management. Some institutions, such as the De Hoogstraat Rehabilitation Center in the Netherlands, have a restrained prescription policy. This is based on the experience of Kuyper et al., who show poor outcome with prostheses for more proximal deficiencies [1].

Transverse radial deficiency is a relatively common major deficiency and tends to be the most successfully managed with prostheses. The upper third of the forearm is the most common level of transradial deficiency. Humeral shortening and some residual digits or nubbins are frequently present, but surgical intervention is rare. The radius in these patients can be unstable and sublux with elbow extension. Prosthetic fitting in the child with shorter transradial deficiencies is a little more challenging owing to less socket surface area for fitting. The child with longer transradial deficiencies has better socket fitting and stronger lever arm.

Digital deficiencies are not uncommon, but rarely occur without other deformities. Surgical interventions are common to remove additional digits. In the case of amniotic band syndrome, other amputations may be present. Other syndromes, such as Moebius, have other anomalies in addition to the digits (i.e., cranial nerve deficiencies). Hypoplastic chest may occur with hand anomalies in the case of Poland syndrome. Prosthetic intervention with hand deficiencies, particularly unilateral, is generally not as helpful in increasing function and ultimately may be rejected. The older and adult patient may choose to eventually have a cosmetic prosthesis. Individual digit deficits come with surgical options and are discussed elsewhere. If the thumb is missing, this obviously creates a more serious deficit, best managed with surgery, such as pollicization.

Partial hand and wrist transverse deficiency are not uncommon. Distal nubbins are not usually a problem and are left alone. There is frequently shortening of the radius and ulna as well. Generally, these children can be quite functional without intervention of surgery or prosthetics. They can use the distal residual limb to steady objects, drape over the forearm, or hold objects against the body.

Elbow disarticulation presents another problem in regard to prosthetic fitting. Because of the need for a prosthetic elbow, in the case of the true disarticulation, the center of rotation of the elbow joint will be distal to the contralateral intact side due to lack of room to place a component and maintain symmetrical humeral length. The true elbow disarticulation has a distal growth plate. This does pose the consideration of at some point performing an epiphysiodesis (growth plate screw fixation) to allow for symmetrical elbow location.

Humeral deficiencies are frequently short and are at risk for diaphyseal overgrowth. Multiple surgeries are not uncommon. The result is frequently a short, fairly nonfunctional residual limb.

The child with shoulder deficiency is the most difficult situation to provide meaningful prosthetic function of a limb. The prosthetic fitting and management are extremely demanding technically, and the limb provided is cumbersome, heavy, and not particularly useful. Only if the patient and family desire it strongly should prosthetic fitting be offered. These children will figure out ways to hold items with the residual limb or using other body parts. If there is a portion of humerus, the axilla can be used to steady objects. Children will use their knees or mouth or chin to chest to hold objects for manipulation with the uninvolved side. In the case of bilateral deficiencies, feet may be used functionally to grasp and manipulate. Many body-powered prosthetics require active shoulder excursion. This is difficult to obtain in the case of the intrascapulo-thoracic deficiency, where there is only unilateral scapular motion. Prosthetic use may be quite limited in this situation and rejection is not uncommon.

The case of the bilateral upper limb-deficient patient is yet another complicated case. There can be great variability in the types of deformi-

ties. Thus, there really is no specific protocol for management in these cases. No timetable for prosthetic fitting is suggested. As in any of the other types of deficiencies, prostheses are merely tools. If they are useful to the individual, they will be accepted and used. If not, they will be rejected [2]. As opposed to the patient with unilateral limb deficiency, a patient with bilateral prosthetics is without tactile sensation. Thus, if one limb has a longer deficiency, consideration of unilateral prosthesis would allow the child some tactile interaction with the environment not present in the prosthetic limb. Keeping the prostheses simple and as light as possible is important, as are comfort and some proprioceptive feedback.

Prosthetic Management

Functional Measures

Both body-powered and myoelectric prostheses are available, depending on the amputee. Body-powered terminal devices can be quite versatile, myoelectric, useful, and more cosmetic. With smaller computer components, myoelectric prosthetic options have indeed improved in weight and function. But whether or not that leads to improved acceptance and actual meaningful increases in functional independence is a different story. Thus, valid outcome measures for pediatric prosthetic users are helpful in the decision process. Furthermore, as reimbursement for expensive durable medical equipment is becoming more and more limited, having valid and "real" measures of endpoint improvements will be important. Literature review of functional measures indicates that there have been a number of measures developed over the last few decades but few in regular use. It matters little if one can measure prosthetic capability if the child still ends up rejecting the prosthesis [2–4].

The most well-known and seemingly best-validated measure at this time is the PUFI (Prosthetic Upper Extremity Functional Index). This measures ease of task performance in bimanual activities, the extent to which the child uses the prosthesis, ease of performance both with and without the prosthesis, and perceived usefulness. Gauthier et al. [3] and Wright et al. measured the validity of the PUFI and found it "achieved acceptable discriminant, construct, and criterion validity" and describe prosthetic skill across age groups and different activities [2, 4].

Prosthetic Prescription

In the child with a transradial deficiency, first fitting is usually when the child begins to sit. A simple passive prosthesis is introduced to allow symmetrical two-hand activities. This can also aid in postural responses in the sitting position. A closed hand (crawling hand) will assist with more symmetrical crawling. Other goals for early fitting at this age include improved long-term wearing habits and prosthetic acceptance.

After the child's next major developmental milestone, walking, at around 11–13 months, it is appropriate to introduce a simple release-and-grasp terminal device or hand. It is best to only attempt a simple control mechanism at this age to maximize the chance for success. A single-electrode myoelectric hand is a good simple option. By this age, the child should have adequate attention span for learning and understanding the grasp/release function. An occupational therapist can help facilitate this process. A child's individual tolerance to hands-on therapy and physical handling may limit the success of this, however.

As the child develops and develops more sophisticated ability to control a terminal device and develops particular interests and self-oriented goals, the physiatrist should make a decision about whether a different type of terminal device should be offered. Options include hooks of various shapes, mitts and hands, and custom task-specific devices for sports and work. The preference of the family frequently is for a device that looks most like a normal hand. However, the cosmetic prosthesis may not be the most functional device. Hooks do, unfortunately, look just

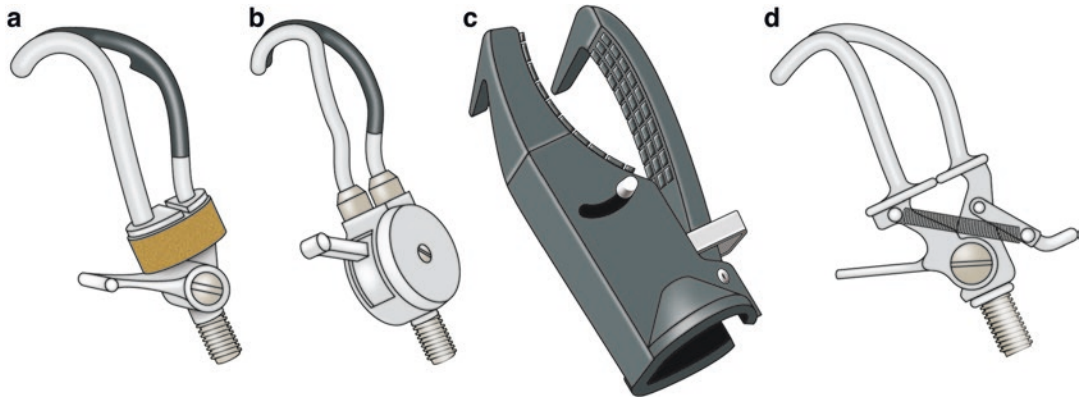

Fig. 5.1 (**a**–**d**) Prosthetic terminal devices: although not cosmetic, hook-type terminal grasping devices are functional and sturdy

like hooks. However, they can be quite versatile and durable (Fig. 5.1). Usually cosmetic hand prostheses are provided as the first terminal device in order to maximize acceptance. As the child ages, he or she will make individual choices.

Transradial Deficiency

The child with a transradial deficiency will do best with a prosthesis with a socket that is self-suspending, with or without a silicone sleeve. It generally will be supracondylar, going just above the elbow, using the condylar width to suspend the socket. The device can be body-powered or myoelectric. A single-electrode myoelectric hand opening mechanism is relatively easy to use. The younger child may not have the strength, shoulder excursion, or cognitive development to work a body-powered device.

By the time the child starts school, he or she should be able to activate most types of devices. At this point, the device that is most functionally appropriate for the child should be chosen. Cosmetic considerations, while important, should not outweigh having the most useful device. Working with an experienced and open-minded prosthetist who is familiar with all types and brands of devices is helpful for the most thorough decision-making. A child may decide to switch the type of prosthesis depending on specific interests and activities.

Transhumeral Deficiency

A child with a transhumeral deficiency will be fitted with a prosthesis even later in development. Because of elbow involvement, the transhumeral prosthesis is often too cumbersome for the infant to handle during the earlier motor developmental milestones such as rolling and crawling. A curved prosthesis with a passive hand and without an elbow hinge is a better choice for the first device. Similarly, for a child with a transradial deficiency, at around the development of walking, a terminal activated device may be offered. The myoelectric hand offers good cosmesis and ease of function as the first terminal device. However, the transhumeral deficiency has the key difference of requiring a prosthetic elbow hinge, which poses a significant additional management challenge. The first elbow will be simple friction with limited range of motion to allow positioning of the terminal device, but block extensive flexion while weight bearing. Electric elbow components are also available and continue to evolve technologically. A harness or silicone sleeve suspends the device.

Components in More Detail

Common hook terminal devices remain the most cost-effective or practical tools in most cases. Technological advances in prosthetic design con-

stitute exciting and "cutting edge" areas of rehabilitation management. However, the challenges of integrating newer technologies are cost, insurance coverage, and practical implementation. More advanced designs require higher degree of discrete control, more training, and more experience. These technologies may be most appropriate for the much older child and adult. A very exciting area of prosthetic management includes activity-specific prosthetics, such as sport-specific and work-specific attachments. Private funding for these devices is usually required, because insurance will not cover these indications.

Body-powered versus electric elbows/shoulders may be considered in the older upper limb-deficient patient. The reader is referred to rehabilitation texts for a discussion of technical details of these options.

Body-powered components include a figure-8 shoulder harness. Control over the elbow and/or terminal device is gained with glenohumeral motion and shoulder protraction and retraction. The elbow can be moved and then locked with one set of motions and then the terminal device activated with another (Figs. 5.2 and 5.3).

With bilateral upper extremity deficiencies, there is no specific timetable of introduction of prosthesis. Introduction needs to be very specific and hand-tailored to the individual based on developmental level and functional goals. Obviously, bilateral upper limb deficiency

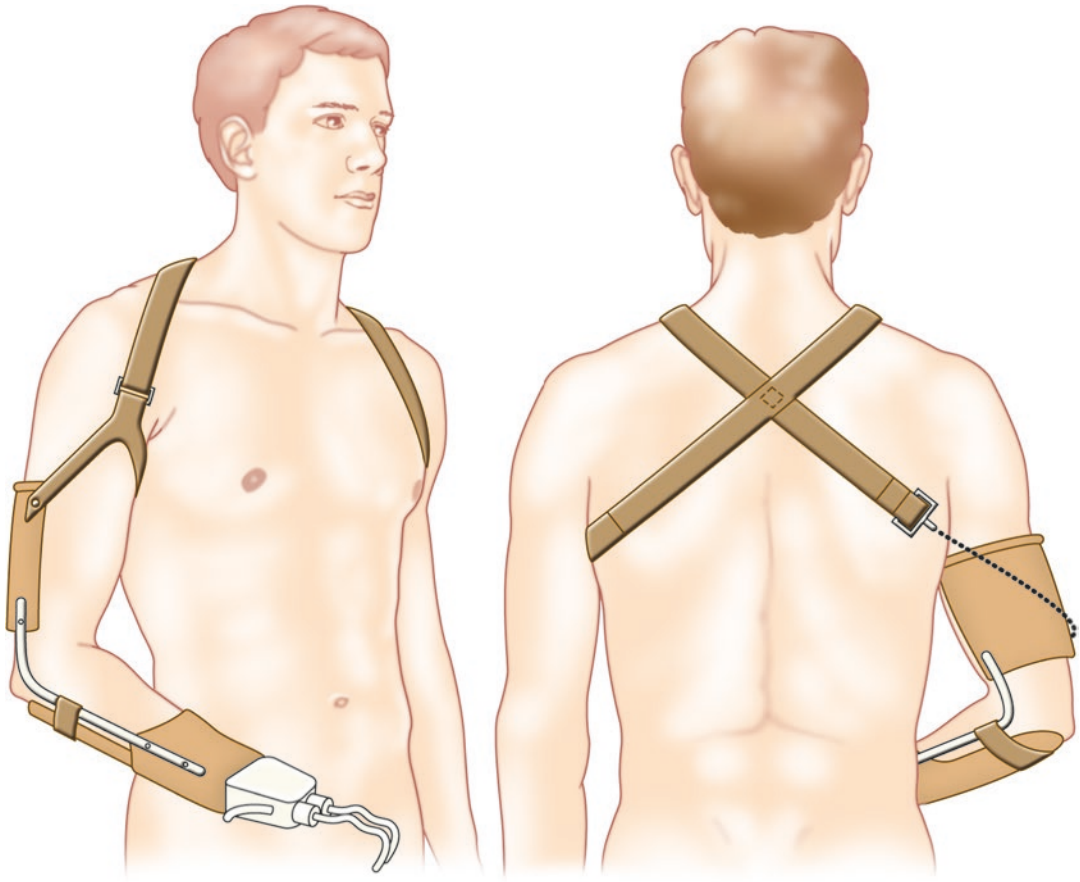

Fig. 5.2 Unilateral transradial prosthesis with figure-8 harness

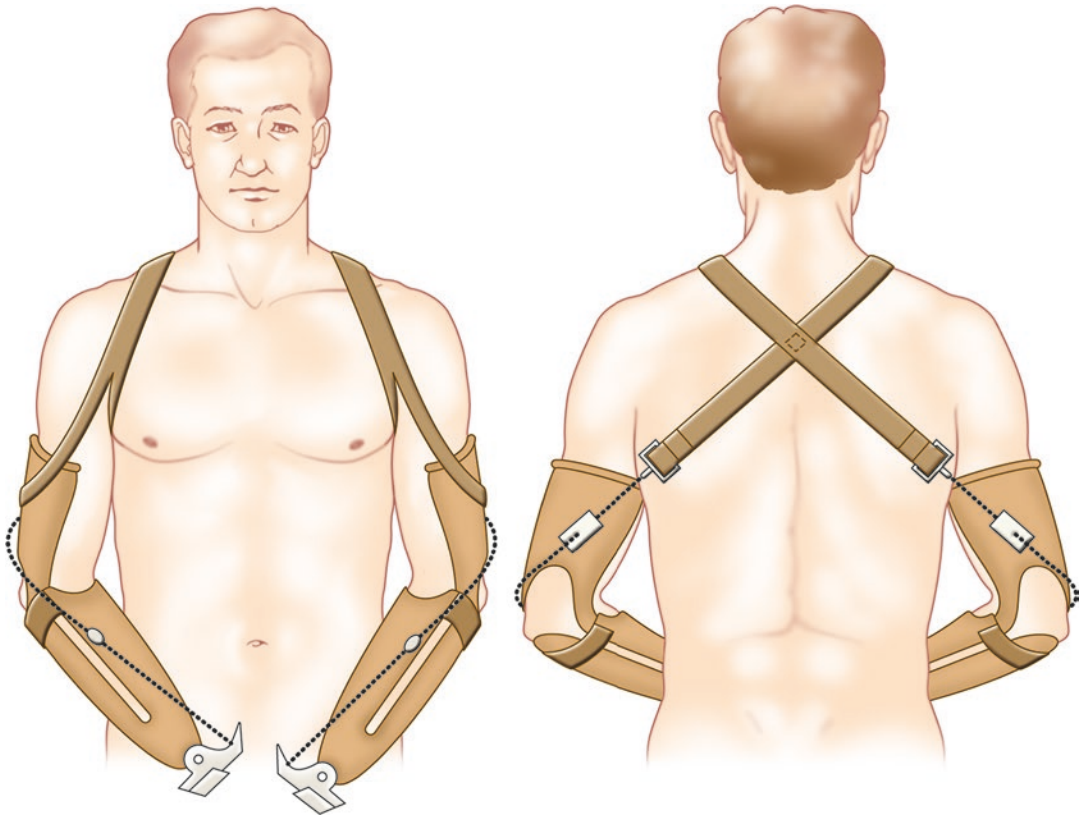

Fig. 5.3 Unilateral transradial prosthesis with gel pin suspension

patients are quite impaired, and prosthetic fitting can be very useful if lightweight and simple to use (Fig. 5.4).

There are, of course, growing fields of more sophisticated prosthetic devices as computer technology advances (more robotic-type prosthetic hands, etc.). These are very interesting and exciting areas of development, but these devices are heavy and quite expensive. Like most electronic development, the cost of these may decrease and may be the future of prosthetic management. Figures 5.5, 5.6, and 5.7 present a few examples of currently available "robotic" hands with myoelectric control from Touch Bionics.

Owing to the complexity and high cost of these prosthetic hands, they are not accessible to children from low-income, uninsured families or to children from developing countries. Advancements in computer-aided design (CAD) programs and three-dimensional (3D) printing make possible fitting simple and cosmetic prosthetic hand devices at a distance and at low cost [4]. Increased manual gross dexterity was seen with the use of a simple 3D-printed prosthesis in children with congenital upper extremity differences [5]. This suggests that 3D-printed prostheses can be used as a transitional device to improve function in children with traumatic or congenital upper limb differences.

Psychosocial Adjustment

A child with a physical difference has significant potential challenges. Body image, shame, and embarrassment can lead to social isolation or even failure. Children bring their own unique coping strategies into play in this regard. Families' support systems, emotional reactions,

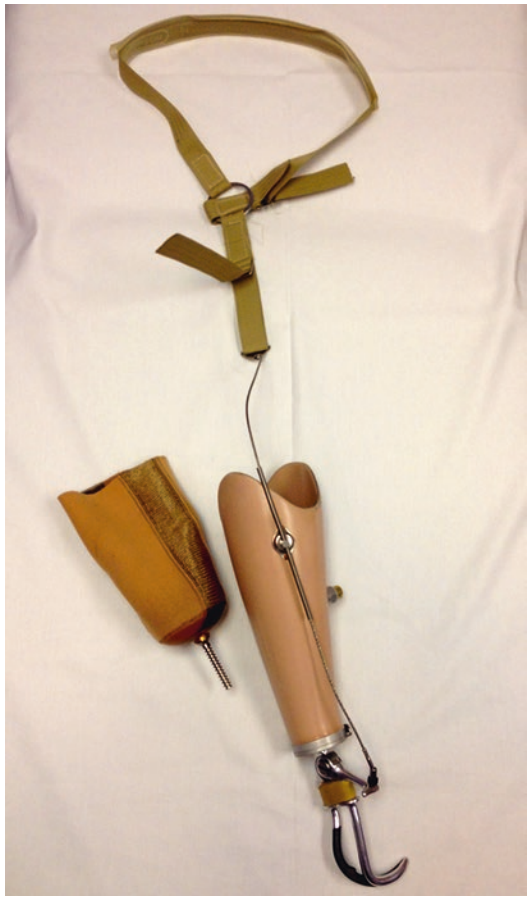

Fig. 5.4 Bilateral transradial prosthesis, body-powered

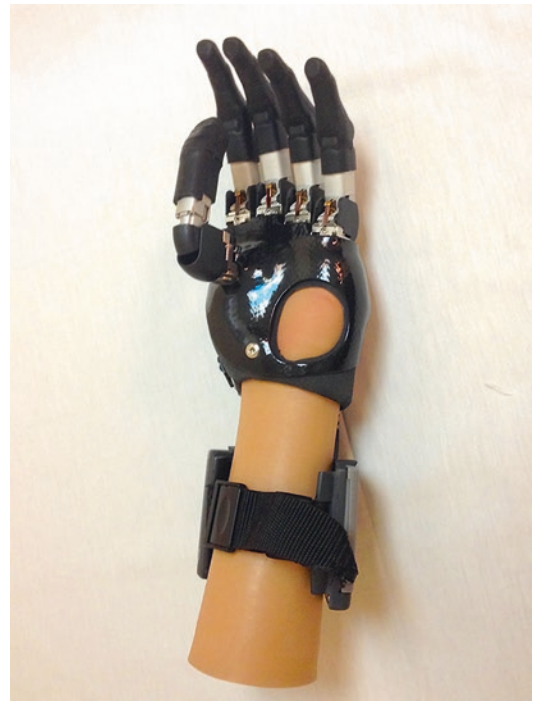

Fig. 5.5 iLimb Digits for use in partial hand amputations

Fig. 5.6 iLimb Ultra for transradial amputees

and handling of the medical situation are also very important. Parents may have their own guilt and shame to deal with. The child will certainly perceive and react to the parent's emotions. Acceptance and use of prostheses are related to the parent's reaction and support of prosthetic appearance. Of equal importance, or perhaps more importance, is the support of peers as the child ages. Having accepting and supporting peers once the child is school age will make a huge difference in the overall emotional health and social success of the child with upper limb deficiency. Hermansson et al. look at adjustment in Swedish children with a myoelectric prosthesis [6]. Children who had a myoelectric hand showed social competence, but tended to be more withdrawn, girls more so, and social activities were lower in older children. Prosthetic users tended to have less delinquency than non-users. Varni et al. found that strain and depression of children with limb deficiencies was mediated by perceived social support. Analysis showed "evidence of the potentially powerful effects of the social environment of the school setting, with perceived classmate social support the only significant predictor variable across

Fig. 5.7 iLimb Ultra holding softball

depressive symptomatology, trait anxiety and general self-esteem" [7].

Inviting a prosthetist into the classroom would offer the opportunity for education and developing interest in advancing technologies. This may lead to more interest and acceptance of the student with limb deficiency.

Summary

Rehabilitation management of the child with congenital upper limb deficiency presents a significant issue in the pediatric rehabilitation population outside of specialty centers that have clinics that draw from the surrounding region. Referral to a larger urban center may be a most appropriate course. However, it is always important to have a good knowledge base in rural areas and developing countries to give appropriate referral and local follow-up. A team approach involving various physicians, therapists, counselors, prosthetists, and medical vendors is an important part of the management of these patients and families. The ultimate goal, of course, is the maximal independent function, highest quality of life, and best possible psychosocial success for the child.

References

1. Kuyper MA, Breedijk M, Mulders AHM, Post MWM, Prevo AJH. Prosthetic management of children in the Netherlands with upper limb deficiencies. Prosthet Orthot Int. 2001;25:228–34.
2. Lambregts SAM, Doornbosch F, Roebroeck ME, Rol M, Arendzen JH, Pexch-Batenburg JMFB, et al., editors. Functional outcome of adolescents and young adults with congenital upper limb reduction deficiency. Proceedings of the 2005 MyoElectric Controls/Powered Prosthetic Symposium. 2005 Aug 17–19, Fredericton, NB, Canada.
3. Wright V, Hubbard S, Naumann S, Jutai J. Evaluation of the validity of the prosthetic upper extremity functional index for children. Arch Phys Med Rehabil. 2003;84:518–27.
4. Zuniga J, Katsavelis D, Peck J, Stollberg J, Petrykowski M, Carson A, Fernandez C. Cyborg beast: a low-cost 3D-printed prosthetic hand for children with upper-limb differences. BMC Res Notes. 2015;8:10.
5. Zuniga JM, Peck JL, Srivastava R, Pierce JE, Dudley DR, Than NA, Stergiou N. Functional changes through the usage of 3D-printed transitional prostheses in children. Disabil Rehabil Assist Technol. 2019;14(1):68–74.
6. Hermansson L, Eliasson AC, Engstrom I. Psychosocial adjustment in Swedish children with upper-limb reduction deficiency and a myoelectric prosthetic hand. Acta Paediatr. 2005;94(4):479–88.
7. Varni J, Setoguchi Y, Rappaport LR, Talbot D. Psychological adjustment and perceived social support in children with congenital/acquired limb deficiencies. J Behav Med. 1992;15(1):31–44.

Suggested Reading

Gaebler-Spira D, Lipschutz R. Pediatric limb deficiencies. In: Alexander M, Matthews D, editors. Pediatric rehabilitation principles and practice. 4th ed. New York: Demos Medical; 2010. p. 339–47.

Gaebler-Spira D, Uellendahl J. Pediatric limb deficiencies. In: Molnar G, Alexander M, editors. Pediatric rehabilitation. 3rd ed. Philadelphia: Hanley and Belfus; 1999. p. 331–9.

Hubbard S. Pediatric upper limb outcome measures. J Prosthet Orthot. 2009;21(48):64–8.

Kelly BM, Davis AJ, Justice D, Miller QL, Nelson VS. Comprehensive care for the child with upper extremity limb deficiency. J Pediatr Rehabil Med. 2009;2:195–208.

Sener F, Yigiter K, Bayar K, Erbahceci F. Effectiveness of prosthetic rehabilitation of children with limb deficiencies present at birth. Prosthet Orthot Int. 1999;23:130–4.

6 Therapy Management of Children with Congenital Anomalies of the Upper Extremity

Ginny Gibson

Introduction

This chapter will first introduce evaluation tools appropriate for children with congenital anomalies of the upper extremity (CAUE). Second, general rehabilitation interventions will be described. Third, attention will be given to interventions for children with selected CAUE who are often served by occupational or physical therapists.

Evaluation

Reviews, reports, and investigations have identified activities of daily living (ADL) and instrumental activities of daily living (IADL) that are problematic for children with CAUE including styling hair, squeezing toothpaste, completing toilet hygiene, tying shoelaces, closing and opening dressing fasteners, tucking shirts into pants at the waistline, donning gloves, retrieving coins from pocket of pants, donning socks, cutting and peeling food, opening a container or a bag of food, sweeping, and vacuuming [1–7]. Educationally related activities that may prove difficult for children with CAUE include writing with a pen or pencil, sharpening a pencil, using a keyboard, carrying books, cutting with scissors, managing a lunch tray, participating fully in playground activities and physical education (e.g., cartwheels, handstands, grasping bars of a play structure), and playing a musical instrument [4–6, 8]. Outside of school, children with CAUE have reported difficulty participating in ball sports, dance, martial arts, snow or ice sports, water sports, gymnastics, cycling, and playing with construction toys [5, 8]. Across populations of children with unilateral CAUE, activities requiring bilateral hand use are likely to be more compromised [9].

Considering subgroups of children with CAUE, younger children have been shown to experience less upper extremity function than older children as measured by the Patient-Reported Outcomes Measurement Information System (PROMIS) [9]. Adults with ulnar longitudinal deficiency (ULD) have reported no difficulty with self-dressing, washing, toileting, eating, closing and opening dressing fasteners, managing the telephone, typing, or opening containers with screw on caps [10]. Children with CAUE involving the entire limb or more of the proximal upper limb may experience less functional ability than children with only hand involvement, as measured by the Pediatric Outcomes Data Collection Instrument (PODCI) [9, 11], and children with unilateral CAUE experience greater functional ability than those with

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bilateral CAUE, as measured by both the PROMIS and PODCI [9]. As classified by the Oberg-Manske-Tonkin Classification, children with upper extremity malformation and deformation experience more functional impairment than children with dysplasia, as measured by the PODCI [11]. In a descriptive study, parents reported their child with ULD reported no difficulty with bimanual self-care, play- or school-related activity [10], whereas in a qualitative study of 33 children of children aged 6–17 years with a broad range of CAUE, children reported difficulty with self-care, school-related activities, and instrumental activities of daily living [12].

Ardon et al. [13] found children with CAUE performed similar to peers without CAUE on the Pediatric Quality of Life inventory (PedsQL), yet mean scores for 13- to 14-year-old children with CAUE were generally lower, and variance among the CAUE group was greater. Further these researchers noted that for 11- to 12-year-old children with CAUE, a frequently cited problem was not being able to "do things that other kids my age can do," whereas children without CAUE did not report this problem (p. 354). Because of these findings, Ardon et al. [13] recommended children with CAUE be screened to identify problems of health-related quality of life.

Impairment and Function

The evaluation of children with CAUE should consider impairment, activity performance, and activity participation as there may or may not be a relationship between the three constructs [4, 14, 15]. Four studies have examined the relationship between impairment or body structure with activity performance or participation for children with radial longitudinal deficiency (RLD). Kotwal et al. [14] retrospectively compared children with RLD who underwent centralization or radialization to those who did not. Although the main purpose of the study was to discern if patients benefitted from surgical correction of wrist deformity, the researchers found strong correlations between Prosthetic Upper Extremity Functional Index (PUFI) scores and three measures of body function, including wrist range of motion (ROM) (r = 0.65– 0.81), long finger ROM (r = 0.93–0.97), and grip strength (r = 0.90–0.97). Buffart et al. [15] examined relationships between hand function impairment and activity performance. Grip and pinch strength, as well as active range of motion (AROM), were measured for the assisting hand. For children with unilateral involvement, the affected hand was measured, and for those with bilateral involvement, the more affected hand was measured. All children completed the Assisting Hand Assessment (AHA), and their parents completed the Ease of Performance Scale on the PUFI. Grip strength significantly correlated with activity performance for the AHA (r = 0.69, p = 0.002) and PUFI (r = 0.52, p = 0.003). Pinch strength significantly correlated with activity performance for the AHA (r = 0.77, p = 0.001) only. Active range of motion of the wrist and second digit significantly correlated with activity performance for the AHA (r = 0.59, p = 0.006 and r = 0.87, p = 0.001) and PUFI (r = 0.71, p = 0.001 and r = 0.59, p = 0.006, respectively). Ekblom et al. [16] found a relationship between outcomes on the AHA and total range of motion (ROM) of digits (p = 0.042) and between self-experienced time of performance on the Children's Hand-use Experience Questionnaire (CHEQ) and total active motion of the wrist (p = 0.043) for children with RLD, yet no relationship was found between the degree of radial deviation and outcomes of the Box and Block Test, AHA, or CHEQ.

The studies cited in the preceding paragraph included children, but similar studies have included adults with RLD. Holtslag et al. [4] investigated the functional implications of RLD for 17 adults who previously underwent surgical or conservative treatment. Measurements included grip and pinch strength, ROM, and hand function during standardized ADL using the Sequential Occupational Dexterity Assessment (SODA). Participation in activity was quantified using the Impact on Participation and Autonomy Questionnaire (IPAQ). Researchers found a positive correlation (r = 0.56, p = 0.02) between digital ROM and SODA outcomes, but no other relationship between body function and hand

function or participation. Ekblom et al. [17] attempted to capture measures of body function, activity level, and activity participation in adults with RLD, in order to relate impairment with activity level and participation. They found correlations of statistical significance between the QuickDASH and forearm length ($p < 0.001$) and total active motion of the elbow and digits ($p = 0.001$ and $p < 0.001$, respectively), and between the Short Form-12 physical component summary and grip strength ($p = 0.016$), forearm length ($p < 0.001$), total active elbow motion and digits ($p < 0.001$ and $p < 0.001$), respectively. Researchers did not find a relationship between radiographic measures of frontal plane alignment and the QuickDASH or Short Form-12 physical component summary. In a retrospective, qualitative study, Carlsson et al. [5] interviewed 15 adults with CAUE to better understand the impact of CAUE, specifically thumb anomaly, on daily life. Participants relayed that they experienced normal cutaneous sensation, pain when loading or inadvertently hitting the hand, and bouts of feeling weak due to overuse of compensatory patterns of hand use. These adults reported "overall good hand function" (p. 70), yet cited impaired fine motor control and dexterity.

Following surgery therapists should provide adjunctive interventions to facilitate optimal wound healing and scar formation, increase range of motion and strength, reduce pain, and promote upper extremity motor control as a means to increase and support activity and participation. However, in other contexts, therapists may more usefully focus on fostering activity and participation. This emphasis on ability rather than impairment is consistent with the Social Model of Disability, which targets environmental, attitudinal, and institutional barriers rather than a person's impairment to maximize activity participation [18, 19]. In the context of therapy following surgery, measurement of impairment is essential to determine a course of intervention and to evaluate the effectiveness of intervention; whereas, when children are referred to therapy in order to increase activity and participation, measures that capture a child's current level of activity and participation are emphasized.

Table 6.1 Tools to measure impairment

Movement restriction	Goniometer [20, 21] Inclinometer [22] Wire tracing [23] Linear measure (calipers, tape measure) [24] Pollexograph [25, 26]
Weakness	Dynamometer (grip and pinch) [20, 21] Myometry [27, 28] Manual muscle testing (MMT) [20, 21]
Edema	Volumetry [29] Tape measure [29]
Pain	Visual analog scale [30] Wong-Baker faces [30] Face, legs, activity, cry, consolability scale [30]
Impaired sensation/ nerve injury	Monofilaments [21] Two-point discrimination [21] Stereognosis [21] Moberg pickup-test [21] Ten test [31, 32] Wrinkle test [21]
Prehension	Box and Block Test [21] Functional Dexterity Test [21, 33] Nine-Hole Peg Test [21] Jebsen-Taylor Hand Function Test [20]

Table 6.1 includes tests and measures of impairment likely to be used when providing habilitative and rehabilitative services to children with CAUE, while Table 6.2 includes tests for which normative information was located.

Outcome Measures Specific to Children with CAUE

Skerik et al. [59] described a standardized process of assessment for all children with CAUE, including analysis of available patterns of pinch and grip and observation of preferred patterns of usage, and measurement of ROM, pinch strength, and hand size. Ho and Clarke [60] conducted a systematic review of studies published between 1966 and 2003 aimed at evaluating outcomes following pollicization of the index finger or centralization for RLD. Of the ten studies reviewed,

Table 6.2 Impairment ratings. Normative studies in typically developing children

Impairment	Normative data					
	Tool	First author and date	Citation	Measure	*n* (participants)	Age (years)
Movement restriction	Goniometer	Soucie (2011)	[34]	Shoulder, elbow, forearm PROM	200	2–19
		Barad (2013)	[35]	Elbow PROM	1361	1–16
		Da Paz (2016)	[36]	Elbow, wrist, metacarpophalangeal and interphalangeal joints, AROM	171	2–16
	Pollexograph	de Kraker (2009)	[26]	Thumb abduction	100	4–12
Weakness	Grippit	Häger-Ross (2002)	[37]	Grip strength	530	4–16
	Takei Digital Grip Strength Dynamometer	Kocher (2019)	[38]	Grip strength	4665	6–18
	Jamar dynamometer	Bowman (1984)	[39]	Grip strength	153	6–9
		Fullwood (1986)	[40]		214	5–12
		DeSmet (2001)	[41]		487	5–15
		Holm (2008)	[42]		376	7–12
		Ploegmakers (2013)	[43]		2241	4–15
		Mathiowetz (1986)	[44]		571	6–19
		Ager (1984)	[45]		474	2–13
		Lee-Valkov (2003)	[46]		17	3–5
	Preston pinch gauge	Lee-Valkov (2003)	[46]	Pinch strength	17	3–5
		Ager (1984)	[45]		474	2–13
		DeSmet (2006)	[47]		262	5–12
	B and L pinch gauge	Surrey (2001)	[48]	Pinch strength	414	5–12
		Mathiowetz (1986)	[44]		571	6–19
Impaired sensation	Two-point discrimination	Cope (1992)	[49]	Two-point discrimination	112	2–13
		Hermann (1996)	[50]	Moving two-point discrimination	313	4–18
		Dua (2016)	[51]	Static and moving two-point discrimination	251	2–18
	Monofilaments	Dua (2016)	[51]	Threshold testing	251	2–18
Reduced manual dexterity	Box and Block Test	Mathiowetz (1985)	[52]	Manual dexterity	471	6–19
		Jongbloed-Pereboom (2013)	[53]	Manual dexterity	215	3–10
	Functional Dexterity Test	Gogola (2013)	[54]	In-hand manipulation	175	3–17
	Nine-Hole Peg Test	Smith (2000)	[55]	Manual dexterity	826	5–10
		Poole (2005)	[56]		409	4–19
		Wang (2015)	[57]		2776	3–17
	Purdue Pegboard	Wilson (1982)	[58]	Manual dexterity	206	2.6–5.1

six attempted to measure ADL or functional use of the hand, but only one did so using a standardized instrument.

Since Ho and Clarke's review, other outcome studies have been published in which standardized assessment tools were employed to evaluate children with CAUE. Buffart et al. [61] set out to identify appropriate assessment tools for use with children with transverse or longitudinal reduction deficiency using as criteria inclusion of bimanual tasks, measures of movement quality, and appealing tasks. These researchers recommended the AHA, Unilateral Below Elbow Test (UBET), ABILHAND-Kids, and PUFI. In a follow-up study [62], the AHA, UBET, ABILHAND-Kids, and PUFI were administered to 20 children with RLD, aged 4–12 years. The AHA and PUFI were deemed most valid for children with RLD, due to the relationships found with type of RLD ($r = -0.82$ and -0.64, respectively), functional hand grips ($r = 0.58$ and 0.46, respectively), and the therapist's global assessment of hand function ($r = 0.85$ and 0.63, respectively).

Several researchers have developed outcomes specifically for evaluating results of index finger pollicization. Percival et al. [63] developed a battery of seven tests for which a maximum score is 22. Included in this battery is a measure or observation of tip pinch and pulp pinch strength; opposition of the thumb to the middle, ring, and small finger; grasping of two balls of different size; active movement of the thumb at three joints; two-point discrimination; and cosmesis (length and position of the thumb). Scores were characterized as excellent (>20) good (16–19), fair (12–15), or poor (<12). Kollitz et al. [64] developed the Thumb Grasp and Pinch assessment (T-GAP) to specifically evaluate thumb function after pollicization in children, 18 months to 18 years of age, with a range of possible scores between 0 and 63 (higher score reflecting a higher level of function). Nine components are assessed with different tasks provided for children in the 18 months to 4-year-old age group, 5- to 7-year-old age group, and 8- to 18-year-old age group. These tasks include tip pinch, lateral key pinch, small grasp, medium grasp, large grasp, manipulation, resistance, school, and ADL. Zlotolow et al. [65] introduced a new tool composed of a subjective and objective measure to evaluate thumb appearance and function following pollicization. Subjectively, two scales are utilized to determine the extent to which the thumb "looks like a thumb" and "works like a thumb" (p. 1785). Objectively, the thumb is evaluated for length, girth, rotation, composite flexion and extension of the thumb, thumb CMC adduction, thumb CMC abduction, MCP and interphalangeal arc of motion, pinch strength, and object acquisition (grasping a small bead, die, table tennis ball, and sticker). Researchers found a moderate correlation between scores for "looks like a thumb" with the sticker test ($r = 0.56$ and 0.57) and moderate correlations between "works like a thumb" with the sticker test ($r = 0.50$–0.61), tip pinch strength ($r = 0.50$), bead acquisition ($r = 0.51$), die acquisition ($r = 0.55$), and table tennis ball acquisition ($r = 0.53$). Of note, the sticker test correlated to surgeon, therapist, and parent assessment of "works like a thumb." This test requires the child to remove a sticker from the paper backing.

Table 6.3 presents performance-based assessments specifically designed for children with CAUE, children with normal use of one hand only, or children with disability but no specific diagnostic population.

Assessments that measure satisfaction with or perceptions of activity performance and participation should include the child with CAUE, but in some cases the caregiver may need to serve as proxy. The extent to which parents and children agree on satisfaction with or perceptions of activity performance and activity participation has been studied by several research groups. Kaplan and Jones [87] used the Pediatric Outcomes Data Collection Instrument (PODCI) to determine outcomes following microsurgical toe transfers for thumb reconstruction across 10 adolescents and 15 parents of pediatric and adolescent patients who underwent toe-to-hand transfers. While mean scores were not statistically significant between adolescents with toe-to-hand transfer and the general population of adolescents, parents of adolescents undergoing

Table 6.3 Performance-based assessment

Assessment tool	Target populations	Target age (years)	Studies describing psychometrics		
			Validity	Reliability	Responsiveness
ABILHAND-Kids	Children with cerebral palsy	6–15	[62]	[62, 66]	–
AHA	Children with typical function in one hand only	1.6–12.8	[67]	[67–70]	[67]
ASK	Children with musculoskeletal limitations	5–15	[71]	[71]	–
CAPP-FSI	Children with limb deficiency	8–17	[72]	[72]	–
CHEQ	Children with typical function in one hand only	6–18	[73, 74]	[74]	–
PedsQL	Children with acute or chronic illness	2–18	[75]	[75]	[76]
PEDI	Children with physical disability	6 mo-7.5	[77–80]	[80]	–
PODCI	Children with orthopedic conditions	2–18	[81, 82]	[81]	[83, 84]
PUFI	Children who use an upper extremity prosthesis	3–18	[62, 85]	[62, 85]	–
UBET	Children and young adults with transverse reduction deficiency	2–21	[62]	[62, 86]	–

AHA Assisting Hand Assessment, *ASK* Activities Scale for Kids, *CAPP-FSI* Child Amputee Prosthetics Project – Functional Status Inventory, *CHEQ* Children's Hand-use Experience Questionnaire, *PedsQL* Pediatric Quality of Life Inventory, *PEDI* Pediatric Evaluation of Disability Inventory, *PODCI* Pediatric Outcomes Data Collection Instrument, *PUFI* Prosthetic Upper Extremity Functional Index, *PROMIS* Patient-Reported Outcomes Measurement Information System, *UBET* Unilateral Below Elbow Test

toe-to-hand transfer underestimated their adolescent children's function in terms of sports/physical function and happiness. Netscher et al. [88] examined children's ability to participate in activities following index finger pollicization. In addition to measuring impairment level and ability to participate in simulated tasks reflecting participation in a larger activity, researchers administered a non-validated novel questionnaire to nine children and their parents to determine perceptions of appearance, social participation, and performance skills. The mean score for children was 22, with 12 being the best score and 60 the worst. Although parents tended to assess their children's skills as slightly better than the children did of themselves, there was no statistically significant difference between parents' and children's scores, suggesting that parents may serve well as proxy. Ardon et al. [89] found similar results when parents and their children with CAUE separately completed the PedsQL. No statistically significant differences were observed for mean total score and mean score accross five domains (physical health, emotional functions, social functioning, school functioning, psychosocial health). The researchers noted analysis of individual scores showed children and parents tended to disagree and the variables that influenced disagreement included number of affected digits and unilateral versus bilateral involvement [89]. Similarly, in a large multi-center study, significant differences were found between parents and their children with congenital below elbow deficiency (CBED) for upper extremity physical function ($p < 0.001$), pain/comfort ($p < 0.05$), and social functioning ($p < 0.001$) using the PODCI and PedsQL [90]. In summary, use of a parent as proxy should be limited; effort to elicit children's participation is desirable.

Interventions to Address Impairments

Current estimates of the rate of congenital upper limb differences include 1 in 506 live births [90], 5.25 in 10,000 live births [91], and 21.5 per 10,000 live births [92]. In two reports of the incidence of all congenital limb reductions, 75% to 81% involved the upper extremities [93, 94]. Within these estimates, not all children with

CAUE will require surgical intervention and subsequent rehabilitation. When indicated, rehabilitation efforts may initially emphasize interventions to address impairment with simultaneous or subsequent attention to participation in activity. The studies presented in the following sections are not specific to children.

Edema

Edema management is often addressed via rest, ice, compression, and elevation. Postoperative dressings and casts provide rest and compression yet preclude icing. Chronic edema that persists after removal of postoperative immobilization may be treated with gentle compression and elevation, although younger children may not be amenable to elevation. Despite wide use of elevation, the efficacy of elevation following hand surgery is unclear. In two prospective and randomized comparison trials, no statistically significant differences were noted in those who elevated the limb and those who did not for adults undergoing Dupuytren's release [95] or carpal tunnel decompression [96]. Gentle compression may be achieved with self-adherent wrap [97]; however, only one case report of an adult with burn injury could be located to support its use [98]. In a systematic review of RCT, Miller et al. [99] examined treatments to reduce upper limb subacute edema. Of studies assessing treatment of edema following musculoskeletal trauma or surgery, the authors recommended the use of elevation, active/passive exercises, and compression (e.g., string wrapping, compression glove, intermittent pneumatic pressure, self-adherent wrap), but did not recommend manual edema mobilization as a first course of treatment.

Scar

In addition to being a cosmetic concern, postoperative scar may lead to motion restriction, pain, and pruritus. These impairments may in turn reduce function and participation in activities. Intervention should first concentrate on prevention of hypertrophic and keloid scars, but once these scars are present, efforts should be made to reduce the extent or deleterious effects of the existing scar. Widgerow et al. [100] advocated for an early multimodal approach to treatment of scar following surgical incision, which includes scar support to reduce tension, scar hydration, and acceleration of scar maturation. Additionally, scars from surgical incisions may respond well to massage and pressure. In this section, studies that include treatment of scars from burn injury, surgical incision, or other trauma have been included; however, the etiology of a scar should be considered when applying study outcomes to clinical decision-making for a particular patient. Further, in this section discussion of treatment for scar is limited to those therapies typically offered by physical or occupational therapists, and represents only a subset of all treatments available for preventing or reducing hypertrophic or keloid scar.

Massage

Foo and Tristani-Firouzi [101] recommended post-surgical scar massage commence during the proliferative phase for 3–5 minutes, two to three times per day, and for 3–4 months to prevent the onset of hypertrophy. Later, Shin and Bordeaux [102] published a systematic review of studies investigating the effectiveness of scar massage regimes for scars due to burn and trauma and included four randomized controlled studies, three prospective controlled studies, one prospective study, and two case reports. Across 10 reports, the total number of subjects was 220 with 144 receiving scar massage. The standardized outcome measures included the Observer Scar Assessment Scale and the Vancouver Scar Scale, as well as subjective assessments of scar thickness, perfusion, color, pain, and itching. For patients who had surgical scars and received massage, 90% improved. Khansa et al. [103] published a narrative review of scar management techniques (including scars from burn injury, surgical incision, and trauma) and suggested massage may be useful for existing hypertrophic scars, but not for preventing hypertrophic scars.

Pressure

Pressure application may be applied using self-adherent wrap, neoprene orthosis, tubular elastic, or a custom-fit pressure garment. Pressure appears to inhibit fibroblastic activity via ischemia and hypoxia resulting in degeneration of fibroblasts and slowed synthesis of collagen [104, 105]. In a laboratory study of fibroblastic activity under pressure, researchers showed pressure application may be applied at higher levels over shorter periods of time or at lower levels for longer periods of time to reduce fibroblastic proliferation [104]. Costa et al. [105] compared non-treated hypertrophic scar and hypertrophic scar following burn injury. Treated scar was subjected to pressure. At 2 and 7 months, using electron microscopy, researchers found pressure-treated hypertrophic scar showed signs of collagen degradation and myofibroblast apoptosis, whereas these changes were not observed in non-treated hypertrophic scar.

Despite a long history of employing pressure therapy for treatment of scar, definitive evidence regarding its efficacy is lacking. In a meta-analysis of six published randomized controlled trials (no treatment or comparison treatment) and one unpublished trial examining the benefit of pressure therapy for burn scar, researchers found no difference between scars treated with pressure therapy and controls [106]. Two subsequent randomized controlled studies support the use of pressure garments for scar management [107, 108]. In a study by Stienstraesser et al. [107], patients (n = 38) with two similar scars from split-thickness grafts were randomized into either a silicone gel sheeting group + pressure therapy versus pressure therapy alone or a silicone spray group + pressure therapy versus pressure therapy alone. Treatment of burn scar with pressure alone yielded statistically significant improvement on the Vancouver Scar Scale (VSS) ($p < 0.001$), and also improvement with combined pressure therapy and application of silicone gel sheeting ($p = 0.001$) and combined pressure therapy and silicone spray ($p < 0.001$). Differences between the groups were not significant. Engrav et al. [108] compared normal pressure application to low pressure application within the same scar across 54 scars and found statistically significant differences in scar hardness ($p = 0.011$) and thickness (no p value reported). In their discussion, Engrav et al. [108] suggested pressure therapy may be more effective in moderate to severe scarring. In 2016, Sharp et al. [109] conducted a systematic review of studies related to pressure garment therapy following burn injury, but included studies of varied rigor. They concluded pressure therapy is useful for controlling scar height and erythema when used 23 hours per day, when 20–30 mm Hg of pressure is achieved, and if replaced every 2–3 months. The authors did not endorse the use of pressure therapy for increasing scar pliability or to treat hypertrophic scar [109]. In a randomized controlled trial, Wiseman et al. [110] compared pressure therapy alone to silicone gel therapy alone to combined pressure and silicone gel therapy in children with scar due to burn injury (n = 159) and found all scar became thicker at 6 months. However, greater scar thickness was observed in the combined therapy group compared to silicone gel alone group ($p = 0.05$). Children in the pressure therapy only group had less scar thickness than the combined therapy group, but differences were not statistically significant ($p = 0.07$). Researchers found no differences between the silicone gel therapy alone and pressure therapy alone groups. Of note, those in the pressure therapy only group reported more adverse effects (skin irritation, sensory symptoms, and wound breakdown). Fabrication of pressure garments requires precise measures be taken to achieve recommended pressure application, but this may be difficult to achieve. Nedelec et al. [111] found significant reductions in pressure application between baseline (immediately following garment fabrication) and 1 month later ($p = 0.0002$) and between 1 and 2 months ($p = 0.03$). Further, immediately following fabrication, pressure applied by the garment was suboptimal, but within recommended range and by 1 month was below the recommended range of pressure application.

Although Widgerow [112] suggested pressure garments are more appropriate for widespread scar seen in burn injury, for young children maintenance of tape or silicone gel sheeting on the hand is often challenging. For this reason a pressure garment may increase adherence with other topical scar treatment by reducing the likelihood of self-removal. If using self-adherent wrap to hold topical products in place on a child's hand, rather than a pressure garment, care in wrapping and maintained supervision are indicated to avoid a tourniquet-like effect due to lifting, slippage, and rolling [113]. Alternatively, use of neoprene patches or orthoses for at least 8 hours per day was retrospectively studied in a small population of children and young adults with burn scar ($n = 8$ participants, 12 scars). Duration of treatment ranged from 1 to 11 months. Scars were evaluated pre- and post-treatment and differences for mean VSS were significantly lower after treatment ($p = 0.0001$). This study is useful to therapists working with children because neoprene orthoses are often used long-term across many diagnostic groups for limb positioning and so could also serve to manage scar [114].

Silicone

The proposed mechanism of action of silicone gel is thought to be hydration and occlusion [115], though nonsilicone gels may be equally effective as silicone. In a prospective, randomized study, patients ($n = 24$) with existing hypertrophic or keloid scars ($n = 41$) present for longer than 3 months, including incisional scars, were randomly assigned to one of three groups: treatment with silicone gel ($n = 16$ scars), treatment with nonsilicone gel ($n = 14$ scars), or control ($n = 11$ scars). Treatment was applied 24 hours per day for 4.5 months. No statistically significant differences were found between silicone gel and a nonsilicone gel groups for color, size, induration, and symptoms, although significant differences were noted when silicone gel and a nonsilicone gel were compared to controls for color, size, induration, and scar pliability [116]. O'Brien and Pandit [117] conducted a meta-analysis to determine the effectiveness of silicone gel to prevent hypertrophic or keloid scarring in people with newly healed wounds and to treat established keloid or hypertrophic scars. The study included randomized or quasi-randomized controlled trials and controlled clinical trials comparing silicone gels to other non-surgical treatment, no treatment, or placebo. Included trials compared adhesive silicone gel with control, nonsilicone dressings, silicone gel plates with added vitamin E, laser therapy, triamcinolone acetonide injection, and non-adhesive silicone gels. Scar quality was determined by blood flow, color change, hyperpigmentation, thickness, and shape. Studies that set out to determine the effectiveness of silicone to treat existing scars measured change in scar size and did so using a ruler, taking an impression, or via ultrasound. Across 15 studies, 615 people between 2 and 81 years of age were included. Compared with no treatment, silicone reduced the incidence of hypertrophic scar (RR 0.46, 95% CI 0.21–0.98). For established keloid and hypertrophic scar, silicone gel sheeting significantly reduced scar thickness (RR −1.99, 95% CI −2.13 to −1.85) and improved color (RR 3.05, 95% CI 1.57–5.96). Silicone gels produced superior results compared to controls in two trials, no difference was found in two trials, and the control group fared better in one trial. This study included clinical trials of varied rigor and most were subject to bias. An update to this review was published in 2013; five new studies were included but the same conclusion was offered [118]. In a more recent meta-analysis of six randomized controlled trials, researchers found evidence for efficacy of silicone gel and silicone gel sheeting for reducing pigmentation, height, and pliability scores postoperatively compared with placebo or no treatment [119]. Like de Oliveira [116], Wang [119] found similar positive benefits of topical silicone gel treatment compared to other nonsilicone topical treatment. As described earlier, Wiseman et al. [110] found silicone gel therapy alone may be superior to combined treatment of silicone gel and pressure therapy. In summary, the evidence to support use of silicone gel sheeting is conflicting.

Tape

Tension on scar is believed to stimulate collagen production due to mechanosensitive fibroblasts [120–123]. Tape applied to scars may reduce tension and thus prevent or minimize hypertrophic scar [100, 124]. Porous tape should be applied longitudinal to and directly over the scar to adequately provide support and reduce tension [112]. When scars cross joints, use of an orthosis may help to reduce to tension on scar by immobilizing the joint.

Motion Restriction

Clinicians utilize AROM (Fig. 6.1), active-assisted range of motion, passive range of motion (PROM), joint mobilization, and orthoses to achieve greater range of movement. For young children, use of play and leisure activity may prove more useful for exercise adherence. Michlovitz et al. [125] conducted a systematic review of interventions to promote joint motion in the upper extremity. The review included 26 studies examining interventions in adults, but excluded children and congenital hand differences. In their summary, the researchers noted moderate evidence for the use of orthoses or casts and passive exercise to increase ROM after joint trauma or immobilization. Following this study, Glasgow et al. [126] published a narrative review of 29 studies of varying rigor to develop a set of recommendations for mobilizing the stiff hand and recommended active and active-assisted exercise during all stages of tissue healing, passive exercise during the proliferative and remodeling phases, and joint mobilization during the remodeling phase. Orthoses for management of stiffness via mobilization was recommended during the proliferative and remodeling phases.

Fig. 6.1 Music Glove

When the purpose of an orthosis is to increase motion, orthosis prescription must consider tissue compliance and the length of time the restriction has been present. Therapists must decide on orthosis type (including no orthosis), wear time (hours per day and duration), and the magnitude of force to apply. Flowers [127] offered a hierarchy for decision-making when treating stiff joints using a modified Week's test [128]. After pre-conditioning, those whose PROM measures changed by 20° may not need an orthosis; by 15°, may require a static orthosis with no overpressure; by 10°, may require a dynamic orthosis; and by 5° or less, may require a static progressive orthosis with overpressure. This decision-making process may prove useful with older children, but may not be feasible with infants and toddlers due to required exposure to thermotherapy.

Consensus on wear time of an orthosis to resolve motion restrictions is lacking, although many studies provide guidance. Flowers and LaStayo [129] executed a study to determine if duration of orthosis use impacted outcomes for stiff joints. Patients ($n = 15$) with 20 PIP flexion contractures between 15° and 60° were randomly assigned to continuous casting for 6 days, then 3 days, or 3 days, then 6 days. Researchers found a statistically significant difference ($p < 0.005$) in gains made with 6 days of wear achieving a mean increase of 5.3° and 3 days of

wear achieving 3°. Glascow et al. [130] prospectively investigated optimal hours of daily orthoses wear in 43 subjects with joint restrictions in the hand following trauma. Subjects with similar levels of stiffness – as determined via torque range of motion (TROM) – were randomly allocated to a <6-hour or 6- to 12-hour-per-day group. Researchers found a statistically significant difference in TROM values between the groups, with better TROM observed in the 6- to 12-hour group. It is not clear if increasing time more than 12 hours provides greater benefit. In a follow-up randomized study of 22 patients with PIP joint flexion contractures, no significant differences were found for PROM, AROM, or TROM between 6 and 12 hours of wear and 12 to 16 hours of orthosis wear after 8 weeks of treatment [131]. Valdez et al. [132] conducted a systematic review of studies investigating orthotic use to increase active PIP extension, but excluded children younger than 12 years, and recommended wearing an orthosis for at least 6 hours per day with sufficient extension torque such that the patient remain pain-free but feels tissues are being stretched. In summary, extended periods of orthosis wear appear superior to shorter periods of wear.

Interventions to Address Activity Performance and Participation

Assuming a child with CAUE is otherwise typically developing, interventions to improve activity performance or participation may occur immediately following surgery or intermittently – when the child encounters specific problem with activity performance or participation. Following surgery, impairment-based interventions may be emphasized concurrently with activity performance and participation via activity modification or introduction to assistive devices [4]. Across 48 studies of people who underwent surgical reconstruction for CAUE between 0 and 18 years of age and completed patient-reported outcome measures, most reported favorable outcomes; however, participants in five studies (including children with RLD, duplicate thumb, and toe-to-hand transfer) reported persistent functional impairment [133].

Health professionals should recognize multiple strategies exist to manage limitations in activity performance and participation that may be acceptable to the child with CAUE including using other body parts (Fig. 6.2), activity modification, choosing varying levels of participation, receiving assistance from another, using assistive devices, or wearing a prosthesis [8]. Kelly et al. [12] suggested children with CAUE, as they get older, adapt to or accommodate for their unique upper limb difference, yet de Jong et al. [8] found health professionals may be less apt to recognize as many strategies as children with CAUE and their parents. Furthermore, health professionals may identify assistive devices and prosthetics more frequently as potential solutions for success in activity performance and increased participation [8]. In a qualitative study investigating perceptions of children 8–20 years of age with unilateral CBED, participants described their own activity performance and participation and generally reported no limitations. Further, these children reported similar levels of participation as peers without CBED. The researchers suggested, for children in this study, perceptions of activity participation may have been limited to actual chosen activities rather than potential chosen activities (activities that may have been chosen if participants had two hands) [8].

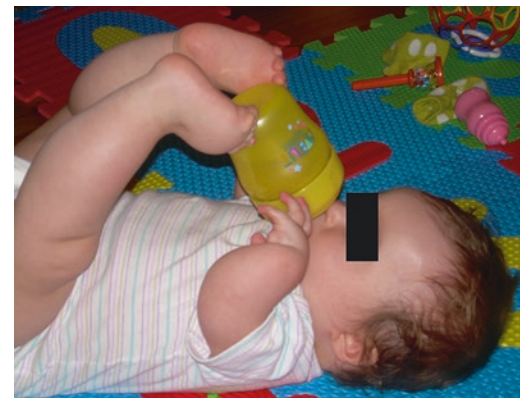

Fig. 6.2 This child with thrombocytopenia-absent radii has self-identified strategies for participation in activities

Diagnosis-Specific Intervention

Camptodactyly: Conservative Management

Range of Motion Exercise

While orthotic management and surgery are intervention options for camptodactyly [134], ROM exercises may prove beneficial especially for children with an infantile onset of deformity. Rhee et al. [135] retrospectively evaluated the effectiveness of passive stretching to correct flexion deformities in children younger than 3 years with camptodactyly. Records of children diagnosed with simple camptodactyly, who had not received surgery or intervention with an orthosis were included but those with flexion contractures of less than 10° were excluded. Parents were taught a PROM technique, to be implemented at home, requiring the PIP joint be extended with the wrist and metacarpophalangeal (MCP) joint in extension. Instructions were to complete gentle PROM, while the child was sleeping, 20 or more times per day with a hold time of 5 minutes. Exercise frequency was reduced to five or ten times per day when near-full extension was achieved. Duration of intervention was individualized and poorly defined. Pre- and post-intervention measurements, recorded by the same physician, were compared. Across groups, 13 males and 9 females with a mean age of 12 months (range 3–36 months) were included in the study. Digits were further classified into mild deformity (<30°, $n = 12$ digits), moderate deformity (30–60°, $n = 36$), and severe deformity (>60°, $n = 13$) as per goniometric measures. Groups were expected to be different with regard to the extent of deformity, but no analysis was performed to assure they were similar for age, sex, and dominance. Final PROM for PIP extension was compared to initial measures. Mean changes in PROM were as follows: −20° to −1° for the mild group, −39° to −12° for the moderate group, and −75° to −28° for the severe group. Differences from pretest to posttest were significant for all groups: mild ($p < 0.001$), moderate ($p < 0.001$), and severe ($p < 0.001$). Mean time from start to end of intervention (either correction or cessation of change) for the mild group was 5 months, moderate group was 10 months, and severe group 13 months. Researchers found a relationship between degree of flexion contracture at the start of intervention and final measure. No relationship was found between initial flexion contracture, handedness, digit involvement, and number of digits or hands involved. Differences between pretest and posttest AROM values were statistically significant. No statistical analysis was performed to determine clinical significance; however, all but two children (in the moderate group) improved and gains were maintained during a prolonged follow-up period (mean of 26 months, range of 12–47 months). The researchers concluded children under 3 who have camptodactyly should be treated with PROM only and orthoses are not necessary; however, this statement is unfounded since no comparison was made between PROM and use of an orthosis. The researchers recognized the weaknesses of the study including the use of retrospective design and the absence of a control group. The outcomes cannot be applied to all children with camptodactyly because only children under the age of 3 with simple syndactyly were studied, and children with syndromic or adolescent onset camptodactyly were not included [135].

Orthotics

In a descriptive case series, Hori et al. [136] evaluated the effectiveness of dynamic orthoses on increasing digital extension in 24 (34 fingers) children with camptodactyly. A Capener-type coil spring was applied initially for 24 hours per day and then only 8 hours per day during a maintenance period. Duration of treatment was individualized and not described. Measurement technique was unclear in 10 patients but an explicit statement regarding measurement was provided for 14 patients (21 fingers). The researchers noted "almost full correction" [136, p. 1062] in 14 patients (20 fingers). Eight patients (9 fingers) improved, three patient (3 fingers) were not improved, and two patients (2 fingers) worsened. Of the 14 patients (21 fingers) measured, mean flexion contracture before and after intervention was 40° and 10°, respectively.

Reoccurrence was noted in one patient. This study lacked a control group, randomization, and blinding. No statistical analysis was undertaken, thus limiting generalizations to the larger population. Significant bias is likely since for some patients, AROM may have been determined by visual observation alone.

Miura et al. [137] also examined the effectiveness of a dynamic orthoses on increasing digital extension but did so prospectively and included a larger sample than Hori et al. [136]. The study included children (n = 142) with non-traumatic flexion deformities. Of these, 62 had small finger involvement, 16 had small finger plus one or more other finger involvement, 41 had other finger involvement (not small finger), and 23 had syndromic camptodactyly. A dynamic orthosis (Capener-type coil spring) was applied to children with contracture of the small finger only for 24 hours per day, although only 12 hours per day for children under 7 years of age. During a maintenance period wear time was reduced. Outcomes were dichotomized into *failed to respond* or *responded* to treatment. Of 142 patients, only 5 failed to respond to treatment. Reoccurrence was observed in 2 patients. From this study alone no definitive statements can be made regarding treatment of children with camptodactyly using orthoses; however, given the number of patients who made gains, low-level evidence is offered [137]. Figure 6.3 depicts a serial static orthosis used to correct and improve joint motion in the context of camptodactyly.

Fig. 6.3 Orthosis for camptodactyly involving multiple digits

Contrary to the aforementioned studies, Netcher et al. [7] advocated for only 6–9 hours of nighttime use of an orthosis. Further, they recommended the use of a DIP, PIP, and MCP composite extension splint if the PIP joint cannot extend with the extrinsic flexor on slack, and an MCP flexion with PIP and DIP extension orthosis if the extrinsic flexors are too short [7]. Regarding the latter scenario, the orthosis could be progressively modified to achieve greater amounts of extrinsic flexor elongation while assuring the PIP joint remains extended.

Orthotics and PROM

Benson et al. [138] retrospectively evaluated the effectiveness of orthoses and PROM to conservatively treat camptodactyly across three subtypes involving the PIP joint. In this case series, in which only descriptive analysis was performed, researchers treated contracted digits of 18 patients (50 PIP joints) to promote PIP extension. Wear time for the orthosis ranged from 15 to 18 hours per day for infants and 10 to 12 hours per day for older children who were not inclined to sleep during the daytime. Parents performed daily PROM prior to application of the orthosis, although duration of treatment was individualized and poorly defined. Using goniometry, the same rater measured PROM before and after the intervention period. For analysis, children were assigned to one of three groups, including (1) infantile camptodactyly between the age of 0.3–2.3 years (n = 13 patients, 24 digits), (2) adolescent camptodactyly between the age of 14.5–17.0 years (n = 4 patients, 5 digits), and (3) syndromic camptodactyly between the age of 0.1–13.4 years (n = 5 patients, 30 digits). Full passive extension was achieved in 18 of 24 PIP joints for children with infantile camptodactyly. The group mean at start and end of treatment was −22.9° and end −4.3°, respectively. For children with adolescent onset of camptodactyly, only one (1 PIP joint) underwent a full program of orthosis wear and achieved full extension. Two others (2 PIP joints) elected surgery and worsened. The fourth patient (2 PIP joints) abandoned orthosis wear after 1 month and worsened. The group mean at start and end of treatment was −29.0°

and −32.0°, respectively. In the syndromic group, 4 patients (24 PIP joints) were treated with an orthosis and demonstrated a group mean at the start and end of treatment of −23.0° and −1.0°, respectively. Two patients elected surgery and gained motion; one achieved full extension in two of two PIP joints and the other achieved an average of 41° of improvement across four digits. This study suggests conservative management with an orthosis may be prudent prior to electing surgery and perhaps more so for patients who present with infantile camptodactyly; however, in the absence of a control group, randomization, blinding, long-term follow-up, and inferential statistical analysis, the outcomes are inconclusive [138].

Camptodactyly: Postoperative Management

In their systematic review of 16 studies reporting outcomes following conservative and surgical treatment of camptodactyly, Wang et al. [139] reported complications including loss of active flexion, joint stiffness, and worsening contracture. Rehabilitation following surgery will require scar management [7], orthotic management [7, 139, 140], and ROM [7, 139, 141]. Wall et al. [140] recommended orthosis wear for 6 weeks followed by nighttime wear for an additional 6 weeks, whereas Singh et al. [141] recommended 2–3 weeks of fulltime static orthosis wear followed by prolonged use of a nighttime orthosis. Netscher et al. [7] provided detailed tissue-specific recommendations for postoperative care, recognizing that rarely is only one structure implicated in camptodactyly. Recommendations included 4 weeks of orthosis use with the hand in the intrinsic plus position followed by scar management, stretching of volar soft tissue structures (e.g., skin, palmer plate), stretching of intrinsic and extrinsic muscles, and activation of intrinsic and extrinsic muscles. Following the postoperative orthosis, a three-point pressure orthosis or serial casting may be employed to better assure full PIP extension is achieved or maintained, and a relative motion orthosis or MCP extension block orthosis may be employed to facilitate greater active PIP extension [7].

Hypoplasia of the Thumb

Therapy interventions for children with thumb hypoplasia will vary depending upon the severity of involvement and surgical management. This section will include interventions for children undergoing surgical procedures for Grade IIIA hypoplasia including web deepening, stabilization of the MCP joint, and tendon transfers, and those for Grade IIIB, Grade IV, and Grade V including pollicization or free toe transfer.

Range of Motion

First Web Space Deepening, MCP Stabilization, Opponensplasty

At 6 weeks following abductor digiti minimi opponensplasty, supervised AROM and light activity is commenced [142, 143], with emphasis on opposition and palmer abduction, and PROM may commence 8 weeks following surgery [143] as well as resistive pinching [142] (Fig. 6.4). Taping of the index finger to the middle finger may help to promote opposition of the index to the thumb by restricting interdigital grip (also known as lateral prehension) between the index and middle finger; however, no studies have been located to verify the effectiveness of this strategy.

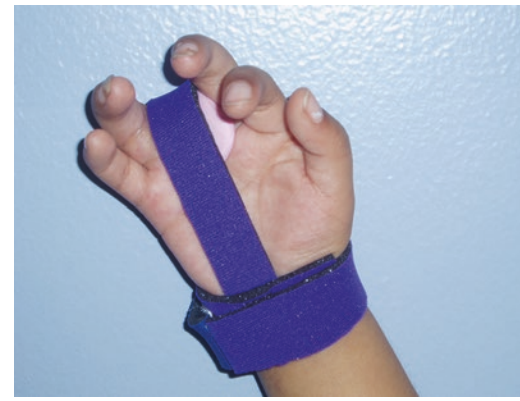

Fig. 6.4 Scar pad for web creep following syndactyly release

Pollicization or Free Toe Transfer

For pollicization and free toe transfer, Egerszegi [144] recommended initiation of AROM at 3–4 weeks and PROM 1–2 weeks later. Kozin [145] advocates for initiation of therapy at 4–5 weeks with thumb use progressing by first grasping large objects and advancing to precise pinch. More conservatively, Goldfarb et al. [143] recommended PROM not begin until 8 weeks following surgery. Roper and Turnbull [146] advocated for discouraging an interdigital grasp after pollicization. Taping of middle finger to the ring finger may encourage opposition of the pollicized index finger to the middle finger by restricting interdigital grip between the middle and ring fingers; however, no studies have located to verify the effectiveness of this strategy.

Orthotics

First Web Space Deepening, MCP Stabilization, Opponensplasty

Following abductor digiti minimi opponensplasty, the hand and wrist should be completely immobilized for 4–6 weeks, after which an orthosis is fabricated to maintain a wide, open first web space with the thumb in opposition and palmer abduction [142, 143]. de Roode et al. [142] specifically recommended a neoprene orthosis. Regardless of orthosis type, the orthosis should be worn continuously until the eighth postoperative week [142, 143] and removed for washing, with supervised activity and exercise. Goldfarb et al. [143] recommended discontinuing all orthoses 12 weeks following surgery, whereas de Roode et al. [142] recommended weaning orthosis wear to nighttime wear only, but did not indicate when or if the nighttime orthosis should be discontinued. Goldfarb et al. [143] recommended similar immobilization regardless of opponensplasty technique; however, Kozin and Ezaki [147] recommended a long arm thumb spica cast with the elbow in 90° of flexion for only 2–3 weeks after flexor digitorum superficialis opponensplasty. These authors did not indicate a need for a thermoplastic orthosis following cast removal.

Pollicization or Free Toe Transfer

Regarding pollicization, Egerszegi [144] recommended continuous immobilization for 3–4 weeks with a continuously worn thermoplastic orthosis replacing the post-surgical orthosis for an additional week followed by six more weeks of orthotic use at night and during vigorous activity. In the case of free toe transfer, a similar program of orthosis wear is indicated. Evidence of bony union signifies discontinuance of fulltime wear of an orthosis and transition to nighttime wear. Kozin [145] recommended a slightly longer duration of post-surgical immobilization of 4–5 weeks, with gradual weaning and discontinuance of the orthosis at 12 weeks. The orthosis should place the thumb in opposition and palmar abduction [143].

Radial Longitudinal Deficiency

Range of Motion Exercise

Children with RLD may have limitations in elbow motion in addition to wrist deformity [1, 148]. Brooks [2] recommended active and passive elbow ROM for 5–10 minutes, five times per day. In a series of 27 children with RLD and restriction in elbow flexion, Lamb [1] observed an increase in active elbow flexion for 20 children when an orthosis was applied to the wrist. Restricting wrist motion may facilitate greater active elbow motion by preventing a functional pattern of wrist radial deviation to bring the hand toward the trunk and face. Brooks [2] later cautioned practitioners to carefully weigh the benefit of increasing elbow motion with impeded functional use of the wrist.

Regarding the wrist, PROM alone may be indicated to preserve tissue length when the wrist can easily be brought into a neutral position. Bednar et al. [149] recommended passive stretch into ulnar deviation for 5–10 minutes, four to five times per day. If not passively correctable to neutral, the addition of orthotic management should be considered. Damore et al. [150] have recommended PROM only until 3 months of age at which time a nighttime only orthosis is introduced.

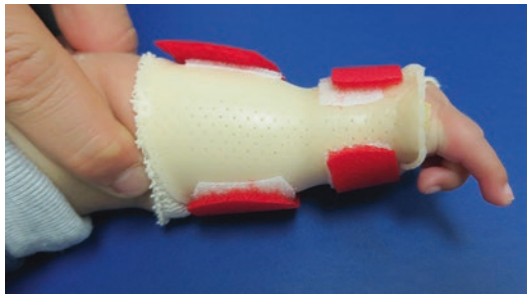

Fig. 6.5 Orthosis for RLD with thumb aplasia

Following centralization procedures, Goldfarb et al. [143] recommended digital ROM begin immediately and supervised light active use of the hand (out of the orthosis) by 6 weeks. Wrist range of motion (excluding passive radial deviation) may begin 6 months following surgery. Brooks [2] recommended earlier introduction of wrist AROM, at 6 weeks, and specifically recommended tendon gliding exercises.

Orthotics

Conservative management of RLD includes the use of a cast or orthosis (Fig. 6.5) to preserve or increase tissue length across the radial wrist and/or the elbow [1, 2, 151–153]. For children with functional flexion of the elbow, but with limitations in extension, applying an orthosis to preserve or increase elbow extension may be indicated, more so for the child with bilateral RLD [2].

The required duration of orthosis wear to achieve or approximate passive correction of the wrist will depend upon the degree of deformity and the load required to bring the wrist toward neutral; however, this may need to be balanced by time out of the orthosis for play exploration and maintenance of skin integrity. Children with RLD who undergo centralization of the ulna or other soft tissue procedures will require prolonged use of an orthosis pre- and postoperatively [1, 2, 14, 154, 155]. Many authors have recommended commencing with orthosis use or serial casting soon after birth and continuing until surgery [149–151, 154], which may need to continue until skeletal maturity. Postoperatively, an orthosis worn during the day serves to preserve the centralization or radialization, while an orthosis worn at night may be required to elongate the extrinsic digital flexors [2]. Fuller [152] recommended a wrist orthosis be applied radially, but cover 80% of both the volar and dorsal forearm. Kotwal et al. [14] proposed aggressive preoperative use of an orthosis to minimize the amount of tissue disruption and subsequent fibrosis that would otherwise contribute to further deforming forces on the wrist. Following centralization and 6–8 weeks of pinning and postoperative orthosis, Danmore et al. [150] employed fulltime orthosis use followed by weaning toward nighttime wear until skeletal maturity. Goldfarb et al. [143] recommended discontinuing use of the orthosis during the day by 6 months but continuing nighttime wear until skeletal maturity. For both centralization and radialization, and after 8–12 weeks of internal fixation and orthosis, Kotwal et al. [14] introduced fulltime use of an orthosis for 1 year followed by intermittent daytime use for an additional 1–2 years. No mention was made of nighttime use during this latter period.

Kennedy [156] reported outcomes after applying an orthosis to correct excessive radial deviation and minimize soft tissue reconstruction during corrective surgery, or to maintain or improve correction postoperatively. In this case series, children with RLD who were using an orthosis were treated preoperatively ($n = 5$) or postoperatively ($n = 4$). Each child received a custom-fabricated neoprene orthosis with thermoplastic reinforcement to centrally align the hand to the carpus and wore the orthosis fulltime. Duration of treatment for the preoperative group ranged from 3 weeks to 6 months to achieve correction, whereas duration of treatment for the postoperative group ranged from 6 weeks to 2 years to achieve correction. Wrist alignment was the desired outcome but the measurement technique was not described. For the preoperative group, all children obtained a neutral wrist with four children achieving 90°and one 45° of improvement. For the postoperative group, mean correction of residual deformity in three children was 30°.

Correction was maintained in the fourth child. The author reported subjective observations of improved activity participation (with the orthosis on) including the use of cutlery and tying shoelaces. This study lacked a control group, randomization, blinding, use of objective repeatable measures, and statistical analysis, but thoroughly described an orthosis and provided descriptive outcomes for a small group of children with RLD [156].

Assistive Technology

Holtslag [4] examined participation levels among adults with mild and severe RLD using the Impact on Participation and Autonomy Questionnaire (IPAQ). No significant differences were noted between the groups, and both groups exhibited good levels of participation (median IPAQ score of 2.4), with a score of zero being very good and a score of four being poor. Some participants in this study indicated a need for activity modification or assistive device to perform fastening of buttons, squeezing a tube of toothpaste, carrying heavy objects, and cutting food. In a series of 117 patients with RLD, Lamb [1] noted no functional impairment for children with unilateral RLD, but for those with bilateral impairment, fastening buttons, cutting meat, combing hair, and putting on socks proved difficult. Buffart et al. [15] also identified specific activities found to be difficult for children with RLD including fastening buttons, spreading jam, donning gloves, and cutting firm textured foods. These are important activities to practice with children with RLD. Additionally, children with RLD may desire to explore assistive devices or alternative strategies to maximize activity participation.

Syndactyly: Postoperative Management

Complications following syndactyly release include scar formation, web creep, rotational and angular deformities, and limitations in AROM [157–162] for which ROM, application of an orthosis, and scar management may be indicated [162].

Range of Motion Exercise

Fuller [152] recommended parents be taught PROM following syndactyly release. Extension deficits can be managed using an orthosis, while limitations in active flexion might be better managed with combined PROM and AROM during the day.

Orthotics

Goldfarb et al. [162] noted patterns of deformity following syndactyly release for children with complex syndactyly not related to a syndrome or other CAUE, including a trend for the released digit to rotate away from and deviate toward the previously adjoined digit. After postoperative dressings and immobilization have been discontinued, a thermoplastic orthosis may be indicated to maintain the MCP joints in abduction, to correct an extension deficit, or to align the digits along the horizontal and frontal planes [163]. Fuller [152] recommended a static forearm-based orthosis with elevation of the material between adjacent digits and individual finger straps, whereas Moran and Tomhave [164] recommended a hand-based orthosis with individual finger straps.

Scar Management

Scar management options may be narrowed since children with syndactyly often undergo release during the infant or toddler years, and so choice of modality must include products less likely to pose a choking hazard. For this reason, a pressure garment with Silon sewn into the garment may prove useful for young children, whereas gel or elastomer could be held in place with self-adherent elastic wrap for older children.

Trigger Thumb: Conservative Management

Baek and Lee [165] conducted a prospective observational study of 71 trigger thumbs in 53 children whose mean age when diagnosed was 2 years with a mean flexion contracture of 26°. These children were followed for 49 months. Forty-five of 71 thumbs (63%) spontaneously

resolved. In a systematic review of operative and nonoperative (orthosis or stretching) management of trigger thumb, Farr et al. [166] noted better rates of improvement in patients who underwent A1 pulley release; however, the researchers noted that the majority of those treated had locked interphalangeal joints. To identify practice patterns, Marek [167] surveyed pediatric hand surgeons, and of the 27 respondents, 52% indicated they would observe a 2-year-old child with intermittent triggering without pain, whereas the remaining would pursue orthotic management, surgery, or injection. For these reasons, children with intermittent trigger thumb are often observed or offered conservative treatment, including ROM and application of an orthosis.

Range of Motion Exercise

Three groups of researchers [168–170] investigated PROM as a conservative treatment for trigger thumb. In a prospective, case series, Wantabe et al. [168] described 58 thumbs in 46 children treated with daily passive extension exercises only. Thumbs were identified as: Stage 0, no trigger or flexion posture; Stage 1, locking, active movement with triggering; Stage 2, locking, passive movement with triggering; or Stage 3, locked. A satisfactory result was noted in 96% of cases at follow-up (mean 44 months), while complete recovery was noted in 27% of thumbs at follow-up (mean 62 months). A cure rate of 80% was reported for Stage 2 thumbs at follow-up (mean 56 months) and 25% for Stage 3 thumbs at follow-up (mean 68 months). The cure rate for initial Stage 2 thumbs was significantly higher than for initial Stage 3 thumbs ($p < 0.05$) [168]. In a similar prospective, consecutive case series, Jung et al. [169] examined treatment with PROM only in 30 children ($n = 35$ thumbs). Passive range of motion was applied 10–20 times per day. Digits were categorized as: Grade OA, extension beyond 0° without triggering; Grade OB, extension to 0° without triggering; Grade 1 active extension with triggering; Grade 2 passive extension with triggering; and Grade 3, locked. Before treatment, thumbs were identified as: Grade 1 thumbs 6 thumbs (17%); 25 thumbs (71%); 3 thumbs (25%). Post-test results were: Grade OA, 7 thumbs (20%); Grade OB, 25 thumbs (21%); Grade I, 5 thumbs (14%); Grade II, 2 thumbs (6%); and No change = 1 thumb. The researchers found children with bilateral trigger thumb and children with a Grade III thumb were more likely to have an unfavorable outcome. Given this, PROM seems useful for Grades 1 and 2, but may not be useful for Grade 3 trigger thumb. Additionally, PROM may be useful to correct deformity but triggering may persist [169]. These studies provide limited to moderate support for use of PROM to reduce triggering and improve motion for children with trigger thumb. In a retrospective study, Forlin et al. [170] evaluated outcomes for 11 children (13 thumbs) whose parents were asked to stretch the thumb if persistent flexion was noted. Upon follow-up, at a mean of 10 years, there was full correction in 7 thumbs, partial correction in 3 thumbs, and no correction in 3 thumbs. Of those with unsatisfactory results, the age of diagnosis was greater than 30 months, whereas satisfactory results (total or partial improvement) were observed in two patients diagnosed at greater than 30 months and eight patients were diagnosed before 24 months.

Orthotics

Three studies have described the effectiveness of orthoses to treat trigger thumb with varying outcomes [171, 172]. Koh et al. [171] conducted a retrospective, non-randomized, controlled study by reviewing medical records of children with locked interphalangeal (IP) joint. Parents self-selected whether to have their child wear an orthosis ($n = 26$) or undergo observation alone ($n = 38$). Children receiving a custom-made, coil orthosis to hold the IP joint in extension while preventing hyperextension of the MCP joint wore the orthosis at night. Duration of treatment or observation was individualized until either resolution was achieved or surgery was indicated. The targeted outcome was full AROM of the thumb IP joint without snapping, but no measurement technique was described. Of patients treated with an orthosis, 24 (92%) experienced complete resolution within 22 months, whereas 23 (60%) in the observation group had complete

resolution in 59 months. After an additional 11 months, 14 more patients in the observation group experienced resolution of snapping. All patients in both groups experienced complete resolution, but four (two from each group) required surgery due to continued snapping. Those receiving an orthosis had significantly higher rates of resolution ($p < 0.05$) and shorter resolution time ($p < 0.01$) compared to observation alone. This study suggests patients with locked trigger thumbs who wear a coil orthosis may have faster rates of resolution compared to those receiving no treatment [171]. Using a similar design, Lee et al. [172] compared treatment with an orthosis to observation alone for management of trigger thumb. In this non-randomized, non-blinded, and case-controlled study, parents of children self-selected to receive an orthosis ($n = 31$ thumbs) or be observed ($n = 31$ thumbs). An orthosis maintaining the MCP joint and IP joint in extension was custom-fabricated from thermoplastic for patients in the orthosis group and was to be worn all day for 6–12 weeks in the child's usual environments. The orthosis was worn at night only once active extension was achieved. Mean duration of treatment was 11.7 weeks ±6.6 weeks. The outcome classification was cured (full AROM), improved (full AROM with snapping less than once per week), or non-improved (persistent flexion deformity or surgery was requested). Regarding AROM, no measurement technique was described. In the group that received an orthosis, 12 were cured, 10 were improved, and nine were non-improved. In the observation alone group, 4 were cured, 3 were improved, and 24 were nonimproved. The difference between the groups was statistically significant ($p < 0.05$). Response rates were 71% for the orthosis group and 23% for the observation alone group [172]. In a study that included trigger thumbs ($n = 40$) and fingers ($n = 3$), Nemoto et al. [173] placed a polyethylene orthosis on the involved interphalangeal joint at night and during naps to hold the joint in maximum extension. Of the participants who remained in the study (8 participants, 10 digits, dropped out), 24 digits recovered completely and 7 digits improved. These studies provide limited support for use of an orthosis to manage trigger thumb when conservative treatment is desired.

References

1. Lamb DW. Radial club hand. A continuing study of sixty-eight patients with one hundred and seventeen club hands. J Bone Joint Surg Am. 1977;59(1):1–13.
2. Brooks C. Rehabilitation of radial club hand. Tech Hand Up Extrem Surg. 1998;2(1):78–85.
3. Lake A. Hand therapy for children with congenital hand differences. Tech Hand Up Extrem Surg. 2010;14(2):78–84.
4. Holtslag I, van Wijk I, Hartog H, van der Molen AM, van der Sluis C. Long-term functional outcome of patients with longitudinal radial deficiency: cross-sectional evaluation of function, activity and participation. Disabil Rehabil. 2013;35(16):1401–7.
5. Carlsson IK, Dahlin LB, Rosberg HE. Congenital thumb anomalies and the consequences for daily life: patients' long-term experience after corrective surgery. A qualitative study. Disabil Rehabil. 2018;40(1):69–75.
6. Goodell PB, Bauer AS, Oishi S, Arner M, Laurell T, Taylor SL, et al. Functional assessment of children and adolescents with symbrachydactyly: a unilateral hand malformation. J Bone Joint Surg Am. 2017;99(13):1119–28.
7. Netscher DT, Staines KG, Hamilton KL. Severe camptodactyly: a systematic surgeon and therapist collaboration. J Hand Ther. 2015;28(2):167–74; quiz 75.
8. de Jong IG, Reinders-Messelink HA, Tates K, Janssen WG, Poelma MJ, van Wijk I, et al. Activity and participation of children and adolescents with unilateral congenital below elbow deficiency: an online focus group study. J Rehabil Med. 2012;44(10):885–92.
9. Bae DS, Canizares MF, Miller PE, Waters PM, Goldfarb CA. Functional impact of congenital hand differences: early results from the Congenital Upper Limb Differences (CoULD) Registry. J Hand Surg Am. 2018;43(4):321–30.
10. Blair WF, Shurr DG, Buckwalter JA. Functional status in ulnar deficiency. J Pediatr Orthop. 1983;3(1):37–40.
11. Wall LB, Shen T, Roberts S, Goldfarb CA. Parental assessment of status of congenital upper limb differences: analysis of the pediatric outcomes data collection instrument. J Hand Surg Am. 2016;41(3):381–6.e1.
12. Kelley BP, Franzblau LE, Chung KC, Carlozzi N, Waljee JF. Hand function and appearance following reconstruction for congenital hand differences: a qualitative analysis of children and parents. Plast Reconstr Surg. 2016;138(1):73e–81e.

13. Ardon MS, Janssen WG, Hovius SE, Stam HJ, Selles RW. Low impact of congenital hand differences on health-related quality of life. Arch Phys Med Rehabil. 2012;93(2):351–7.
14. Kotwal PP, Varshney MK, Soral A. Comparison of surgical treatment and nonoperative management for radial longitudinal deficiency. J Hand Surg Eur Vol. 2012;37(2):161–9.
15. Buffart LM, Roebroeck ME, Janssen WG, Hoekstra A, Selles RW, Hovius SE, et al. Hand function and activity performance of children with longitudinal radial deficiency. J Bone Joint Surg Am. 2008;90(11):2408–15.
16. Ekblom AG, Dahlin LB, Rosberg HE, Wiig M, Werner M, Arner M. Hand function in children with radial longitudinal deficiency. BMC Musculoskelet Disord. 2013;14:116.
17. Ekblom AG, Dahlin LB, Rosberg HE, Wiig M, Werner M, Arner M. Hand function in adults with radial longitudinal deficiency. J Bone Joint Surg Am. 2014;96(14):1178–84.
18. Goering S. Rethinking disability: the social model of disability and chronic disease. Curr Rev Musculoskelet Med. 2015;8(2):134–8.
19. Anastasiou D, Kauffman JM. The social model of disability: dichotomy between impairment and disability. J Med Philos. 2013;38(4):441–59.
20. Ho E, Clarke H. Functional evaluation in children with congenital upper extremity malformations. Clin Plast Surg. 2005;32(4):471–83, v.
21. Ashworth S. Physical examination of the pediatric upper extremity. In: Absug J, Kozin S, Neiduski R, editors. Pediatric hand therapy. Philadelphia: Elsevier; 2020. p. 25–30.
22. Vauclair F, Aljurayyan A, Abduljabbar FH, Barimani B, Goetti P, Houghton F, et al. The smartphone inclinometer: a new tool to determine elbow range of motion? Eur J Orthop Surg Traumatol. 2018;28(3):415–21.
23. Macionis V. A technique of direct tracing for recording digital range of motion. J Hand Surg Am. 2008;33(4):612–4.
24. Macdermid JC, Fox E, Richards RS, Roth JH. Validity of pulp-to-palm distance as a measure of finger flexion. J Hand Surg Br. 2001;26(5):432–5.
25. de Kraker M, Selles RW, Schreuders TA, Hovius SE, Stam HJ. The Pollexograph: a new device for palmar abduction measurements of the thumb. J Hand Ther. 2009;22(3):271–6; quiz 7.
26. de Kraker M, Selles RW, Molenaar TM, Schreuders TA, Hovius SE, Stam HJ. Palmar abduction measurements: reliability and introduction of normative data in healthy children. J Hand Surg Am. 2009;34(9):1704–8.
27. Cornett KM, North KN, Rose KJ, Burns J. Muscle weakness in children with neurofibromatosis type 1. Dev Med Child Neurol. 2015;57(8):733–6.
28. Sloan C. Review of the reliability and validity of myometry with children. Phys Occup Ther Pediatr. 2002;22(2):79–93.
29. Lavelle K, Breger Stanton D. Measurement of edema in the hand. In: MacDermid J, editor. Clinical assessment recommendations. 3rd ed. Mount Laurel: American Society of Hand Therapists; 2015. p. 71–80.
30. Beltramini A, Milojevic K, Pateron D. Pain assessment in newborns, infants, and children. Pediatr Ann. 2017;46(10):e387–e95.
31. Strauch B, Lang A, Ferder M, Keyes-Ford M, Freeman K, Newstein D. The ten test. Plast Reconstr Surg. 1997;99(4):1074–8.
32. Strauch B, Lang A. The ten test revisited. Plast Reconstr Surg. 2003;112(2):593–4.
33. Iba K, Takayama S, Kawabata H, Horii E, Kazuki K. Assessment of hand function using the functional dexterity test after opponensplasty in young children with Blauth type 2 hypoplastic thumb. J Pediatr Orthop B. 2020;
34. Soucie JM, Wang C, Forsyth A, Funk S, Denny M, Roach KE, et al. Range of motion measurements: reference values and a database for comparison studies. Haemophilia. 2011;17(3):500–7.
35. Barad JH, Kim RS, Ebramzadeh E, Silva M. Range of motion of the healthy pediatric elbow: cross-sectional study of a large population. J Pediatr Orthop B. 2013;22(2):117–22.
36. Da Paz SN, Stalder A, Berger S, Ziebarth K. Range of motion of the upper extremity in a healthy pediatric population: introduction to normative data. Eur J Pediatr Surg. 2016;26(5):454–61.
37. Hager-Ross C, Rosblad B. Norms for grip strength in children aged 4-16 years. Acta Paediatr. 2002;91(6):617–25.
38. Kocher MH, Oba Y, Kimura IF, Stickley CD, Morgan CF, Hetzler RK. Allometric grip strength norms for American children. J Strength Cond Res. 2019;33(8):2251–61.
39. Bowman OJ, Katz B. Hand strength and prone extension in right-dominant, 6 to 9 year olds. Am J Occup Ther. 1984;38(6):367–76.
40. Fullwood D. Australian norms for hand and finger strength of boys and girls aged 5-12 years. Aust Occup Ther J. 1986;33(1):26–37.
41. De Smet L, Vercammen A. Grip strength in children. J Pediatr Orthop B. 2001;10(4):352–4.
42. Holm I, Fredriksen P, Fosdahl M, Vollestad N. A normative sample of isotonic and isokinetic muscle strength measurements in children 7 to 12 years of age. Acta Paediatr. 2008;97(5):602–7.
43. Ploegmakers JJ, Hepping AM, Geertzen JH, Bulstra SK, Stevens M. Grip strength is strongly associated with height, weight and gender in childhood: a cross sectional study of 2241 children and adolescents providing reference values. J Physiother. 2013;59(4):255–61.
44. Mathiowetz V, Wiemer DM, Federman SM. Grip and pinch strength: norms for 6- to 19-year-olds. Am J Occup Ther. 1986;40(10):705–11.
45. Ager CL, Olivett BL, Johnson CL. Grasp and pinch strength in children 5 to 12 years old. Am J Occup Ther. 1984;38(2):107–13.

46. Lee-Valkov PM, Aaron DH, Eladoumikdachi F, Thornby J, Netscher DT. Measuring normal hand dexterity values in normal 3-, 4-, and 5-year-old children and their relationship with grip and pinch strength. J Hand Ther. 2003;16(1):22–8.
47. De Smet L, Decramer A. Key pinch force in children. J Pediatr Orthop B. 2006;15(6):426–7.
48. Surrey LR, Hodson J, Robinson E, Schmidt S, Schulhof J, Stoll L, et al. Pinch strength norms for 5-to 12-year-olds. Phys Occup Ther Pediatr. 2001;21(1):37–49.
49. Cope EB, Antony JH. Normal values for the two-point discrimination test. Pediatr Neurol. 1992;8(4):251–4.
50. Hermann RP, Novak CB, Mackinnon SE. Establishing normal values of moving two-point discrimination in children and adolescents. Dev Med Child Neurol. 1996;38(3):255–61.
51. Dua K, Lancaster TP, Abzug JM. Age-dependent reliability of Semmes-Weinstein and 2-point discrimination tests in children. J Pediatr Orthop. 2019;39(2):98–103.
52. Mathiowetz V, Federman S, Wiemer D. Box and block test of manual dexterity: norms for 6–19 year olds. Can J Occup Ther. 1985;52(5):241.
53. Jongbloed-Pereboom M, Nijhuis-van der Sanden MW, Steenbergen B. Norm scores of the box and block test for children ages 3-10 years. Am J Occup Ther. 2013;67(3):312–8.
54. Gogola GR, Velleman PF, Xu S, Morse AM, Lacy B, Aaron D. Hand dexterity in children: administration and normative values of the functional dexterity test. J Hand Surg Am. 2013;38(12):2426–31.
55. Smith YA, Hong E, Presson C. Normative and validation studies of the Nine-hole Peg Test with children. Percept Mot Skills. 2000;90(3 Pt 1):823–43.
56. Poole JL, Burtner PA, Torres TA, McMullen CK, Markham A, Marcum ML, et al. Measuring dexterity in children using the Nine-hole Peg Test. J Hand Ther. 2005;18(3):348–51.
57. Wang YC, Bohannon RW, Kapellusch J, Garg A, Gershon RC. Dexterity as measured with the 9-Hole Peg Test (9-HPT) across the age span. J Hand Ther. 2015;28(1):53–9; quiz 60.
58. Wilson BC, Iacoviello JM, Wilson JJ, Risucci D. Purdue Pegboard performance of normal preschool children. J Clin Neuropsychol. 1982;4(1):19–26.
59. Skerik SK, Weiss MW, Flatt AE. Functional evaluation of congenital hand anomalies. Am J Occup Ther. 1971;25(2):98–104.
60. Ho E, Clarke H. Upper extremity function in children with congenital hand anomalies. J Hand Ther. 2005;18:352–64.
61. Buffart LM, Roebroeck ME, Pesch-Batenburg JM, Janssen WG, Stam HJ. Assessment of arm/hand functioning in children with a congenital transverse or longitudinal reduction deficiency of the upper limb. Disabil Rehabil. 2006;28(2):85–95.
62. Buffart LM, Roebroeck ME, Janssen WG, Hoekstra A, Hovius SE, Stam HJ. Comparison of instruments to assess hand function in children with radius deficiencies. J Hand Surg Am. 2007;32(4):531–40.
63. Percival NJ, Sykes PJ, Chandraprakasam T. A method of assessment of pollicisation. J Hand Surg Br. 1991;16(2):141–3.
64. Kollitz KM, Tomhave WA, Van Heest AE, Moran SL. A new, direct measure of thumb use in children after index pollicization for congenital thumb hypoplasia. J Hand Surg Am. 2018;43(11):978–86.e1.
65. Zlotolow DA, Tosti R, Ashworth S, Kozin SH, Abzug JM. Developing a pollicization outcomes measure. J Hand Surg Am. 2014;39(9):1784–91.
66. Arnould C, Penta M, Renders A, Thonnard JL. ABILHAND-Kids: a measure of manual ability in children with cerebral palsy. Neurology. 2004;63(6):1045–52.
67. Krumlinde-Sundholm L, Holmefur M, Kottorp A, Eliasson AC. The Assisting Hand Assessment: current evidence of validity, reliability, and responsiveness to change. Dev Med Child Neurol. 2007;49(4):259–64.
68. Holmefur M, Krumlinde-Sundholm L, Eliasson AC. Interrater and intrarater reliability of the Assisting Hand Assessment. Am J Occup Ther. 2007;61(1):79–84.
69. Holmefur M, Aarts P, Hoare B, Krumlinde-Sundholm L. Test-retest and alternate forms reliability of the assisting hand assessment. J Rehabil Med. 2009;41(11):886–91.
70. Louwers A, Krumlinde-Sundholm L, Boeschoten K, Beelen A. Reliability of the Assisting Hand Assessment in adolescents. Dev Med Child Neurol. 2017;59(9):926–32.
71. Young NL, Williams JI, Yoshida KK, Wright JG. Measurement properties of the activities scale for kids. J Clin Epidemiol. 2000;53(2):125–37.
72. Pruitt SD, Varni JW, Setoguchi Y. Functional status in children with limb deficiency: development and initial validation of an outcome measure. Arch Phys Med Rehabil. 1996;77(12):1233–8.
73. Skold A, Hermansson LN, Krumlinde-Sundholm L, Eliasson AC. Development and evidence of validity for the Children's Hand-use Experience Questionnaire (CHEQ). Dev Med Child Neurol. 2011;53(5):436–42.
74. Amer A, Eliasson AC, Peny-Dahlstrand M, Hermansson L. Validity and test-retest reliability of Children's Hand-use Experience Questionnaire in children with unilateral cerebral palsy. Dev Med Child Neurol. 2016;58(7):743–9.
75. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Med Care. 2001;39(8):800–12.
76. Schlenz AM, Schatz J, McClellan CB, Roberts CW. Responsiveness of the PedsQL to pain-related changes in health-related quality of life in pediatric sickle cell disease. J Pediatr Psychol. 2012;37(7):798–807.

77. Haley S, Coster W, Faas R. A content validity study of the Pediatric Evaluation of Disability Inventory. Pediatr Phys Ther. 1991;3:177–84.
78. Feldman AB, Haley SM, Coryell J. Concurrent and construct validity of the Pediatric Evaluation of Disability Inventory. Phys Ther. 1990;70(10):602–10.
79. Wright F, Boschen K. The Pediatric Evaluation of Disability Inventory (PEDI): validation of a new functional assessment outcome instrument. C J Rehab. 1993;7:41–2.
80. Nichols D, Case-Smith J. Reliability and validity of the Pediatric Evaluation of Disability Inventory. Pediatr Phys Ther. 1996;8:41–2.
81. Daltroy LH, Liang MH, Fossel AH, Goldberg MJ. The POSNA pediatric musculoskeletal functional health questionnaire: report on reliability, validity, and sensitivity to change. Pediatric Outcomes Instrument Development Group. Pediatric Orthopaedic Society of North America. J Pediatr Orthop. 1998;18(5):561–71.
82. Pencharz J, Young NL, Owen JL, Wright JG. Comparison of three outcomes instruments in children. J Pediatr Orthop. 2001;21(4):425–32.
83. Amor CJ, Spaeth MC, Chafey DH, Gogola GR. Use of the Pediatric Outcomes Data Collection Instrument to evaluate functional outcomes in arthrogryposis. J Pediatr Orthop. 2011;31(3):293–6.
84. Haynes RJ, Sullivan E. The Paediatric Orthopaedic Society of North America Paediatric Orthopaedic Functional Health Questionnaire: an analysis of normal. J Pediatr Orthop. 2001;21(5):619–21.
85. Wright FV, Hubbard S, Jutai J, Naumann S. The Prosthetic Upper Extremity Functional Index: development and reliability testing of a new functional status questionnaire for children who use upper extremity prostheses. J Hand Ther. 2001;14(2):91–104.
86. Bagley AM, Molitor F, Wagner LV, Tomhave W, James MA. The Unilateral Below Elbow Test: a function test for children with unilateral congenital below elbow deficiency. Dev Med Child Neurol. 2006;48(7):569–75.
87. Kaplan JD, Jones NF. Outcome measures of microsurgical toe transfers for reconstruction of congenital and traumatic hand anomalies. J Pediatr Orthop. 2014;34(3):362–8.
88. Netscher DT, Aliu O, Sandvall BK, Staines KG, Hamilton KL, Salazar-Reyes H, et al. Functional outcomes of children with index pollicizations for thumb deficiency. J Hand Surg Am. 2013;38(2):250–7.
89. Ardon MS, Selles RW, Roebroeck ME, Hovius SE, Stam HJ, Janssen WG. Poor agreement on health-related quality of life between children with congenital hand differences and their parents. Arch Phys Med Rehabil. 2012;93(4):641–6.
90. Sheffler LC, Hanley C, Bagley A, Molitor F, James MA. Comparison of self-reports and parent proxy-reports of function and quality of life of children with below-the-elbow deficiency. J Bone Joint Surg Am. 2009;91(12):2852–9.
91. Koskimies E, Lindfors N, Gissler M, Peltonen J, Nietosvaara Y. Congenital upper limb deficiencies and associated malformations in Finland: a population-based study. J Hand Surg Am. 2011;36(6):1058–65.
92. Ekblom AG, Laurell T, Arner M. Epidemiology of congenital upper limb anomalies in 562 children born in 1997 to 2007: a total population study from Stockholm, Sweden. J Hand Surg Am. 2010;35(11):1742–54.
93. Froster-Iskenius UG, Baird PA. Limb reduction defects in over one million consecutive livebirths. Teratology. 1989;39(2):127–35.
94. Evans JA, Vitez M, Czeizel A. Congenital abnormalities associated with limb deficiency defects: a population study based on cases from the Hungarian Congenital Malformation Registry (1975-1984). Am J Med Genet. 1994;49(1):52–66.
95. Baker RP, Field J, Gozzard C, Wyatt MC, Robertson Y. Does postoperative hand elevation reduce swelling? A randomized study. J Hand Surg Eur Vol. 2010;35(3):192–4.
96. Fagan DJ, Evans A, Ghandour A, Prabhkaran P, Clay NR. A controlled clinical trial of postoperative hand elevation at home following day-case surgery. J Hand Surg Br. 2004;29(5):458–60.
97. Enos L, Lane R, MacDougal BA. Brief or new: the use of self-adherent wrap in hand rehabilitation. Am J Occup Ther. 1984;38(4):265–6.
98. Lowell M, Pirc P, Ward RS, Lundy C, Wilhelm DA, Reddy R, et al. Effect of 3M Coban Self-Adherent Wraps on edema and function of the burned hand: a case study. J Burn Care Rehabil. 2003;24(4):253–8; discussion 2.
99. Miller LK, Jerosch-Herold C, Shepstone L. Effectiveness of edema management techniques for subacute hand edema: a systematic review. J Hand Ther. 2017;30(4):432–46.
100. Widgerow AD, Chait LA, Stals PJ, Stals R, Candy G. Multimodality scar management program. Aesthetic Plast Surg. 2009;33(4):533–43.
101. Foo CW, Tristani-Firouzi P. Topical modalities for treatment and prevention of postsurgical hypertrophic scars. Facial Plast Surg Clin North Am. 2011;19(3):551–7.
102. Shin DH, Bohn DK, Agel J, Lindstrom KA, Cronquist SM, Van Heest AE. Hand function with touch screen technology in children with normal hand formation, congenital differences, and neuromuscular disease. J Hand Surg Am. 2015;40(5):922–7. e1
103. Khansa I, Harrison B, Janis JE. Evidence-based scar management: how to improve results with technique and technology. Plast Reconstr Surg. 2016;138(3 Suppl):165S–78S.
104. Chang LW, Deng WP, Yeong EK, Wu CY, Yeh SW. Pressure effects on the growth of human scar fibroblasts. J Burn Care Res. 2008;29(5):835–41.
105. Costa AM, Peyrol S, Porto LC, Comparin JP, Foyatier JL, Desmouliere A. Mechanical forces induce scar remodeling. Study in non-pressure-

treated versus pressure-treated hypertrophic scars. Am J Pathol. 1999;155(5):1671–9.
106. Anzarut A, Olson J, Singh P, Rowe BH, Tredget EE. The effectiveness of pressure garment therapy for the prevention of abnormal scarring after burn injury: a meta-analysis. J Plast Reconstr Aesthet Surg. 2009;62(1):77–84.
107. Steinstraesser L, Flak E, Witte B, Ring A, Tilkorn D, Hauser J, et al. Pressure garment therapy alone and in combination with silicone for the prevention of hypertrophic scarring: randomized controlled trial with intraindividual comparison. Plast Reconstr Surg. 2011;128(4):306e–13e.
108. Engrav LH, Heimbach DM, Rivara FP, Moore ML, Wang J, Carrougher GJ, et al. 12-Year within-wound study of the effectiveness of custom pressure garment therapy. Burns. 2010;36(7):975–83.
109. Sharp PA, Pan B, Yakuboff KP, Rothchild D. Development of a best evidence statement for the use of pressure therapy for management of hypertrophic scarring. J Burn Care Res. 2016;37(4):255–64.
110. Wiseman J, Ware RS, Simons M, McPhail S, Kimble R, Dotta A, et al. Effectiveness of topical silicone gel and pressure garment therapy for burn scar prevention and management in children: a randomized controlled trial. Clin Rehabil. 2020;34(1):120–31.
111. Nedelec B, De Oliveira A, Calva V, Couture MA, Poulin C, LaSalle L, et al. Longitudinal evaluation of pressure applied by custom fabricated garments worn by adult burn survivors. J Burn Care Res. 2020;41(2):254–62.
112. Widgerow AD, Chait LA. Scar management practice and science: a comprehensive approach to controlling scar tissue and avoiding hypertrophic scarring. Adv Skin Wound Care. 2011;24(12):555–61.
113. Hart RG, Wolff TW, O'Neill WL Jr. Preventing tourniquet effect when dressing finger wounds in children. Am J Emerg Med. 2004;22(7):594–5.
114. Yelvington M, Brown S, Castro MM, Nick TG. The use of neoprene as a scar management modality. Burns. 2013;39(5):866–75.
115. Sawada Y, Sone K. Hydration and occlusion treatment for hypertrophic scars and keloids. Br J Plast Surg. 1992;45(8):599–603.
116. de Oliveira GV, Nunes TA, Magna LA, Cintra ML, Kitten GT, Zarpellon S, et al. Silicone versus nonsilicone gel dressings: a controlled trial. Dermatol Surg. 2001;27(8):721–6.
117. O'Brien L, Pandit A. Silicone gel sheeting for preventing and treating hypertrophic and keloid scars. Cochrane Database Syst Rev. 2006;(1):CD003826.
118. O'Brien L, Jones DJ. Silicone gel sheeting for preventing and treating hypertrophic and keloid scars. Cochrane Database Syst Rev. 2013;(9):CD003826.
119. Wang F, Li X, Wang X, Jiang X. Efficacy of topical silicone gel in scar management: a systematic review and meta-analysis of randomised controlled trials. Int Wound J. 2020;17(3):765–73.
120. Widgerow AD. Cellular/extracellular matrix cross-talk in scar evolution and control. Wound Repair Regen. 2011;19(2):117–33.
121. Rustad KC, Wong VW, Gurtner GC. The role of focal adhesion complexes in fibroblast mechanotransduction during scar formation. Differentiation. 2013;86(3):87–91.
122. Aarabi S, Bhatt KA, Shi Y, Paterno J, Chang EI, Loh SA, et al. Mechanical load initiates hypertrophic scar formation through decreased cellular apoptosis. FASEB J. 2007;21(12):3250–61.
123. Chiquet M, Gelman L, Lutz R, Maier S. From mechanotransduction to extracellular matrix gene expression in fibroblasts. Biochim Biophys Acta. 2009;1793(5):911–20.
124. Atkinson JA, McKenna KT, Barnett AG, McGrath DJ, Rudd M. A randomized, controlled trial to determine the efficacy of paper tape in preventing hypertrophic scar formation in surgical incisions that traverse Langer's skin tension lines. Plast Reconstr Surg. 2005;116(6):1648–56; discussion 57–8.
125. Michlovitz SL, Harris BA, Watkins MP. Therapy interventions for improving joint range of motion: a systematic review. J Hand Ther. 2004;17(2):118–31.
126. Glasgow C, Tooth LR, Fleming J. Mobilizing the stiff hand: combining theory and evidence to improve clinical outcomes. J Hand Ther. 2010;23(4):392–400. quiz 1
127. Flowers KR. A proposed decision hierarchy for splinting the stiff joint, with an emphasis on force application parameters. J Hand Ther. 2002;15(2):158–62.
128. Weeks P, Wray R. Management of acute hand injuries. 2nd ed. St. Louis: Mosby; 1978.
129. Flowers KR, LaStayo P. Effect of total end range time on improving passive range of motion. J Hand Ther. 1994;7(3):150–7.
130. Glasgow C, Wilton J, Tooth L. Optimal daily total end range time for contracture: resolution in hand splinting. J Hand Ther. 2003;16(3):207–18.
131. Glasgow C, Fleming J, Tooth LR, Peters S. Randomized controlled trial of daily total end range time (TERT) for Capener splinting of the stiff proximal interphalangeal joint. Am J Occup Ther. 2012;66(2):243–8.
132. Valdes K, Boyd JD, Povlak SB, Szelwach MA. Efficacy of orthotic devices for increased active proximal interphalangeal extension joint range of motion: a systematic review. J Hand Ther. 2019;32(2):184–93.
133. Bickham RS, Waljee JF, Chung KC, Adkinson JM. Postoperative patient- and parent-reported outcomes for children with congenital hand differences: a systematic review. Plast Reconstr Surg. 2017;139(6):1422–9.
134. Ty JM, James MA. Failure of differentiation: part II (arthrogryposis, camptodactyly, clinodactyly, madelung deformity, trigger finger, and trigger thumb). Hand Clin. 2009;25(2):195–213.
135. Rhee SH, Oh WS, Lee HJ, Roh YH, Lee JO, Baek GH. Effect of passive stretching on simple campto-

dactyly in children younger than three years of age. J Hand Surg Am. 2010;35(11):1768–73.
136. Hori M, Nakamura R, Inoue G, Imamura T, Horii E, Tanaka Y, et al. Nonoperative treatment of camptodactyly. J Hand Surg Am. 1987;12(6):1061–5.
137. Miura T, Nakamura R, Tamura Y. Long-standing extended dynamic splintage and release of an abnormal restraining structure in camptodactyly. J Hand Surg Br. 1992;17(6):665–72.
138. Benson LS, Waters PM, Kamil NI, Simmons BP, Upton J 3rd. Camptodactyly: classification and results of nonoperative treatment. J Pediatr Orthop. 1994;14(6):814–9.
139. Wang AMQ, Kim M, Ho ES, Davidge KM. Surgery and conservative management of camptodactyly in pediatric patients: a systematic review. Hand. 2019;15(6):761–70.
140. Wall LB, Ezaki M, Goldfarb CA. Camptodactyly treatment for the lesser digits. J Hand Surg Am. 2018;43(9):874.e1–4.
141. Singh V, Haq A, Priyadarshini P, Kumar P. Camptodactyly: an unsolved area of plastic surgery. Arch Plast Surg. 2018;45(4):363–6.
142. de Roode CP, James MA, McCarroll HR Jr. Abductor digit minimi opponensplasty: technique, modifications, and measurement of opposition. Tech Hand Up Extrem Surg. 2010;14(1):51–3.
143. Goldfarb C, Calhoun V, Daily L, Manske P. Hand and upper extremity therapy: congenital, pediatric, adolescent. St Louis protocols. St. Louis Shriner's Hospital for Children; 2011.
144. Egerszegi EP. Reconstruction of congenital hand anomalies to provide stable pinch and/or grasp: case pictorial series. J Pediatr Rehabil Med. 2009;2(3):173–9.
145. Kozin SH. Pollicization: the concept, technical details, and outcome. Clin Orthop Surg. 2012;4(1):18–35.
146. Roper BA, Turnbull TJ. Functional assessment after pollicisation. J Hand Surg Br. 1986;11(3):399–403.
147. Kozin SH, Ezaki M. Flexor digitorum superficialis opponensplasty with ulnar collateral ligament reconstruction for thumb deficiency. Tech Hand Up Extrem Surg. 2010;14(1):46–50.
148. Manske PR, Goldfarb CA. Congenital failure of formation of the upper limb. Hand Clin. 2009;25(2):157–70.
149. Bednar MS, James MA, Light TR. Congenital longitudinal deficiency. J Hand Surg Am. 2009;34(9):1739–47.
150. Damore E, Kozin SH, Thoder JJ, Porter S. The recurrence of deformity after surgical centralization for radial clubhand. J Hand Surg Am. 2000;25(4):745–51.
151. Banskota AK, Bijukachhe B, Rajbhandary T, Pradhan I, Singh A. Radial club hand deformity – the continuing challenges and controversies. Kathmandu Univ Med J (KUMJ). 2005;3(1):30–4.
152. Fuller M. Treatment of congenital differences of the upper extremity: Therapist's commentary. J Hand Ther. 1999;12(2):174–7.
153. Butts DE, Goldberg MJ. Congenital absence of the radius: the occupational therapist and a new orthosis. Am J Occup Ther. 1977;31(2):95–100.
154. VanHeest A. Wrist centralization using the dorsal rotation flap in radial longitudinal deficiency. Tech Hand Up Extrem Surg. 2010;14(2):94–9.
155. Wall LB, Ezaki M, Oishi SN. Management of congenital radial longitudinal deficiency: controversies and current concepts. Plast Reconstr Surg. 2013;132(1):122–8.
156. Kennedy SM. Neoprene wrist brace for correction of radial club hand in children. J Hand Ther. 1996;9(4):387–90.
157. Muzaffar AR, Rafols F, Masson J, Ezaki M, Carter PR. Keloid formation after syndactyly reconstruction: associated conditions, prevalence, and preliminary report of a treatment method. J Hand Surg Am. 2004;29(2):201–8.
158. Deunk J, Nicolai JP, Hamburg SM. Long-term results of syndactyly correction: full-thickness versus split-thickness skin grafts. J Hand Surg Br. 2003;28(2):125–30.
159. Lumenta DB, Kitzinger HB, Beck H, Frey M. Long-term outcomes of web creep, scar quality, and function after simple syndactyly surgical treatment. J Hand Surg Am. 2010;35(8):1323–9.
160. Vekris MD, Lykissas MG, Soucacos PN, Korompilias AV, Beris AE. Congenital syndactyly: outcome of surgical treatment in 131 webs. Tech Hand Up Extrem Surg. 2010;14(1):2–7.
161. Mallet C, Ilharreborde B, Jehanno P, Litzelmann E, Valenti P, Mazda K, et al. Comparative study of 2 commissural dorsal flap techniques for the treatment of congenital syndactyly. J Pediatr Orthop. 2013;33(2):197–204.
162. Goldfarb CA, Steffen JA, Stutz CM. Complex syndactyly: aesthetic and objective outcomes. J Hand Surg Am. 2012;37(10):2068–73.
163. Pehnke M, Schmieg S, Shah A. Congenital-syndactyly. In: Abzug J, Kozin S, Neiduski R, editors. Pediatric hand therapy. Philadelphia: Elsevier; 2020. p. 93–107.
164. Moran S, Tomhave W. Management of congenital hand anomalies. In: Skirven T, O'sterman A, Fedorzyk J, Amadio P, editors. Rehabilitation of the hand and upper extremity. 6th ed. Philadelphia: Elsevier Mosby; 2011. p. 1631–50.
165. Baek GH, Lee HJ. The natural history of pediatric trigger thumb: a study with a minimum of five years follow-up. Clin Orthop Surg. 2011;3(2):157–9.
166. Farr S, Grill F, Ganger R, Girsch W. Open surgery versus nonoperative treatments for paediatric trigger thumb: a systematic review. J Hand Surg Eur Vol. 2014;39(7):719–26.
167. Marek DJ, Fitoussi F, Bohn DC, Van Heest AE. Surgical release of the pediatric trigger thumb. J Hand Surg Am. 2011;36(4):647–52.e2.
168. Watanabe H, Hamada Y, Toshima T, Nagasawa K. Conservative treatment for trigger thumb in children. Arch Orthop Trauma Surg. 2001;121(7):388–90.

169. Jung HJ, Lee JS, Song KS, Yang JJ. Conservative treatment of pediatric trigger thumb: follow-up for over 4 years. J Hand Surg Eur Vol. 2012;37(3):220–4.
170. Forlin E, Kaetsu EY, de Vasconcelos JE. Success of conservative treatment of trigger thumb in children after minimum follow-up of five years. Rev Bras Ortop. 2012;47(4):483–7.
171. Koh S, Horii E, Hattori T, Hiroishi M, Otsuka J. Pediatric trigger thumb with locked interphalangeal joint: can observation or splinting be a treatment option? J Pediatr Orthop. 2012;32(7):724–6.
172. Lee ZL, Chang CH, Yang WY, Hung SS, Shih CH. Extension splint for trigger thumb in children. J Pediatr Orthop. 2006;26(6):785–7.
173. Nemoto K, Nemoto T, Terada N, Amako M, Kawaguchi M. Splint therapy for trigger thumb and finger in children. J Hand Surg Br. 1996;21(3):416–8.

7 Visible Distinctions and Congenital Anomalies of the Upper Extremities: Psychological Considerations

Sondra E. Solomon

You came so nearly perfect from the hand of nature that this slightest possible defect, which we hesitate whether to term a defect or a beauty, shocks me as being the visible mark of earthly imperfection. [1]

In most cultures physical perfection is the standard by which a person's competence, intelligence, and humanity are assessed [2–5]. Visible attributes that challenge physical perfection are not well-tolerated by normal-appearing others [3]. When a person possesses a visible attribute that does not conform to a narrowly defined metric of appearance acceptability, the bearer of that negatively valued visible attribute may be at risk for social exclusion, prejudice, discrimination, and stigma by perceived normal-appearing others [6–8]. Furthermore, when the visible attribute in question is determined by genetic or medical factors, psychological well-being may be affected [9].

Early consensus in the psychological literature suggested that individuals with visible atypical body or facial attributes would always be at a social disadvantage, since in addition to managing their own appearance-related thoughts, feelings and behaviors, they had to manage the reactions of normal-appearing others toward their appearance [10]. Contemporary research acknowledges the complex interactions of individual, social, and cultural factors that shape the experiences and psychological well-being of individuals with atypical visible features [8, 11]. Facial appearance has been at the forefront of this research, and, at first blush, it is easy to understand why disruptions in facial appearance receive so much consideration. The face is a primary vehicle of human communication, and individuals make immediate judgments about others based on facial appearance. When facial integrity is disrupted, social interaction is disrupted [7, 12]. However, the hands and arms have salient cultural meaning as well. The hands and arms are essential for (1) interacting with and manipulating the physical world, (2) communicating with others, and (3) establishing and maintaining intimate physical contact with others. Like the face, the hands and arms are difficult to conceal. Disruptions in the appearance of hands and arms have the potential to affect psychological well-

Editor's Note Sondra Solomon was born with neurofibromatosis. The reaction by some to her physical disfigurement led her to her scholarly study of the role of physical stigma in society. Her contribution to this book reflects both her scholarly work and her personal struggle. She passed away recently of an unrelated disease, but this chapter is published in the second edition in her memory. DL

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being, yet there is limited research on the psychological functioning of individuals living with visible characteristics associated with congenital anomalies of the upper extremities (CAUE).

Definitions

In an effort to promote psychological well-being among individuals living with CAUE, it might be useful to re-evaluate the words we use to describe the population. The language we use to describe the people we treat has the potential to foster a strong therapeutic alliance as we work toward promoting long-term positive adjustment and psychological well-being for our patients. It is suggested that those who serve individuals living with CAUE employ the terminology offered in the following section. When possible and appropriate, these terms will be used throughout this chapter.

Distinction

The term *distinction* will be used when referring to what the CAUE literature has characterized as aberrant, deformed, disfigured, defective, deficient, malformed, and abnormal attributes. The term *distinction* is relatively benign and can be substituted for the pejorative and negative labels that describe the visible characteristics of CAUE that affect appearance. It is recognized that some authors prefer the term *physical difference* [11, 13]; however, *distinction* is a relatively neutral word and is an appropriate descriptor for a visibly and culturally devalued attribute related to appearance.

Impairment and Disability

Most readers familiar with genetics, rehabilitation, and disability literature will recognize the following definitions; however, it is useful to mention them again. *Impairment* is linked to a loss or a disruption of an anatomical structure or function and can be biologically determined or acquired via a disease process during a person's life, and d*isability* is the consequence of the impairment and involves any restriction in the person's ability to perform an activity in the manner or within the range considered appropriate for individuals without the impairment [14–17]. Disability is the physical consequence of the impairment and is linked to how the impairment is manifested in the culture (i.e., the child with a congenital below the elbow anomaly has difficulty with motor function). The term *handicap* or *social handicap* should only be used when one considers how the person with the impairment is treated in the culture (i.e., the adult with a congenital below the elbow impairment is denied housing or employment due to processes that involve prejudice, exclusion, and discrimination).

Stigma and Stigmatization

Erving Goffman [18] began a discourse spanning 50 years, transforming the way we examine how human beings manage the minute and salient differences between us. These differences place most people in two camps based on various personal characteristics and attributes. People can join and/or be excluded from the two camps based on where they happen to be at the time (cultural context) and which attributes are valued at the time (temporal salience). Also, it may be possible for a person to be a member of both camps at the same time. Undesirable attributes may be fixed and unquestionable (e.g., congenital disorders, facial distinctions, excessive weight, cognitive deficits, old age, ethnicity, disability, diagnoses of severe and/or chronic psychopathology, perceived to be engaged in non-normative behavior, etc.). Other attributes may be may be less so (e.g., maturity, material wealth).

Goffman defined *stigma* as a spoiled identity or a deeply discrediting characteristic which may arise from physical deformities; blemishes of individual character that are interpreted to reflect weakness, unnatural passions, and dishonesty; and one's lineage [18]. Possession of the devalued attribute or distinction places the affected individual at a social disadvantage. One early

model to explain this disadvantaged social status suggests that stigma is a form of deviance that leads perceived normal-appearing others to judge individuals with the stigma as unworthy for participation in most social interchanges. They are viewed as incompetent, unpredictable, unreliable, or threatening [19]. This perception places the individual beyond the protection of a number of implicit norms that regulate social interaction. The disruptive impact of the distinction may be a function of how visible the distinction is to others, how much of the person's body is affected by the distinction, and how easily the distinction can be identified or seen by others [19, 20].

Researchers have been trying to understand and deconstruct the various processes contributing to devalued identities and subsequent spoiled interactions that devolve from possession of or contact with the undesirable attribute. Some have noted that it is difficult to identify a single defining feature of stigma and suggest that stigmatized people are believed to possess a feature, quality, or trait that portrays a social identity that is devalued in a particular social context [21]. In this view, stigma arises from one's membership in a group or category that is negatively valued in a specific situation (i.e., the adolescent with a below the elbow congenital anomaly is unable to participate in an activity in the same way that adolescents without the congenital anomaly).

Stigmatization may be conceptualized as a social process that seeks to reproduce inequality and exclusion [22–25]. There is an interaction between the environment and the individual with the distinction to recreate and perpetuate social and structural inequalities [25, 26]. Individuals with a devalued visible attribute may experience rejection, discrimination, and exclusion, and these experiences have the potential to shape psychological, cognitive, and affective responses that affirm or impede healthy behaviors and psychological well-being [5].

Visible Distinctions and Stigma

An accepted definition of a *visible distinction* is that the attribute in question represents a departure from a culturally defined norm which is difficult to conceal from others, and as a result, the attribute has the potential to shape interpersonal interaction with perceived normal-appearing others [27]. The attribute is perceived by others to be atypical, non-normative, and noticeable and excludes those attributes that are consistent with a body dysmorphic presentation [11, 27]. A *visible distinction* can have a powerful influence on the affected individual. A *visible distinction* is a social disability, since in addition to influencing the thoughts, feelings, and behavior of the person with the visible distinction, it is also likely to shape the behavior of other people toward the affected individual [28, 29]. Research suggests that the extent to which a visible distinction results in social disability involves a complex interaction of social and individual factors [8, 11, 30]. We live in a culture that emphasizes physical perfection, and individuals who possess visible attributes that are devalued occupy a special role in the culture, and this role places them at a distinct advantage. The narrowly defined cultural appearance standard dictates who is accepted and who gets cast aside.

Stigma, Stigmatization, and Coping with Visible Distinctions

The stigmatized person is diminished in the eyes of the observer and may experience a variety of stressors. A stressor is an event in which environmental or internal demands tax or exceed the adaptive resources of the individual [31]. Stigma can increase demands on the affected individual because perceived normal individuals may hold stereotyped expectancies about what stigmatized people are like, harbor prejudiced attitudes toward stigmatized people, and behave in a discriminatory manner toward stigmatized people [32, 33]. Psychological responses such as anger, anxiety, hopelessness, resentment, and fear [3–5, 31, 34] may be experienced by the affected individual.

Visible distinctions are particularly stigmatizing because they remind the observer that the body is fragile and depending on the etiology of

the distinction may compel the observer to feel less compassion toward the individual with the distinction and to attribute more blame to them for having the distinction [35–37]. Children, adolescents, and adults living with CAUE frequently have visible attributes involving variations of limb formation, differentiation, duplication, overgrowth, and undergrowth, congenital constriction band syndrome, generalized skeletal irregularities, and comorbid facial irregularities [38]. Distinctions, such as those that can occur in CAUE, are particularly stigmatizing because the actual social identity – the attribute the individual possesses – does not meet society's normative expectations of the attribute the individual should possess [26]. Social identity is flawed, and the affected individual is presumed unable to fulfill the basic requirements of social interaction. Physical perfection is the gold standard for social inclusion. Social exclusion and subsequent threats to psychological well-being may be inevitable if the devalued attribute is visible and involves the hands and arms.

Psychological Research on Visible Distinctions Associated with CAUE

Investigators have begun to explore how individuals adapt to a variety of stigmatizing attributes (e.g., diabetes, cancer, altered body appearance, HIV) [8, 39–42]. An excellent review of the processes involved in managing visible distinctions acknowledged that successful outcomes are linked to (1) the individual's perception of the visible distinction, (2) their self-concept, (3) perceived and actual social support, (3) cultural contexts, (4) interpersonal encounters with others, (4) and the social skills they employ to manage difficult social encounters [11]. While this review was useful for a general understanding of psychological adjustment for those with visible distinctions (e.g., burns, dermatological disorders, and cleft palate), there was little to offer regarding those living with CAUE.

The broad spectrum of CAUE is rare but not entirely infrequent disorders with a prevalence of 6.5–21.5 cases per 10,000 births [43]. They represent complex and variable pathologies with regard to the clinical severity of symptom presentation [44]. Some CAUE present in isolation, and others present with associated systemic disorders and skeletal discrepancies [45]. Classification systems for the CAUE have been previously described [38, 45, 46]; however the taxonomy endorsed by the International Federation of Societies for Surgery of the Hand is widely accepted [47, 48]. CAUE can be diagnosed in utero, at birth, or during early childhood, and decisions regarding surgical intervention vary depending on the presentation of the specific genetic condition.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA) [49] criteria were followed in an attempt to identify studies on psychological sequelae for individuals living with visible distinctions related to CAUE. Articles published as of August 2013 in English using literature searches of PubMed, Web of Science, and PsycINFO were sought. Searches were conducted using the literature terms upper extremity congenital anomalies, limb deficiencies, and hand and arm, in conjunction with one or more of the following key terms: psychosocial, adjustment, coping, well-being, quality of life, and appearance. It was difficult to identify empirical studies published during the past decade in which psychological well-being, coping, and adjustment to CAUE appearance-related concerns were the primary outcome variable.

The preponderance of the research, energy, and attention on CAUE has focused on neonates, children, adolescents, and families. Most studies have been concerned with the timing of the surgery during childhood, surgical intervention, or post-surgical satisfaction [50–53] and longer-term functional outcomes [54–59]. There are few studies on adults living with CAUE [60–64].

Children and Adolescents Living with a CAUE

Some studies have demonstrated that living with a CAUE has an effect on the child's and adoles-

cent's psychological well-being across several domains including self-esteem, internalizing behaviors (e.g., depression), and social interaction [65–69]. For example, one study of 66 children and adolescents living with a CAUE fitted with a myoelectric prosthetic hand reported that there were higher levels of withdrawn behavior for all children and adolescents living with a CAUE compared to a normative sample and that females living with a CAUE reported lower social interaction competence when compared their male counterparts [65]. This finding is not surprising given the prevailing negative cultural attitudes toward visible physical distinctions which are particularly salient for females.

Recently, participation in day-to-day activities and quality of life (QOL) have received attention in the literature on successful outcomes for children and adolescents living with a CAUE. Participation and quality of life can be viewed as proxy measures for psychological well-being. Participation is the extent to which an individual is involved in various life situations and may include, but not limited to, the cultural context or attitudes of community members, family interest in recreation, and the affected individual's personal characteristics (e.g., gender and social competence) [70]. QOL refers to an individual's perceptions of their position in life within cultural and value systems in which they live and in relation to their goals and expectations. QOL has been used in lieu of psychological symptomology; QOL can comprise physical, psychological, spiritual, environmental, and interpersonal domains [71].

Depending on the severity of the disorder, it may be presumed that children and adolescents with CAUE may be at risk for limited participation in social activities and report poor quality of life and psychological well-being, yet the literature reports inconsistent findings. A recent narrative review of 15 cross-sectional studies of children and adolescents with congenital limb deficiencies noted that the literature lacks sufficient information to support or refute this presumption and further acknowledged that while full participation and enhanced QOL are considered the main goals in pediatric rehabilitation, the literature provides limited empirical data on how children and adolescents with CAUE participate and how they view their QOL [70]. These authors also note that while some of the studies in their review used sound psychometric measures, most studies used small sample sizes and employed descriptive, exploratory, and cross-sectional research designs [70]. They also reported that direct comparison between the studies was difficult due to age range (2–20 years) and lack of knowledge regarding the heterogeneity of CAUE [70]. A 2012 qualitative study [72] of 42 children and adolescents between the ages of 8 and 20 years with unilateral congenital below the elbow deficiencies (UCBED) found the majority of respondents did not report limitations in self-care, school, or recreational activities. While older respondents reported difficulties with novel social encounters, they were attributed to restrictions placed on them by their school or work environment and not to appearance-related concerns [72].

The experience of living with a visible distinction associated with a CAUE during adolescence has not been thoroughly examined. Research on the social psychology of facial appearance has documented that conditions that threaten appearance may place the adolescent at risk for psychosocial and interpersonal challenges [73]. Studies examining the significance of visible distinctions on psychological well-being have emphasized a number of psychosocial challenges, including those related to social interaction [8], the potential impact of negative self-perceptions on the development of the self-concept [74], and the ability to initiate and maintain romantic relationships [73]. A recent study acknowledged that poor psychological adjustment, specifically internalizing behaviors (e.g., depression), and poor health-related QOL were predicted by the adolescent's reports of perceived stigmatization (e.g., absence of friendly behavior, staring, hostile behavior) [75]. Yet, another study reported positive adjustments to visible facial distinctions [76] and noted that protective factors (e.g., positive self-schemas, strong family ties, and external social supports) could counteract appearance-related distress. While it is encouraging to report

these findings, it is distressing that the question of whether an adolescent living with a CAUE is more or less likely to experience psychological distress during this developmental period remains unanswered. Perhaps CAUE-related visible distinctions may also result in similar outcomes.

Adults Living with a CAUE

There are a few studies on adults living with CAUE or on aging with CAUE. Case studies and reports on physical function are common [60–63]. One study commissioned by the Thalidomide Trust [60] reviewed the current health status and psychosocial sequelae of adults living with the consequences of thalidomide in the United Kingdom. Of the 400 adults living with Thalidomide-related difficulties in the UK, merely 12 men and 16 women participated in this study. The authors acknowledged these participants were married or had partners and many were employed and reported good QOL and did not define themselves as disabled [60]. While these findings are encouraging, it is difficult to determine if other adults would offer similar reports given the study's small and biased sample size. Furthermore, this study did not examine the appearance-related concerns related to living with a visible distinction.

Parental Coping and the Child with CAUE

Parental coping and adjustment to the birth of a child with a CAUE is an emotional family event [77]. Parental adjustment to the distinction and associated medical, financial, social, and emotional demands may place enormous stressors on the family system [78, 79]. Parents face multiple challenges involving the management of grief-related emotions, finding an appropriate way to communicate with their children, and making appropriate medical decisions [72]. Immediate and longer-term factors contributing to the level of family distress may include but not necessarily be limited to (1) the extent and severity of the impairment and visibility of the distinction, (2) preexisting parental coping strategies, (3) the family's economic and psychological resources, (3) prevailing cultural attitudes toward the appearance of the child, and (4) the developmental age of the child [80, 81].

Visible distinctions associated with CAUE may sometimes bias or otherwise impede a parent or caregiver's ability to effectively bond with their child [82, 83]. A successful transition through the first year of life characterized by bonding and parental affection and consistency in care are necessary conditions for the development of a child's sense of separate and valued self and for the development of positive self-esteem [84, 85]. Researchers exploring the interactions between family adjustment and the presence of a child with a visible distinction have noted that parents have reported heightened distress levels and that parental psychological well-being prior to may be related to long-term psychological well-being adjustment [86]; however, it should be noted that findings are not consistent across studies due to inconsistencies in methodological approaches, small sample sizes, and scant longitudinal data. Such an approach may permit the development of integrated interventions within a biosocial medical model to improve functioning within this population.

Directions for Future Research

The research on the psychosocial sequelae of individuals living with visible distinctions associated with CAUE is limited, and findings are inconsistent. CAUE research energy and attention has centered on children, adolescents, and families. Data on the transition between adolescence to the early adult years is not evident. Data on adults coping with visible distinctions associated with CAUE are modest, and few investigators have made coping with CAUE in across the lifespan a priority. For adults living with a CAUE case studies or the personal narrative within the context of overcoming adversity prevails. Perhaps there is a presumption that the adult with a CAUE would have few, if any, appearance-related con-

cerns because child and adolescent issues have been resolved and the adult should have "gotten over it by now." Published studies are hindered by the lack of psychometrically validated measures and methodological approaches that were descriptive or qualitative. It is also noted that sufficient funding to support basic, clinical/translational research and clinical intervention trials is limited. While there is a need for high-quality research in this area, we should not be discouraged. The open landscape offers an opportunity to develop a research agenda with an eye toward intervention.

We know from the extensive literature on psychological difficulties associated with facial appearance that the most common problems affected individuals encounter relate to negative self-perceptions, anticipatory anxiety regarding negative evaluations by others, and difficulties with social interactions [27]. Also, in contrast to early research examining the difficulties that individuals with visible facial distinctions encounter, investigators are devoting attention to the factors associated with adaptive coping strategies that affected individuals employ to manage a frequently hostile and unpredictable social landscape. The extensive literature on coping with stigmatizing attributes (e.g., obesity, HIV/AIDS) [25, 42, 87, 88] may provide some direction as well.

Coping has been defined as cognitive, emotional, and behavioral strategies individuals employ to manage a variety of stressful experiences [31]. One coping model proposes two key responses: engagement and disengagement coping [89, 90]. Engagement coping can best be described by behaviors that engage with the stressful situation and/or by responses that help the individual to adapt to the stressful situation [42]. For example, the individual with a below the elbow anomaly may be confronted by persistent and unwelcome inquiries about his or her appearance. In response to these questions, the affected individual may have at the ready a repertoire of responses to offer the curious observer. Disengagement coping involves responses that distance the individual from the stressor and includes avoidance, denial, and/or wishful thinking [42]. In this instance the affected individual may avoid social encounters or engage in ruminative thoughts about his/her visible distinction.

Prior research also has demonstrated that the stigma associated with HIV poses various psychological challenges to people living with HIV and that the consequences of stigma-related stressors on psychological well-being depend on the ability of affected individuals to employ engagement coping strategies [42, 91]. The stigma associated with CAUE appearance-related stigma may similarly pose psychological challenges to individuals living with visible distinctions associated with these anomalies, yet little is known about these processes. It may be useful to employ stress and coping models to inform future research.

Researchers might examine the relationship between reports of appearance-related stigma, coping strategies used to manage the stigmatizing events, and associated psychological outcomes (e.g., depression, anxiety, anxiety sensitivity, resilience). What is the role of severity and visibility of the visible distinction? Are severity and visibility predictors of psychological difficulty? Are there risk or protective factors that may enhance positive outcomes? Are women, older adults, and members of under-represented groups (e.g., African Americans, Latino/s, economically disadvantaged) at greater risk? What is the role of social support, family, and cultural context in the management of CAUE appearance-related stigma?

Investigators should use normative groups of similarly aged individuals without a CAUE or compare findings to the reports of a first-degree relative (e.g., same gendered non-affected sibling). Reliable and valid instruments to measure coping, perceptions of appearance-related stigma, and psychological outcomes must be used. Longitudinal studies would also be beneficial.

These factors should be considered in future research protocols. Findings from this preliminary wave of research may inform appropriate interventions.

Some Closing Comments and a Personal Story: It's Not About Me

The opportunity to write about the psychosocial aspects of living with a visible distinction associated with CAUE brought to mind my experience as a clinical psychologist, researcher, professor, and woman who lives with a genetic disorder and comorbid visible distinctions. Neurofibromatosis 1 (NF1), von Recklinghausen's disorder, or peripheral NF is one of several autosomal dominant neuro-cutaneous disorders caused by mutations of the gene on chromosome 17 (17q11.2) responsible for cell division [92]. Prevalence of NF1 is approximately 1 in 3500 live births, and the disorder is highly random or variable regarding the clinical severity of symptom presentation [93, 94].

Clinical expressions of NF1 include café au lait spots, hamartomas (Lisch nodules), neurofibromas (Schwann cell tumors of four types, focal or diffuse cutaneous, subcutaneous, spinal, and nodular or diffuse plexiform), optic gliomas, freckling in the axillary or inguinal regions, and distinctive bone lesions [92]. Common complications in individuals with NF1 are cognitive and learning disabilities [95]. While general intellectual functioning may be intact, identifiable and explicit cognitive deficits have been acknowledged among some affected individuals (e.g., perception, attention, executive functioning, language functions, learning disabilities, and visuospatial deficits) [96]. Surgical interventions to ameliorate or manage tumor growth have been reported in the literature. For example, surgical excision of plexiform neurofibromas of the face is complex and may require several medical interventions to debulk tumor growth; however, the cosmetic result is sometimes disappointing [97–99]. Also, individuals with NF1 are followed by various medical and mental health specialists (e.g., neurologists, neurosurgeons, ophthalmologists, orthopedic surgeons, reconstructive surgeons, genetic counselors, special educators, social workers, physical therapists, psychiatrists, neuropsychologists, psychologists, social workers) to manage symptoms, problems, or multiple impediments.

While most NF1 tumors are benign, some individuals experience psychological distress as a result of the distinctive appearance associated with multiple visible tumors. Why mention NF1 in a chapter devoted to CAUE? Individuals living with CAUE and NF1 may share some appearance-related concerns due to the visible distinctions associated with each disorder. I thought it would be useful to provide readers of this chapter with a firsthand account of what it is like to live with a visible distinction with an eye toward enriching clinical practice and research.

During my second year of doctoral training at the University of Vermont, I was enrolled in a seminar in Community Clinical Psychology. On the first day of class, we were asked to answer the following question: What is important to know about you? While not a fan of the "ice-breaker exercise," when it was my turn, I complied and told my story. I said that I grew up in a housing project in New York City, in Northeast Bronx. When I was a young girl, New York City housing projects were transitional housing for the upwardly mobile working class of the late 1950s and early 1960s. The Bronx River Housing Project was a diverse community of Europeans, African Americans, Latinos, South Americans, Pacific East Islanders, and Asians. Of course, we did not call ourselves by those names back then (we were Negro, Jew, Oriental, Irish, Italian, Greek, French, German, etc.). One day my father and mother announced to my sister and me that he had bought a home and we were going to move from Northeast Bronx to Riverdale. Riverdale was and remains an upscale residential community in Northwest Bronx. We were one of the first families of color to move to the area. To this day I do not know how my father was able to gather the financial resources to purchase a home for his family. At the time he worked for City of New York and earned $75.00 to $100.00 a week. I told the class that my father inspired me and continues to inspire me. He never said these words to me explicitly, but the implicit message that my father's behavior modeled for me was that as long as you are alive, you can do, shape, or change anything. As long as you have a goal, a dream, and a neuron firing in your skull, you can achieve a vision. Your life condition does not

matter. Your economic status, appearance privilege, weight, or age does not matter. As long as you can move and think, you can shape a plan and implement that plan. I told the class that was the reason I decided to return to graduate school to become a psychologist when I was 41 years old. I told the class that the most important thing to know about me was that I was resilient.

Later that evening, a friend and fellow student called me. He said that he was baffled by the story I told in class, asked why I told that story, and wondered why I didn't talk about my NF. While I told the students in that seminar a story about me, what they wanted to hear is a story about my appearance. When people meet me, they want to know: "What are those things on your skin?" "Why do you look like that?" "What is wrong with you?"

Individuals with visible distinctions must answer these questions every day. Parents have to answer these questions for their children. These questions are part of the stressors that individuals with visible distinctions encounter. More often than not, individuals with visible distinctions have to make it easier for others to engage in social encounters. The burden of initiating and maintaining the social encounter is on the shoulders of the individual with the visible distinction. Perceived normal-appearing others ask questions that reduce their anxiety or personal curiosity. The bearer of a visible distinction is frequently in the spotlight, on display, and under public scrutiny.

When asked about my visible distinction, I must be ready to provide an answer. Children *always* receive my full attention and compassion because children are curious, and it is good practice to let them know that individuals who do not look like them should not be feared or avoided. The reader should know that I have encountered well-meaning individuals who said, "Sondra, I can't imagine how you do it." Others have said, "I can't imagine what I would do if I looked like you." As I listen to the familiar refrain, I imagine they are waiting for me to share some special magical life skill I possess to manage my visible distinction related to NF1. I used to engage in lengthy conversation with people. I noticed that when they were sufficiently satisfied with my answer, they would walk away. Now, when I am asked that question, I respond with a smile and say, "Yes, I imagine you can't." This response is my attempt to ally with the person who is confused and anxious about my appearance. This response shifts the burden away from me and directs it toward the person who was compelled to break the social contract. The question is not about me at all but is about the anxiety, fragility, and vulnerability experienced by normal-appearing others when they encounter children, adolescents, and adults who do not look like them. This response is part of a number of engagement coping strategies that I employ to deflect the slings and arrows of outrageous fortune that are part and parcel of living in a culture that demands perfection.

References

1. Hawthorne N. The birthmark. Mosses from an old manse. New York: Wiley and Putnam; 1846.
2. Sheridan J, Scior K. Attitudes towards people with intellectual disabilities: a comparison of young people from British South Asian and White British backgrounds. Res Dev Disabil. 2013;34(4):1240–7. PubMed PMID: WOS:000316532700016. English.
3. Kurzban R, Leary MR. Evolutionary origins of stigmatization: the functions of social exclusion. Psychol Bull. 2001;127(2):187–208. PubMed PMID: ISI:000170928000001.
4. MacDonald G, Leary MR. Why does social exclusion hurt? The relationship between social and physical pain. Psychol Bull. 2005;131(2):202–23. PubMed PMID: ISI:000227423200004.
5. Richman LS, Leary MR. Reactions to discrimination, stigmatization, ostracism, and other forms of interpersonal rejection: a multimotive model. Psychol Rev. 2009;116(2):365–83. PubMed PMID: ISI:000264913000004.
6. Harcourt D, Rumsey N, Paraskeva N. Appearance and body image. Psychologist. 2011;24(12):895–6. PubMed PMID: WOS:000297614100025. English.
7. Rumsey N. The psychology of appearance: why health psychologists should "do looks". Psychol Health. 2008;23:16. PubMed PMID: WOS:000260047300010. English.
8. Rumsey N, Clarke A, White P, Wyn-Williams M, Garlick W. Altered body image: appearance-related concerns of people with visible disfigurement. J Adv Nurs. 2004;48(5):443–53. PubMed PMID: WOS:000225369600003. English.

9. Ablon J. The nature of stigma and medical conditions. Epilepsy Behav. 2002;3(6):S2–9. PubMed PMID: WOS:000184307700002. English.
10. Macgregor FC. After plastic surgery: adaptation and adjustment. New York: Praeger; 1979.
11. Thompson A, Kent G. Adjusting to disfigurement: processes involved in dealing with being visibly different. Clin Psychol Rev. 2001;21(5):663–82. PubMed PMID: WOS:000169442100001. English.
12. Wallace M, Harcourt D, Rumsey N. Experiences of healthcare provision in adolescents with an altered appearance. Psychol Health. 2008;23:270. PubMed PMID: WOS:000260047300633. English.
13. Egan K, Harcourt D, Rumsey N, Appearance Res C. A qualitative study of the experiences of people who identify themselves as having adjusted positively to a visible difference. J Health Psychol. 2011;16(5):739–49. PubMed PMID: WOS:000291676700005. English.
14. Scheer J, Groce N. Impairment as a human constant – cross-cultural and historical perspectives on variation. J Soc Issues. 1988;44(1):23–37. PubMed PMID: WOS:A1988N062700003. English.
15. Susman J. Disability, stigma and deviance. Soc Sci Med. 1994;38(1):15–22. PubMed PMID: WOS:A1994MK27000003. English.
16. Zola IK. Self, identity and the naming question – reflections on the language of disability. Soc Sci Med. 1993;36(2):167–73. PubMed PMID: WOS:A1993KE81500009. English.
17. Van Brakel WH, Anderson AM, Mutatkar RK, Bakirtzief Z, Nicholls PG, Raju MS, et al. The Participation Scale: measuring a key concept in public health. Disabil Rehabil. 2006;28(4):193–203. PubMed PMID: WOS:000235427800002. English.
18. Goffman E. Stigma: notes on the management of spoiled identity. Englewood Cliffs: Prentice-Hall; 1963. 147 p
19. Elliott GC, Ziegler HL, Altman BM, Scott DR. Understanding stigma – dimensions of deviance and coping. Deviant Behav. 1982;3(3):275–300. PubMed PMID: WOS:A1982NV59700005. English.
20. Stafford MC, Scott RR. Stigma, deviance and social control. In: AInlay SC, Becker GB, Coleman SC, editors. The dilemma of difference: a multidisciplinary view of stigma. New York: Plenum Press; 1986. p. 77–90.
21. Crocker J, Major B, Steele C. Social stigma. In: Gilbert D, Fiske ST, Lindzey G, editors. Handbook of social psychology. 4th ed. Boston: McGraw Hill; 1998.
22. Castro A, Farmer P. Understanding and addressing AIDS-related stigma: from anthropological theory to clinical practice in Haiti. Am J Public Health. 2005;95(1):53–9.
23. Link BG, Phelan JC. Conceptualizing stigma. Annu Rev Sociol. 2001;27:363–85.
24. Malcolm A, Aggleton P, Bronfman M, Galvao J, Mane P, Verrall J. HIV-related stigmatization and discrimination: its forms and contexts. Crit Public Health. 1998;8(4):347–70.
25. Parker R, Aggleton P. HIV and AIDS-related stigma and discrimination: a conceptual framework and implications for action. Soc Sci Med. 2003;57(1):13–24.
26. Mill JE, Edwards N, Jackson RC, MacLean L, Chaw-Kant J. Stigmatization as a social control mechanism for persons living with HIV and AIDS. Qual Health Res. 2010;20(11):1469–83. PubMed PMID: WOS:000283250900005. English.
27. Rumsey N, Harcourt D. The psychology of appearance. New York: Open Univeristy Press; 2005. 237 p
28. MacGregor FC. Social, psychological and cultural dimensions of cosmetic and reconstructive plastic-surgery. Aesthetic Plast Surg. 1989;13(1):1–8. PubMed PMID: WOS:A1989T620100001. English.
29. MacGregor FC. Patient dissatisfaction with results of technically satisfactory surgery. Aesthetic Plast Surg. 1981;5(1):27–32. PubMed PMID: WOS:A1981LM55500003. English.
30. Harcourt D, Rumsey N. Psychology and visible difference. Psychologist. 2008;21(6):486–9. PubMed PMID: WOS:000256831200018. English.
31. Folkman S, Lazarus RS, Dunkelschetter C, Delongis A, Gruen RJ. Dynamics of a stressful encounter: cognitive appraisal, coping and encounter outcomes. J Pers Soc Psychol. 1986;50(5):992–1003. PubMed PMID: WOS:A1986C306700013. English
32. Crocker J, Major B. Social stigma and self-esteem: the self-protective properties of stigma. Psychol Rev. 1989;96(4):608–30. PubMed PMID: ISI:A1989AU66600004.
33. Miller CT, Kaiser CR. A theoretical perspective on coping with stigma. J Soc Issues. 2001;57(1):73–92. PubMed PMID: ISI:000168242500005.
34. Folkman S, Greer S. Promoting psychological well-being in the face of serious illness: when theory, research and practice inform each other. Psychooncology. 2000;9(1):11–9. PubMed PMID: ISI:000085499100002.
35. Ben-Naim S, Aviv G, Hirschberger G. Strained interaction: evidence that interpersonal contact moderates the death-disability rejection link. Rehabil Psychol. 2008;53(4):464–70. PubMed PMID: WOS:000261518900005. English.
36. Hirschberger G. Terror management and attributions of blame to innocent victims: reconciling compassionate and defensive responses. J Pers Soc Psychol. 2006;91(5):832–44. PubMed PMID: WOS:000241548100003. English.
37. Hirschberger G, Florian V, Mikulincer M. Fear and compassion: a terror management analysis of emotional reactions to physical disability. Rehabil Psychol. 2005;50(3):246–57. PubMed PMID: WOS:000231741200009. English.
38. Kozin SH. Upper-extremity congenital anomalies. J Bone Joint Surg-Am. 2003;85A(8):1564–76. PubMed PMID: WOS:000184552100021. English.
39. Schabert J, Browne JL, Mosely K, Speight J. Social stigma in diabetes a framework to under-

stand a growing problem for an increasing epidemic. Patient. 2013;6(1):1–10. PubMed PMID: WOS:000315586900001. English.
40. Sterba KR, Zapka J, Gore EI, Ford ME, Ford DW, Thomas M, et al. Exploring dimensions of coping in advanced colorectal cancer: implications for patient-centered care. J Psychosoc Oncol. 2013;31(5):517–39. PubMed PMID: WOS:000324001300003. English.
41. Rumsey N. Body image and congenital conditions with visible differences. In: Cash TF, Pruzinsky T, editors. Body image: a handbook of theory, research, and clinical practice. London: The Guilford Press; 2002b.
42. Varni SE, Miller CT, McCuin T, Solomon S. Disengagement and engagement coping with HIV/AIDS stigma and psychological well-being of people with HIV/AIDS. J Soc Clin Psychol. 2012;31(2):123–50. PubMed PMID: WOS:000300333400002. English.
43. Giele H, Giele C, Bower C, Allison M. The incidence and epidemiology of congenital upper limb anomalies: a total population study. J Hand Surg Am. 2001;26(4):628–34.
44. Ardon MS, Janssen WG, Hovius SE, Stam HJ, Selles RW. Low impact of congenital hand differences on health-related quality of life. Arch Phys Med Rehabil. 2012;93(2):351–7. PubMed PMID: WOS:000300338900026. English.
45. Aucourt J, Budzik JF, Manouvrier-Hanu S, Mezel A, Cotten A, Boutry N. Congenital malformations of the hand and forearm in children: what radiologists should know. Semin Musculoskelet Radiol. 2012;16(2):146–58. PubMed PMID: WOS:000304677600009. English.
46. Linder JA, Pincus DJ, Panthaki Z, Thaller SR. Congenital anomalies of the hand: an overview. J Craniofac Surg. 2009;20(4):999–1004. PubMed PMID: WOS:000268400400008. English.
47. Manske PR, Oberg KC. Classification and developmental biology of congenital anomalies of the hand and upper extremity. J Bone Joint Surg-Am. 2009;91A:3–18. PubMed PMID: WOS:000267673900002. English.
48. Oberg KC, Feenstra JM, Manske PR, Tonkin MA. Developmental biology and classification of congenital anomalies of the hand and upper extremity. J Hand Surg-Am. 2010;35A(12):2066–76. PubMed PMID: WOS:000285371300024. English.
49. Moher D, Liberati A, Tetzlaff J, Altman DG, Grp P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. J Clin Epidemiol. 2009;62(10):1006–12. PubMed PMID: WOS:000270250500003. English.
50. Bellew M, Haworth J, Kay SP. Toe to hand transfer in children: ten year follow up of psychological aspects. J Plast Reconstr Aesthet Surg. 2011;64(6):766–75. PubMed PMID: WOS:000290562600020. English.
51. Vasluian E, de Jong IGM, Janssen WGM, Poelma MJ, van Wijk I, Reinders-Messelink HA, et al. Opinions of youngsters with congenital below-elbow deficiency, and those of their parents and professionals concerning prosthetic use and rehabilitation treatment. PLoS One. 2013;8(6). PubMed PMID: WOS:000321738400104. English.
52. Staines KG, Majzoub R, Thornby J, Netscher DT. Functional outcome for children with thumb aplasia undergoing pollicization. Plast Reconstr Surg. 2005;116(5):1314–23. PubMed PMID: WOS:000232421100017. English.
53. Hardwicke J, Khan MAA, Richards H, Warner RM, Lester R. Macrodactyly – options and outcomes. J Hand Surg-Eur. 2013;38E(3):297–303. PubMed PMID: WOS:000317916800011. English.
54. Hadders-Algra M, Reinders-Messelink HA, Huizing K, van den Berg R, van der Sluis CK, Maathuis CGB. Use and functioning of the affected limb in children with unilateral congenital below-elbow deficiency during infancy and preschool age: a longitudinal observational multiple case study. Early Hum Dev. 2013;89(1):49–54. PubMed PMID: WOS:000314073900010. English.
55. Ekblom AG, Dahlin LB, Rosberg HE, Wiig M, Werner M, Arner M. Hand function in children with radial longitudinal deficiency. BMC Musculoskelet Disord. 2013;14:116. PubMed PMID: WOS:000318296200001. English.
56. Korkmaz M, Erbahceci F, Ulger O, Topuz S. Evaluation of functionality in acquired and congenital upper extremity child amputees. Acta Orthop Traumatol Turc. 2012;46(4):262–8. PubMed PMID: WOS:000309801300007. English.
57. Nemec SF, Kasprian G, Brugger PC, Bettelheim D, Amann G, Nemec U, et al. Abnormalities of the upper extremities on fetal magnetic resonance imaging. Ultrasound Obstet Gynecol. 2011;38(5):559–67. PubMed PMID: WOS:000297512300014. English.
58. Oberg KC, Harris TE, Wongworawat MD, Wood VE. Combined congenital radial and ulnar longitudinal deficiencies: report of 2 cases. J Hand Surg-Am. 2009;34A(7):1298–302. PubMed PMID: WOS:000269414600019. English.
59. Huizing K, Reinders-Messelink H, Maathuis C, Hadders-Algra M, van der Sluis CK. Age at first prosthetic fitting and later functional outcome in children and young adults with unilateral congenital below-elbow deficiency: a cross-sectional study. Prosthet Orthot Int. 2010;34(2):166–74. PubMed PMID: WOS:000283117200005. English.
60. Bent N, Tennant A, Neumann V, Chamberlain MA. Living with thalidomide: health status and quality of life at 40 years. Prosthet Orthot Int. 2007;31(2):147–56. PubMed PMID: WOS:000248726400004. English.
61. Holtslag I, van Wijk I, Hartog H, van der Molen AM, van der Sluis C. Long-term functional outcome of patients with longitudinal radial deficiency: cross-sectional evaluation of function, activity and participation. Disabil Rehabil. 2013;35(16):1401–7. PubMed PMID: WOS:000321465200011. English.

62. Goh ESY, Li CM, Horsburgh S, Kasai Y, Kolomietz E, Morel CF. The Roberts syndrome/SC phocomelia spectrum-a case report of an adult with review of the literature. Am J Med Genet A. 2010;152A(2):472–8. PubMed PMID: WOS:000274508300034. English.
63. Cetik O, Uslu M, Cirpar M, Eksioglu F. Experience with the surgical treatment of radial polydactyly in adults. Ann Plast Surg. 2005;55(4):363–6. PubMed PMID: WOS:000232282800006. English.
64. Eskandari MM, Oztuna V, Demirkan F. Late psychosocial effects of congenital hand anomaly. Hand Surg. 2004;9(02):257–9.
65. Hermansson L, Eliasson AC, Engstrom I. Psychosocial adjustment in Swedish children with upper-limb reduction deficiency and a myoelectric prosthetic hand. Acta Paediatr. 2005;94(4):479–88. PubMed PMID: WOS:000228451400018. English.
66. Varni JW, Rubenfeld LA, Talbot D, Setoguchi Y. Determinants of self-esteem in children with congenital/acquired limb deficiencies. J Dev Behav Pediatr. 1989;10(1):13–6. PubMed PMID: WOS:A1989T156700003. English.
67. Varni JW, Setoguchi Y. Screening for behavioral and emotional problems in children and adolescents with congenital or acquired limb deficiencies. Am J Dis Child. 1992;146(1):103–7. PubMed PMID: WOS:A1992GY44600027. English.
68. Varni JW, Setoguchi Y. Effects of parental adjustment on the adaptation of children with congenital or acquired limb deficiencies. J Dev Behav Pediatr. 1993;14(1):13–20. PubMed PMID: WOS:A1993KK64300003. English.
69. Varni JW, Setoguchi Y. Perceived physical appearance and adjustment of adolescents with congenital/acquired limb deficiencies: a path-analytic model. J Clin Child Psychol. 1996;25(2):201–8. PubMed PMID: WOS:A1996UN35700009. English.
70. Michielsen A, Van Wijk I, Ketelaar M. Participation and quality of life in children and adolescents with congenital limb deficiencies: a narrative review. Prosthet Orthot Int. 2010;34(4):351–61. PubMed PMID: WOS:000284360400001. English.
71. Cohen JS, Biesecker BB. Quality of life in rare genetic conditions: a systematic review of the literature. Am J Med Genet A. 2010;152A(5):1136–56. PubMed PMID: WOS:000277739800008. English.
72. de Jong IGM, Reinders-Messelink HA, Janssen WGM, Poelma MJ, van Wijk I, van der Sluis CK. Mixed feelings of children and adolescents with unilateral congenital below elbow deficiency: an Online Focus Group Study. PLoS One. 2012;7(6). PubMed PMID: WOS:000305336800003. English.
73. Griffiths C, Williamson H, Rumsey N. The romantic experiences of adolescents with a visible difference: exploring concerns, protective factors and support needs. J Health Psychol. 2012;17(7):1053–64. PubMed PMID: WOS:000309354700015. English.
74. Gussy M, Kilpatrick N. The self-concept of adolescents with cleft lip and palate: a pilot study using a multidimensional/hierarchical measurement instrument. Int J Paediatr Dent. 2006;16(5):335–41. PubMed PMID: WOS:000239876300004. English.
75. Masnari O, Schiestl C, Rossler J, Gutlein SK, Neuhaus K, Weibel L, et al. Stigmatization predicts psychological adjustment and quality of life in children and adolescents with a facial difference. J Pediatr Psychol. 2013;38(2):162–72. PubMed PMID: WOS:000315417800007. English.
76. Feragen KB, Kvalem IL, Rumsey N, Borge AIH. Adolescents with and without a facial difference: the role of friendships and social acceptance in perceptions of appearance and emotional resilience. Body Image. 2010;7(4):271–9. PubMed PMID: WOS:000284348500002. English.
77. Bradbury ET, Kay SPJ, Hewison J. The psychological impact of microvascular free toe transfer for children and their parents. J Hand Surg-Br Eur. 1994;19B(6):689–95. PubMed PMID: WOS:A1994QJ56000003. English.
78. Fonseca A, Nazare B, Canavarro MC. Parental psychological distress and quality of life after a prenatal or postnatal diagnosis of congenital anomaly: a controlled comparison study with parents of healthy infants. Disabil Health J. 2012;5(2):67–74. PubMed PMID: WOS:000301868700002. English.
79. Fonseca A, Nazare B, Canavarro MC. Clinical determinants of parents' emotional reactions to the disclosure of a diagnosis of congenital anomaly. Jognn. 2013;42(2):178–90. PubMed PMID: WOS:000316279500009. English.
80. Warfield ME, Krauss MW, Hauser-Cram P, Upshur CC, Shonkoff JP. Adaptation during early childhood among mothers of children with disabilities. J Dev Behav Pediatr. 1999;20(1):9–16. PubMed PMID: WOS:000078764900002. English.
81. Hauser-Cram P, Warfield ME, Shonkoff JP, Krauss MW. IV. Results: predictors of functioning and change in children's development and parent Well-being. Monogr Soc Res Child Dev. 2001;66(3):54–78.
82. Wallander JL, Varni JW, Babani L, Banis HT, Wilcox KT. Family resources as resistance factors for psychological maladjustment in chronically ill and handicapped-children. J Pediatr Psychol. 1989;14(2):157–73. PubMed PMID: WOS:A1989AC65200002. English.
83. Wallander JL, Varni JW. Effects of pediatric chronic physical disorders on child and family adjustment. J Child Psychol Psychiatry Allied Discip. 1998;39(1):29–46. PubMed PMID: WOS:000072047800003. English.
84. Beuf AH. Children coping with impaired appearance: social and psychological influences. Gen Hosp Psychiatry. 1990;6:294–301.
85. Hillbeuf A, JDR P. Children coping with impaired appearance – social and psychologic influences. Gen Hosp Psychiatry. 1984;6(4):294–301. PubMed PMID: WOS:A1984TM50000009. English.
86. Wiegner S, Donders J. Predictors of parental distress after congenital disabilities. J Dev Behav

Pediatr. 2000;21(4):271–7. PubMed PMID: WOS:000088913700003. English.
87. Puhl RM, Brownell KD. Confronting and coping with weight stigma: an investigation of overweight and obese adults. Obesity. 2006;14(10):1802–15. PubMed PMID: WOS:000249605900017. English.
88. Myers A, Rosen JC. Obesity stigmatization and coping: relation to mental health symptoms, body image, and self-esteem. Int J Obes (Lond). 1999;23(3):221–30. PubMed PMID: WOS:000078796900001. English.
89. Compas BE, Connor-Smith JK, Saltzman H, Thomsen AH, Wadsworth ME. Coping with stress during childhood and adolescence: problems, progress, and potential in theory and research. Psychol Bull. 2001;127(1):87–127. PubMed PMID: ISI:000166843700005.
90. Connor-Smith JK, Compas BE, Wadsworth ME, Thomsen AH, Saltzman H. Responses to stress in adolescence: measurement of coping and involuntary stress responses. J Consult Clin Psychol. 2000;68(6):976–92.
91. Varni SE, Miller CT, Solomon SE. Sexual Behavior as a function of stigma and coping with stigma among people with HIV/AIDS in rural New England. AIDS Behav. 2012;16(8):2330–9. PubMed PMID: WOS:000310316200024. English.
92. Evans D, Howard E, Giblin C, Clancy T, Spencer H, Huson S, et al. Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. Am J Med Genet A. 2010;152(2):327–32.
93. Lu-Emerson C, Plotkin S. The neurofibromatoses. Part 2: NF2 and schwannomatosis. Rev Neurol Dis. 2008;6(3):E81–6.
94. Lu-Emerson C, Plotkin S. The Neurofibromatoses. Part 1: NF1. Rev Neurol Dis. 2009;6(2):E47.
95. Hyman SL, Shores A, North KN. The nature and frequency of cognitive deficits in children with neurofibromatosis type 1. Neurology. 2005;65(7):1037–44.
96. Van Es S, North K, McHugh K, De Silva M. MRI findings in children with neurofibromatosis type 1: a prospective study. Pediatr Radiol. 1996;26(7):478–87.
97. Chaudhry IA, Morales J, Shamsi FA, Al-Rashed W, Elzaridi E, Arat YO, et al. Orbitofacial neurofibromatosis: clinical characteristics and treatment outcome. Eye. 2012;26(4):583–92. PubMed PMID: WOS:000302938500015. English.
98. Lantieri L, Meningaud JP, Grimbert P, Bellivier F, Lefaucheur JP, Ortonne N, et al. Repair of the lower and middle parts of the face by composite tissue allotransplantation in a patient with massive plexiform neurofibroma: a 1-year follow-up study. Lancet. 2008;372(9639):639–45. PubMed PMID: WOS:000258622200027. English.
99. Miyawaki T, Billings B, Har-Shai Y, Agbenorku P, Kokuba E, Moreira-Gonzalez A, et al. Multicenter study of wound healing in neurofibromatosis and neurofibroma. J Craniofac Surg. 2007;18(5):1008–11. PubMed PMID: WOS:000249894600004. English.

Part II

Failure of Axis Formation/Differentiation

Radial Longitudinal Deficiency: Radius Hypoplasia

8

Chris Stutz, Terri Beckwith, and Scott Oishi

Introduction

Radial longitudinal deficiency (RLD) comprises a spectrum of clinical manifestations involving phenotypic changes of the upper extremity that range from underdevelopment to complete absence of the radial-sided structures. The majority of cases of RLD are sporadic in occurrence, but the deformity can be passed genetically as well. Treatment for this condition varies depending on the clinical presentation of the patient as well as any associated anomalies that may exist. This chapter will attempt to explain the background and etiology of RLD, outline the conditions that have been associated with the deformity, review the classification of the various phenotypic presentations, and review current treatment patterns and their associated outcomes.

Background

The first documented case of RLD, initially termed "radial club hand," was reported by Petit in 1733 when he described the findings in an infant autopsy. The term "radial club hand" has been largely supplanted in the modern literature with the term "radial longitudinal deficiency." In 1894, Sayre published the first case of RLD treated with centralization to address the radial deviation deformity associated with the condition by outlining the steps of centralizing the carpus on the end of the distal ulna. Since the time of these early publications, there have been significant advances in the understanding of the diagnosis, the deformity, and its associated conditions. Despite these advances, there remains little consensus in opinion regarding the best operative or nonoperative treatment of the radial deformity in children with RLD.

Etiology

The theories regarding the embryologic basis for RLD continue to evolve, as the specific mechanisms of limb bud development are uncovered. In animal models, the progressive reduction of apical ectodermal ridge-associated fibroblastic growth factors causes a progressive reduction in the size and volume of the developing limb bud. These alterations in cellular communication result in deformities that resemble those seen clinically in RLD [1, 2]. Mutagenic agents given to pregnant rats at various time points in gestation resulted in a substantial portion of littermates exhibiting manifestations consistent with RLD. The manifestations correlated with the

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time of administration and the dose of the mutagenic agent [3]. The prevalence of RLD has been reported as 1 in 55,000 live births [4], with a male to female ratio of 3:2 [5–8].

Associated Conditions

The association of RLD with certain medical conditions is well established. Historically, patients diagnosed with RLD were given a poor general prognosis, likely related to the associated morbidity of the related medical conditions [9]. Goldfarb et al. [10] reported on 164 patients with RLD, 67% of which had associated medical or musculoskeletal abnormalities. The investigators reported the relative incidence of associated medical conditions was directly related to the severity of the RLD, with the most common related conditions being cardiac anomalies (20%), thrombocytopenia-absent radius syndrome (15%), VACTERL association (13%), Holt-Oram syndrome (4%), and Fanconi anemia (1%).

Hall et al. defined thrombocytopenia-absent radius as a syndrome in 1969 [11]. The inheritance pattern was thought to be autosomal recessive, but reports of parent-to-child transmission and multiple affected relatives in families suggest either heterogeneity or a different mode of inheritance [12–14]. Further genetic investigations have found a specific microdeletion of chromosome 1q21.1, which is necessary but in itself insufficient to cause the thrombocytopenia-absent radius phenotype [15]. The cardinal findings of TAR syndrome are the absence of radii with the presence of hypoplastic thumbs and thrombocytopenia [16]. The presence of an aberrant muscle, termed the brachiocarpalis, was identified by Oishi and colleagues in the upper extremities of children with TAR syndrome contributing to the radial angulation deformity of the carpus and flexion deformity at the elbow [17]. Unique to this diagnosis is that even though the thrombocytopenia can initially be severe, it usually spontaneously resolves over time without the need for intervention.

VACTERL association is a nonrandom association of birth defects involving vertebral anomalies, anal atresia, cardiovascular anomalies, trachea-esophageal fistula, renal and/or radial anomalies, and limb defects. VACTERL association is likely related to multiple factors but can be seen with chromosomal defects such as Trisomy 18 and is encountered more commonly in children of diabetic mothers [18]. There has been no specific genetic cause identified in VACTERL association to date. RLD patients must have at least three, including RLD, of the possible associations to be considered a VACTERL patient.

Holt-Oram syndrome is an autosomal dominant condition hallmarked by cardiac abnormalities and upper limb anomalies involving the radial ray. The genetic abnormality responsible for the syndrome has been identified as a missense mutation in the TBX5 gene [19]. The upper extremity involvement in Holt-Oram is variable. There is commonly hypoplasia of the radial elements with or without bizarre synostoses between the radius and ulna (Fig. 8.1).

Fanconi anemia is the most common inherited cause of bone marrow failure [20]. Bone marrow failure most commonly occurs between the ages of 5 and 15. Phenotypic variations are common in presentation and include short stature, thumb and radius deformities, hyperpigmentation of the skin, and renal, cardiac, and genitourinary abnormalities [21]. The diagnosis can be made using a chromosome breakage analysis (diepoxybutane analysis). The test is expensive, and its use as a routine screening tool in patients with apparent isolated RLD continues to be debated. However, the advent of successful pediatric bone marrow transplantation has led some authors to feel that diepoxybutane testing is important in every child with an RLD diagnosis.

Unique to many other conditions treated by the discipline of hand surgery, RLD often offers the hand surgeon the opportunity to be the first to make a diagnosis of other associated anomalies. This is related to the fact that the visible difference in upper extremity development often implores the parents and pediatrician to pursue evaluation for treatment of the affected limb. Hence, it is imperative that the hand surgeon be aware of these common associations and perform a complete evaluation of the child in all cases. This evaluation

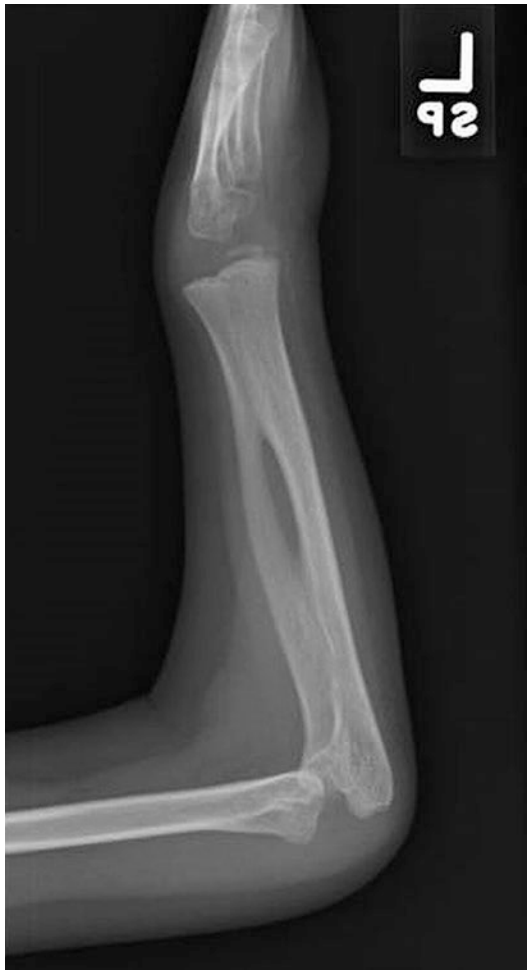

Fig. 8.1 Bizarre forearm synostosis in a patient with Holt-Oram syndrome

should include, at a minimum, a complete musculoskeletal and systemic evaluation, a complete blood count, echocardiogram, abdominal ultrasound, and subsequent evaluation for scoliosis.

Classification

The original classification of RLD was described by Bayne and Klug in 1987 [22]. They based the classification system on the radiographic appearance of the radius and divided the phenotype into four categories. Type I was defined as a short radius with delayed appearance of the distal radial epiphysis. Type II was defined as a "radius in miniature" with growth of both proximal and distal radial epiphyses affected. Type III denoted partial absence of the radius with no distal radial physis. Type IV was defined as complete absence of the radius.

The original classification of scheme of Bayne and Klug was modified by James et al. [23] in 1999 to include Types N and 0 with further delineation of what constituted Type I RLD. The classification was further modified by Goldfarb et al. [24] in 2005 to include more severe proximal manifestations of RLD as Type V. The current state of RLD classification is as follows (Fig. 8.2):

- Type N—The thumb is hypoplastic or absent in the presence of a normal carpus or radius. Radial angulation at the wrist is usually absent or minimal.
- Type 0—The radius is of normal length with proximal and distal physes. The radial carpal bones are hypoplastic or absent. The degree of radial angulation of the wrist is variable. The angulatory deformity is owing to the abnormal carpal bones and the presence of tight soft tissue structures on the radial side of the wrist, including the wrist capsule and musculotendinous structures.
- Type I—The radius is foreshortened by at least 2 mm compared to the distal ulna. The distal radial physis is present but its growth is slowed. The proximal radial physis is present and of normal morphology. Radio-ulnar synostosis or congenital radial head dislocation is variably present.
- Type II—The radius is hypoplastic in its entirety with proximal and distal physes present, the so-called radius in miniature. This can be associated with notable ulnar bowing.
- Type III—The distal portion of the radius is absent. There is no distal radial physis.
- Type IV—The radius is absent in its entirety. This is the most common phenotypic presentation of RLD [22].
- Type V—This represents a severe proximal form of RLD formerly considered phocomelia. Taking into account principles of developmental biology, the concept of a true

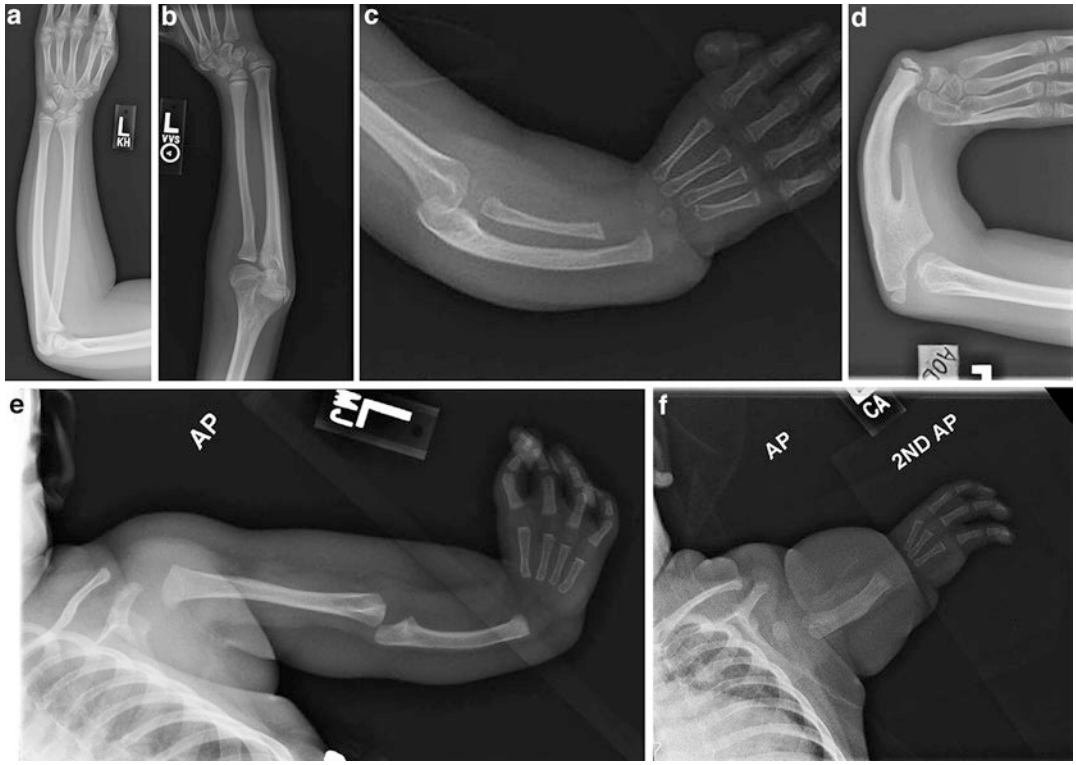

Fig. 8.2 (**a**) Type 0/N. (**b**) Type I. (**c**) Type II. (**d**) Type III. (**e**) Type IV. (**f**) Type V

intercalary defect has been challenged by recent authors [24, 25]. Extremities in this category have an abnormal glenoid, absence of the proximal portion of the humerus, articulation of the distal humerus with the ulna, and radial-sided hand abnormalities.

Clinical Presentation

While the etiology of the condition hinges on the longitudinal dysplasia of the radius, the clinical presentation of patients with radial longitudinal dysplasia is diverse. Patients can often present with skeletal abnormalities that extend beyond the radial deficiency. These include shortening of the forearm and/or bowing of the ulna, absent or limited elbow flexion, and absence or hypoplasia of the scaphoid and other carpal bones. Thumb hypoplasia can be present and consist of hypoplasia of the thenar intrinsic and/or extrinsic musculature, hypoplasia of the skeletal elements with or without associated articular instability, rudimentary presence of the thumb ("pouce floutant"), or complete absence of the thumb. The fingers can exhibit limited flexion, with the radial digits more affected than the ulnar digits. In addition to the manifestations of RLD in the hand, the soft tissues on the radial side of the wrist and forearm are tight contributing to the radial angulation of the hand plate on the distal ulna. The extrinsic wrist extensors are often poorly developed, and the malformed radial soft tissues often form a fibrous tether to the radial side of the wrist. This combination results in the classic presentation of a radial deviated wrist held in a flexed posture.

The abnormalities have both aesthetic and functional consequences. In severe cases, the appearance of the extremity can be unsightly secondary to the shortened forearm and the angled, flexed posture of the wrist and hand. On average, the forearm length is 54% of normal, ranging from 37% to 67% [26]. This limits the extremity's reach and can make two-handed activities

with the normal, opposite extremity difficult. In patients with bilateral upper extremity involvement, the functional limitations can be more severe. James et al. [23] found the incidence of bilateral involvement to be 65% in a study of 104 patients. If poorly functioning digits are present, this can further impede function. Unfortunately, when present, finger dysfunction is rarely amenable to surgical correction. This is in contradiction to thumb limitations, where several options are available to improve function.

Nonoperative Management

The nonoperative care of a child with RLD often begins very early in life. Occupational therapy intervention is commonly instituted during the first few weeks of life, especially if the infant requires hospitalization for associated abnormalities. Those children whose health allows them to be discharged from hospital care in the first few days of life are often referred for outpatient therapy services very early on by their pediatricians.

Therapeutic intervention at this point includes stretching exercises aimed at lengthening the contracted tissues on the radial side of the wrist and improving the hand-forearm angle. Splinting is often used as an adjunct to stretching in an effort to maintain the wrist in the corrected position and provide static resistance to a resting position of radial deviation. Specific therapeutic protocols for treatment of RLD by nonoperative means vary widely from surgeon to surgeon and therapist to therapist. There have been no published reports of therapeutic regimens proven to change the natural history of RLD, although its effectiveness in teaching children to use the affected limb in an efficient and useful manner has been seen clinically by many who care for these patients. Timing of intervention is also a topic of debate among those who treat these children. The authors feel that an early stretching regimen with nap and night splinting can be instituted early in life, but the parents should be encouraged to remove the splints for extended periods while the child is awake to allow him/her to interact appropriately with his/her surroundings and obtain the sensory interaction with the environment that is essential for proper development. Two-handed activities generally begin around the age of 3 months. At this time, splint wear during awake hours may become beneficial to place the hand in a less radially deviated position, functionally increasing the length of the affected extremity and allowing for easier two-handed manipulation of objects.

Operative Management

There have been many procedures described for the management of the wrist and forearm deformity in RLD. Since the original description of centralization by Sayre in 1894, several authors have published similar techniques with slight variations to the original procedure [27–30]. In addition, newer techniques such as radialization, pre-centralization distraction, and microsurgical transfer of vascularized epiphyses have been introduced to treat the deformity [31–34]. No single procedure has proven superior to another. Hence there remains vast disparity in treatment recommendations between surgeons treating the condition. Recurrence of the radial angulation remains the Achilles heel for procedures aimed at correcting the deformity [35, 64].

Reports centered on treatment of Types 0, N, I, and II RLD are sparse.

Type 0

Despite the relative frequency of Type 0 RLD reported by James et al. [23], a small number of these patients require surgical intervention. In 2004, Mo and Manske [36] reported on six wrists in five children treated with surgical correction. They recommended surgical intervention for radial deviation deformity greater than 20°. In their subset of patients, the preoperative hand-forearm angle ranged from 35° to 70° with all wrists lacking active extension to neutral. The authors describe a dorsal approach to the wrist with exposure of the extensor carpi radialis tendon or tendons. The tendon is released from its

distal insertion. Following release, the dorsal-radial wrist capsule, as well as the volar wrist capsule, is released allowing passive correction of the wrist to neutral position. The extensor carpi ulnaris tendon is released, leaving a distal stump for tenorraphy with the radial wrist extensors, effectively removing the radial deviation force and realigning it to gain neutral wrist extension. The proximal stump of the extensor carpi ulnaris tendon is sewn into the dorsal wrist capsule overlying the third metacarpal to further augment active wrist extension. Optionally, a pin can be placed across the carpus into the distal ulna to maintain the wrist in its corrected position. The patient is then casted in neutral to slight wrist extension for 6–8 weeks. The cast and pin, if present, are removed, and the patient is allowed to begin active range-of-motion exercises. At rest the patient is splinted in the corrected position for an extended duration.

Mo and Manske [36] reported favorable outcomes using the above surgical technique. They reported an average improvement of radial deviation at rest from 58° to 12°, with active wrist extension improving an average of 53° and passive wrist extension improving an average of 28°. The average length of follow-up was 19 months (range, 2–38 months).

Types I and II

There have been few published reports on the treatment of Types I and II radial longitudinal deficiencies. Often, children with these types of RLD do not require surgical intervention. When necessary, the most common form of treatment is radial lengthening with release of the tight radial soft tissues and tendon transfer to support the realigned position. Lengthening of the radius is most commonly done by way of osteotomy and lengthening through an external fixator [37–40]. Others have reported on lengthening of the radius acutely, with gains of up to 1.6 cm [41]. Many authors have described techniques of lengthening through an external fixator with slight variations. Depending on surgeon preference, the lengthening can be performed with a single plane fixator [38] or by using a ring-type fixator [40]. When performing acute radius lengthening, Waters et al. [41] described a technique of using a temporary external fixator intraoperatively for distraction of the radius after performing a Z-cut osteotomy, followed by plate fixation of the bone in its new lengthened position.

Matsuno et al. [38] reported on two patients with Type II RLD who underwent radial lengthening with an external fixator. The outcomes demonstrated recurrence of the deformity following fixator removal with an increase in the hand-forearm angle at final follow-up.

Types III and IV

The treatment of Types III and IV RLD is classically described as centralization of the carpus on the distal end of the ulna. Since Sayre first described the original procedure of centralization in 1894, multiple authors have published their experience using this technique, as well as several modifications to the procedure aimed at decreasing the recurrence of the radial angulation deformity. In addition, many others have suggested alternative procedures to accomplish the task of neutralizing the carpus on the end of the forearm. These procedures include radialization of the carpus, transfer of vascularized epiphyses to support the radial side of the carpus, and ulnocarpal fusion [31, 34, 42, 43].

Centralization

The centralization procedure is based on four surgical steps: (1) initial stretching of soft tissues ± pre-centralization distraction, (2) surgical alignment of the carpus on the ulna, (3) balancing of the deforming forces, and (4) maintenance of the corrected position.

Historically, stretching of the radial tissues was accomplished by serial cast application prior to surgical centralization, often carried out within the first several months of life. This technique fails to adequately distract the tight radial soft tissues or translate the carpus distally over the end of the ulna; instead it simply aligns the carpus alongside the distal ulna. In addition, the early

application of casts precludes the use of the extremity by the child during the formative time of "learning" single and two-handed object manipulation. As a result, the use of external fixation to accomplish soft tissue distraction has been advocated in recent years by some surgeons. The application of uniplanar [44], biplanar [32, 45], and ring [33, 46, 47] external fixators has been described. The use of external fixation allows for the correction of the radial deviation deformity through distraction of the radial soft tissues and correction of the volar subluxation of the carpus in relation to the distal ulna. Distraction of the deformity is begun 3–5 days following the application of the fixator and is carried out at a rate of 0.5–1 mm per day until the desired position of the carpus is accomplished. The extremity is then maintained in the fixator for a period of 3–4 weeks prior to surgical stabilization of the carpus in its centralized position to allow the soft tissues to equilibrate.

Originally, the centralization procedure was performed through a longitudinal dorsal incision. Since that time, there have been multiple incisional techniques described to accomplish surgical centralization of the carpus [27, 28, 48, 65]. The pre-centralization distraction of the soft tissues allows for ease in accomplishing surgical centralization while often obviating the need for transposition flaps for soft tissue coverage. Regardless of the incision used, the hypoplastic extensor tendons are carefully identified and retracted. The tight dorsal, radial, and volar wrist capsule and soft tissues are released to allow for a tension-free placement of the carpus onto the distal ulna aligned on the axis of the third metacarpal. Buck-Gramcko described "radialization" of the carpus in which he aligned the carpus on the axis of the second metacarpal in an effort to decrease the tendency toward recurrence of the deformity [31]. With the use of preoperative distraction, the need for "notching" [49] of the carpus to decrease soft tissue tension is usually unnecessary. The importance of obtaining a tension-free centralization has been reinforced by Sestero and Van Heest [50], who demonstrated that ulna in non-centralized radial longitudinal deficient extremities attained 64% of normal length, while the ulnar length in centralized extremities was 58% of normal compared to 48% of normal when notching of the carpus was performed. They postulated that the decrease in longitudinal growth capacity of the ulna was secondary to increased pressure applied to the distal ulnar physis by the centralized carpus. Once an appropriate centralized position is obtained, carpus is pinned to the ulna with longitudinal Kirschner wires (K-wires) taking care to avoid the distal ulnar physis. The pins are cut beneath the skin and often remain in place for up to 6 months postoperatively to maintain the corrected position. Soft tissue rebalancing procedures are then performed to redirect the forces across the centralized carpus. The extensor carpi ulnaris tendon is advanced to improve the ulnar and dorsal vector of pull to the wrist and hand [22, 30, 31]. If present, the radial wrist extensors are transferred ulnarly to alleviate the deforming force caused by their function. The digital extensors are translated in an ulnar direction using a sling of extensor retinaculum to align them along the longitudinal axis of the ulna, hence eliminating another deforming force.

Epiphyseal Transfer

The concept of supporting the hand and carpus by transferring bony elements to the radial side of the wrist to augment the support provided by the distal ulna was introduced in 1928 by Albee [51] and attempted by several subsequent authors [6, 8, 29]. Unfortunately, these early attempts were hindered by the limited growth potential possessed by the transferred nonvascularized tissue. With the advent and refinement of microsurgical techniques, the concept of vascularized epiphyseal transfer with retained growth potential [52–54] rejuvenated the interest in supporting the radial side of the carpus using a structural graft. In 1998, Vilkki [34] reported on the use of the second metatarsophalangeal joint to support the radial side of the carpus.

In contrast to the centralization procedure, the epiphyseal transfer is generally performed at an age of 4–5 years. Prior to embarking on the microsurgical portion of the reconstruction, the

child often undergoes a soft tissue release with de-tethering of the radial side of the carpus with concomitant volar bilobed flap, transposing the excess ulnar-sided soft tissue to the deficient radial side [55]. This early intervention (done at approximately 12–18 months of age) has the advantage of maintaining wrist motion while minimizing risk to the distal ulnar physis. Following release and soft tissue transfer, a protocol of stretching and splinting is maintained through the early childhood years in an effort to preserve the increase in motion.

At an age of 5–6 years, the child is evaluated for the possibility of microsurgical epiphyseal transfer. Often the child and/or child's family decline additional surgery because very few functional limitations exist and cosmesis would be the primary indication for surgery. That said, if further surgical reconstruction is warranted, the microsurgical epiphyseal transfer is preceded by soft tissue distraction using an external fixator as described earlier in the chapter. The frame is applied and the carpus is slowly distracted (0.5–1 mm per day) until the desired anatomic position of the hand is accomplished over the distal ulnar. This can take 6–8 weeks to accomplish. The second toe metatarsophalangeal joint is harvested from the ipsilateral limb maintaining two arterial sources—first and second dorsal metatarsal artery and second and third plantar metatarsal artery [56]. Flexor and extensor tendons are preserved and sutured to the remaining proximal phalanx. The dorsal cutaneous nerves are also preserved to the dorsal skin paddle. The middle and distal phalanges of the toe are excised. Exquisite care must be taken to preserve the vessels to the epiphysis of the proximal phalanx and metatarsal during harvest.

The metatarsophalangeal joint is transferred to the wrist through a dorsal ± volar incision. The metatarsal is anchored to the ulna using K-wires, which are cut and bent beneath the skin. The proximal phalanx is anchored to the base of the second metacarpal, or against the scaphoid if present, in a position of 15–20° of flexion to increase stability. The preserved tendons of the toe are then sutured to the radial flexor and extensor tendons or muscle bellies to confer additional stability. After securing the bony construct, the metatarsophalangeal joint is revascularized.

Oftentimes the radial artery is absent in limbs affected by RLD; hence, the arterial supply for the epiphyseal transfer is provided by a persistent median artery or the ulnar artery. If present, the median artery or radial artery is anastomosed to the dominant vessel of the metatarsophalangeal joint in end-to-end fashion. In those cases where the median and radial artery is absent, the dominant vessel of the metatarsophalangeal joint is anastomosed to the ulnar artery in end-to-side fashion. Following acquisition of arterial inflow, the venous drainage is accomplished by anastomosis of dorsal veins.

The distraction device and K-wires are removed after radiographs have confirmed bony consolidation, usually 6–8 weeks. The arm is then casted for an additional month to protect the maturing transfer.

More recently, reports on the use of a vascularized fibular epiphyseal transfer has emerged as an alternative to vascularized metatarsophalangeal joint transfer [67]. The authors state advantages including sufficient length, predictable vascular pedicle, and similar morphology to the distal radius. The previous concern for deep peroneal nerve injury during pedicle harvest seems to have been obviated by the use of the inferior lateral genicular artery instead of a branch of the anterior tibial artery for inflow.

Ulnocarpal Arthrodesis

Ulnocarpal arthrodesis [43], or epiphyseal ulnocarpal arthrodesis [42] for the skeletally immature, is the procedure that most effectively stabilizes the wrist and improves the appearance of the radial angulation deformity. Despite the improvement in appearance, some have questioned the benefit of arthrodesis citing the maintenance of wrist motion as a substantial benefit in the function of the radial deficient limb [7]. Hence, the procedure is often thought of as a salvage procedure for severe, recurrent deformity. Rayan reported on two cases of recurrent deformity in skeletally mature patients who underwent

ulnocarpal arthrodesis with improvement in both appearance and function [43]. Pike et al. [42] reported on 12 post-centralization wrists treated with ulnocarpal epiphyseal arthrodesis for recurrent radial angulation >45° and/or inability to extend the wrist beyond 25°. Postoperatively, the wrists were stable at an average of 20° radial angulation and 11° of flexion. All reported improvement in appearance and function postoperatively. A trial of ulnocarpal pinning can be considered for patients/parents who have concern regarding postoperative function prior to performing definitive arthrodesis procedure.

Distraction-Lengthening of the Ulna

In order to address the functional limitation of impaired "reach" of the affected extremity, authors have reported lengthening of the ulna using a ring or uniplanar external fixator in several small series ranging from 4 to 9 patients [39, 57–59]. The distraction time ranged from 11 to 15 weeks, followed by a 23- to 32-week consolidation period. Average length gained in each extremity was 4.4–6 cm (46–54% of total length). Complications of lengthening included callus fracture, delayed union, digital and wrist stiffness, pain, pin tract infection, and recurrence of radial angulation. There were no rigid outcomes reported documenting improvement in function of the lengthened extremity.

Outcomes/Complications

Regardless of the type of surgery utilized, the common denominator in the outcomes of the surgical management of RLD is the recurrence of the radial angulation deformity. Multiple studies have documented the recurrence of radial angulation deformity following centralization [26, 35, 60]. An average radial-forearm angle of 21–26° immediately after centralization has been noted in these studies, with an additional 9- to 38-degree increase in radial angulation occurring over time. The avoidance of recurrent deformity has not been alleviated by the use of pre-centralization distraction as shown by Dana et al. [61]. In 2008, Vilkki [62] presented a long-term study of 19 wrists treated with microsurgical epiphyseal transfer with an average of 11 years of follow-up. The average hand-forearm angle was 28° of radial deviation with mean total active wrist motion of 83°. Of the nine wrists included in his original report [34], seven were noted to have increased radial angulation (mean of 12°) over a follow-up period of 15.2 years. Goldfarb et al. [26] reported significant functional limitations of the post-centralized hand, noting a 62% increase in the Jebsen-Taylor timed activity tests compared to normal. Interestingly, the DASH scores showed only mild functional limitation. Buffart et al. [63] observed grip and pinch strength values of 36% and 30%, respectively, when compared to normal controls, and additionally Ekblom et al. noted considerably lower grip strength and Box and Block Tests compared to age-adjusted norms [66]. In all previous studies, there are no comparisons to pre-centralization function, thus making it impossible to determine the effects of surgical deformity correction.

Complications of the surgical treatment of radial deficient limbs are both all-inclusive and dependent of the surgical technique used. Recurrence of deformity is a complication that is ubiquitous despite the treatment modality. Pin tract infections, callus fracture, delayed union, and stiffness are common to all techniques utilizing external fixation. Damage to the distal ulnar physis, further impairing its ability to accomplish longitudinal growth, is the most feared complication of centralization. Hence, the concept of carpal notching has been largely supplanted by newer techniques of pre-distraction centralization, in an effort to diminish the forces exerted across the distal ulnar physis.

Future Directions

The best treatment of RLD and its multiple phenotypes remains a popular topic among surgeons commonly treating the condition. To date, treatment algorithms have encompassed the full circle of management strategies, from nonoperative to operative care at various stages of life for various clinical presentations utilizing a vast array of sur-

gical procedures. Certainly, the definitive "best" treatment has yet to be determined, and likely is not the same for every patient. Future comparisons of those treated for RLD with surgical intervention versus those treated by nonoperative means may shed the most meaningful light on what interventions benefit these children the most.

References

1. Mariani FV, Ahn CP, Martin GR. Genetic evidence that FGFs have an instructive role in limb proximal-distal patterning. Nature. 2008;453(7193):401–5. https://doi.org/10.1038/nature06876. Epub 2008/05/02. PubMed PMID: 18449196; PubMed Central PMCID: PMC2631409.
2. Sun X, Mariani FV, Martin GR. Functions of FGF signalling from the apical ectodermal ridge in limb development. Nature. 2002;418(6897):501–8. https://doi.org/10.1038/nature00902. Epub 2002/08/02. PubMed PMID: 12152071.
3. Kato H, Ogino T, Minami A, Ohshio I. Experimental study of radial ray deficiency. J Hand Surg Br. 1990;15(4):470–6. Epub 1990/11/01. PubMed PMID: 2269841.
4. Lourie GM, Lins RE. Radial longitudinal deficiency. A review and update. Hand Clin. 1998;14(1):85–99. Epub 1998/04/04. PubMed PMID: 9526159.
5. Flatt A. Radial club hand. The care of congenital hand anomalies. 2nd ed. St. Louis: Quality Medical Publishing; 1993. p. 366–410.
6. Heikel HV. Aplasia and hypoplasia of the radius: studies on 64 cases and on epiphyseal transplantation in rabbits with the imitated defect. Acta Orthop Scand. 1959;39:1–155. PubMed PMID: 14400621.
7. Lamb DW. Radial club hand. A continuing study of sixty-eight patients with one hundred and seventeen club hands. J Bone Joint Surg. 1977;59(1):1–13. PubMed PMID: 833156.
8. Riordan DC. Congenital absence of the radius. J Bone Joint Surg. 1955;37-A(6):1129–39; discussion, 39–40. PubMed PMID: 13271460.
9. Kelikian H. Radial ray defect. Congenital deformities of the hand and forearm. Philadelphia: WB Saunders Company; 1974. p. 780–824.
10. Goldfarb CA, Wall L, Manske PR. Radial longitudinal deficiency: the incidence of associated medical and musculoskeletal conditions. J Hand Surg. 2006;31(7):1176–82. PubMed PMID: 16945723.
11. Hall JG, Levin J, Kuhn JP, Ottenheimer EJ, van Berkum KA, McKusick VA. Thrombocytopenia with absent radius (TAR). Medicine. 1969;48(6):411–39. Epub 1969/11/01. PubMed PMID: 4951233.
12. Ward RE, Bixler D, Provisor AJ, Bader P. Parent to child transmission of the thrombocytopenia absent radius (TAR) syndrome. Am J Med Genet Suppl. 1986;2:207–14. Epub 1986/01/01. PubMed PMID: 3146292.
13. Schnur RE, Eunpu DL, Zackai EH. Thrombocytopenia with absent radius in a boy and his uncle. Am J Med Genet. 1987;28(1):117–23. https://doi.org/10.1002/ajmg.1320280117. Epub 1987/09/01. PubMed PMID: 3314504.
14. Edelberg SB, Cohn J, Brandt NJ. Congenital hypomegakaryocytic thrombocytopenia associated with bilateral absence of the radius—the TAR syndrome. Hum Hered. 1977;27(2):147–52. Epub 1977/01/01. PubMed PMID: 863461.
15. Klopocki E, Schulze H, Strauss G, Ott CE, Hall J, Trotier F, et al. Complex inheritance pattern resembling autosomal recessive inheritance involving a microdeletion in thrombocytopenia-absent radius syndrome. Am J Hum Genet. 2007;80(2):232–40. https://doi.org/10.1086/510919. Epub 2007/01/20. PubMed PMID: 17236129; PubMed Central PMCID: PMC1785342.
16. Toriello HV. Thrombocytopenia-absent radius syndrome. Semin Thromb Hemost. 2011;37(6):707–12. https://doi.org/10.1055/s-0031-1291381. Epub 2011/11/22. PubMed PMID: 22102274.
17. Oishi SN, Carter P, Bidwell T, Mills J, Ezaki M. Thrombocytopenia absent radius syndrome: presence of brachiocarpalis muscle and its importance. J Hand Surg. 2009;34(9):1696–9. PubMed PMID: 19773129.
18. Stevenson RE, Hunter AG. Considering the embryopathogenesis of VACTERL association. Mol Syndromol. 2013;4(1–2):7–15. https://doi.org/10.1159/000346192. Epub 2013/05/09. PubMed PMID: 23653571; PubMed Central PMCID: PMC3638783.
19. Huang T. Current advances in Holt-Oram syndrome. Curr Opin Pediatr. 2002;14(6):691–5. Epub 2002/11/19. PubMed PMID: 12436037.
20. Shimamura A, Alter BP. Pathophysiology and management of inherited bone marrow failure syndromes. Blood Rev. 2010;24(3):101–22. https://doi.org/10.1016/j.blre.2010.03.002. Epub 2010/04/27. PubMed PMID: 20417588; PubMed Central PMCID: PMC3733544.
21. Soulier J. Fanconi anemia. Hematology Am Soc Hematol Educ Program. 2011;2011:492–7. https://doi.org/10.1182/asheducation-2011.1.492. Epub 2011/12/14. PubMed PMID: 22160080.
22. Bayne LG, Klug MS. Long-term review of the surgical treatment of radial deficiencies. J Hand Surg. 1987;12(2):169–79. PubMed PMID: 3559066.
23. James MA, McCarroll HR Jr, Manske PR. The spectrum of radial longitudinal deficiency: a modified classification. J Hand Surg. 1999;24(6):1145–55. PubMed PMID: 10584934.
24. Goldfarb CA, Manske PR, Busa R, Mills J, Carter P, Ezaki M. Upper-extremity phocomelia reexamined: a longitudinal dysplasia. J Bone Joint Surg. 2005;87(12):2639–48. PubMed PMID: 16322613.

25. Tytherleigh-Strong G, Hooper G. The classification of phocomelia. J Hand Surg Br. 2003;28(3):215–7. PubMed PMID: 12809650.
26. Goldfarb CA, Klepps SJ, Dailey LA, Manske PR. Functional outcome after centralization for radius dysplasia. J Hand Surg. 2002;27(1):118–24. PubMed PMID: 11810625.
27. Evans DM, Gateley DR, Lewis JS. The use of a bilobed flap in the correction of radial club hand. J Hand Surg Br. 1995;20(3):333–7. PubMed PMID: 7561408.
28. Manske PR, McCarroll HR Jr, Swanson K. Centralization of the radial club hand: an ulnar surgical approach. J Hand Surg. 1981;6(5):423–33. PubMed PMID: 7276473.
29. Starr D. Congenital absence of the radius. A method of surgical correction. J Bone Joint Surg. 1945;27A:572–7.
30. Watson HK, Beebe RD, Cruz NI. A centralization procedure for radial club hand. J Hand Surg. 1984;9(4):541–7. PubMed PMID: 6747239.
31. Buck-Gramcko D. Radialization as a new treatment for radial club hand. J Hand Surg. 1985;10(6 Pt 2):964–8. PubMed PMID: 4078287.
32. Kanojia RK, Sharma N, Kapoor SK. Preliminary soft tissue distraction using external fixator in radial club hand. J Hand Surg Eur Vol. 2008;33(5):622–7. PubMed PMID: 18977832.
33. Sabharwal S, Finuoli AL, Ghobadi F. Pre-centralization soft tissue distraction for Bayne type IV congenital radial deficiency in children. J Pediatr Orthop. 2005;25(3):377–81. PubMed PMID: 15832159.
34. Vilkki SK. Distraction and microvascular epiphysis transfer for radial club hand. J Hand Surg Br. 1998;23(4):445–52. PubMed PMID: 9726542.
35. Damore E, Kozin SH, Thoder JJ, Porter S. The recurrence of deformity after surgical centralization for radial club hand. J Hand Surg. 2000;25(4):745–51. PubMed PMID: 10913218.
36. Mo JH, Manske PR. Surgical treatment of type 0 radial longitudinal deficiency. J Hand Surg. 2004;29(6):1002–9. https://doi.org/10.1016/j.jhsa.2004.06.010. Epub 2004/12/04. PubMed PMID: 15576208.
37. Cheng JC. Distraction lengthening of the forearm. J Hand Surg Br. 1991;16(4):441–5. Epub 1991/11/01. PubMed PMID: 1779163.
38. Matsuno T, Ishida O, Sunagawa T, Suzuki O, Ikuta Y, Ochi M. Radius lengthening for the treatment of Bayne and Klug type II and type III radial longitudinal deficiency. J Hand Surg. 2006;31(5):822–9. PubMed PMID: 16713850.
39. Raimondo RA, Skaggs DL, Rosenwasser MP, Dick HM. Lengthening of pediatric forearm deformities using the Ilizarov technique: functional and cosmetic results. J Hand Surg. 1999;24(2):331–8. PubMed PMID: 10194019.
40. Villa A, Paley D, Catagni MA, Bell D, Cattaneo R. Lengthening of the forearm by the Ilizarov technique. Clin Orthop Relat Res. 1990;250:125–37. Epub 1990/01/01. PubMed PMID: 2293920.
41. Waters PM, Van Heest AE, Emans J. Acute forearm lengthenings. J Pediatr Orthop. 1997;17(4):444–9. Epub 1997/07/01. PubMed PMID: 9364380.
42. Pike JM, Manske PR, Steffen JA, Goldfarb CA. Ulnocarpal epiphyseal arthrodesis for recurrent deformity after centralization for radial longitudinal deficiency. J Hand Surg. 2010;35(11):1755–61. https://doi.org/10.1016/j.jhsa.2010.07.022. Epub 2010/10/12. PubMed PMID: 20932693.
43. Rayan GM. Ulnocarpal arthrodesis for recurrent radial club hand deformity in adolescents. J Hand Surg. 1992;17(1):24–7. PubMed PMID: 1538107.
44. Taghinia AH, Al-Sheikh AA, Upton J. Preoperative soft-tissue distraction for radial longitudinal deficiency: an analysis of indications and outcomes. Plast Reconstr Surg. 2007;120(5):1305–12; discussion 13–4. PubMed PMID: 17898604.
45. Thatte MR, Mehta R. Treatment of radial dysplasia by a combination of distraction, radialisation and a bilobed flap—the results at 5-year follow-up. J Hand Surg Eur Vol. 2008;33(5):616–21. PubMed PMID: 18694912.
46. Goldfarb CA, Murtha YM, Gordon JE, Manske PR. Soft-tissue distraction with a ring external fixator before centralization for radial longitudinal deficiency. J Hand Surg. 2006;31(6):952–9. PubMed PMID: 16843155.
47. Thirkannad SM, Burgess RC. A technique for using the Ilizarov fixator for primary centralization in radial club hand. Tech Hand Up Extrem Surg. 2008;12(2):71–8. PubMed PMID: 18528232.
48. Van Heest A, Grierson Y. Dorsal rotation flap for centralization in radial longitudinal deficiency. J Hand Surg. 2007;32(6):871–5. PubMed PMID: 17606069.
49. Lidge R. Congenital radial deficient club hand. J Bone Joint Surg. 1969;69A:1041–2.
50. Sestero AM, Van Heest A, Agel J. Ulnar growth patterns in radial longitudinal deficiency. J Hand Surg. 2006;31(6):960–7. PubMed PMID: 16843156.
51. Albee FH. Formation of radius congenitally absent: condition seven years after implantation of bone graft. Ann Surg. 1928;87(1):105–10. PubMed PMID: 17865806.
52. Bowen CV, Ethridge CP, O'Brien BM, Frykman GK, Gumley GJ. Experimental microvascular growth plate transfers. Part I—investigation of vascularity. J Bone Joint Surg Br. 1988;70(2):305–10.
53. Bowen CV, O'Brien BM, Gumley GJ. Experimental microvascular growth plate transfers. Part 2—investigation of feasibility. J Bone Joint Surg Br. 1988;70(2):311–4.
54. Donski PK, O'Brien BM. Free microvascular epiphyseal transplantation: an experimental study in dogs. Br J Plast Surg. 1980;33(2):169–78. PubMed PMID: 7388206.
55. Wall LB, Ezaki M, Oishi SN. Management of congenital radial longitudinal deficiency: con-

troversies and current concepts. Plast Reconstr Surg. 2013;132(1):122–8. https://doi.org/10.1097/PRS.0b013e318290fca5. Epub 2013/06/29. PubMed PMID: 23806915.
56. de Jong JP, Moran SL, Vilkki SK. Changing paradigms in the treatment of radial club hand: microvascular joint transfer for correction of radial deviation and preservation of long-term growth. Clin Orthop Surg. 2012;4(1):36–44. https://doi.org/10.4055/cios.2012.4.1.36. Epub 2012/03/02. Pub Med PMID: 22379554; PubMed Central PMCID: PMC3288493.
57. Horii E, Nakamura R, Nakao E, Kato H, Yajima H. Distraction lengthening of the forearm for congenital and developmental problems. J Hand Surg Br. 2000;25(1):15–21. PubMed PMID: 10763716.
58. Peterson BM, McCarroll HR Jr, James MA. Distraction lengthening of the ulna in children with radial longitudinal deficiency. J Hand Surg. 2007;32(9):1402–7. PubMed PMID: 17996775.
59. Pickford MA, Scheker LR. Distraction lengthening of the ulna in radial club hand using the Ilizarov technique. J Hand Surg Br. 1998;23(2):186–91. PubMed PMID: 9607657.
60. Geck MJ, Dorey F, Lawrence JF, Johnson MK. Congenital radius deficiency: radiographic outcome and survivorship analysis. J Hand Surg. 1999;24(6):1132–44. PubMed PMID: 10584933.
61. Dana C, Auregan JC, Salon A, Guero S, Glorion C, Pannier S. Recurrence of radial bowing after soft tissue distraction and subsequent radialization for radial longitudinal deficiency. J Hand Surg. 2012;37(10):2082–7. https://doi.org/10.1016/j.jhsa.2012.07.018. Epub 2012/10/02. PubMed PMID: 23021174.
62. Vilkki SK. Vascularized metatarsophalangeal joint transfer for radial hypoplasia. Semin Plast Surg. 2008;22(3):195–212. https://doi.org/10.1055/s-2008-1081403. Epub 2008/08/01. PubMed PMID: 20567714; PubMed Central PMCID: PMC2884879.
63. Buffart LM, Roebroeck ME, Janssen WG, Hoekstra A, Selles RW, Hovius SE, et al. Hand function and activity performance of children with longitudinal radial deficiency. J Bone Joint Surg. 2008;90(11):2408–15. PubMed PMID: 18978409.
64. Shariatzadeh H, Jafari D, Taheri H, Mazhar FN. Recurrence rate after radial club hand surgery in long term follow up. J Res Med Sci. 2009;14(3):179–86.
65. Van Heest A. Wrist centralization using the dorsal rotation flap in radial longitudinal deficiency. Tech Hand Up Extrem Surg. 2010;14(2):94–9. https://doi.org/10.1097/bth.0b013e3181da05aa.
66. Ekblom AG, Dahlin LB, Rosberg H-E, Wiig M, Werner M, Arner M. Hand function in children with radial longitudinal deficiency. BMC Musculoskelet Disord. 2013;14(1). https://doi.org/10.1186/1471-2474-14-116.
67. Yang J, Qin B, Li P, Fu G, Xiang J, Gu L. Vascularized proximal fibular epiphyseal transfer for Bayne and Klug type III radial longitudinal deficiency in children. Plast Reconstr Surg. 2015;135(1):157e–66e. https://doi.org/10.1097/prs.0000000000000836.

9 Radial Longitudinal Deficiency: Congenital Thumb Hypoplasia

Konrad Mende, Richard Lawson, and Michael A. Tonkin

Introduction

Thumb hypoplasia (underdevelopment) accompanies many congenital conditions, including thumb duplication, transverse deficiencies and symbrachydactyly, brachydactyly, cleft hand complex and ulnar longitudinal deficiency, congenital constriction ring syndrome and other miscellaneous conditions such as the thumb differences seen in Apert and Rubinstein-Taybi syndromes. Each condition represents its own specific challenges, but the principles of treatment remain the same. An optimal thumb demands appropriate size, shape, stability, mobility, strength and sensibility. No matter what the cause, surgery may involve the addition or removal of tissue, correction of deformity, stabilization of unstable joints and/or the creation of joint mobility. At times there is a conflict between stability and mobility. Although generalizations are not necessarily applicable to all individual cases, the achievement of optimal mobility at the carpometacarpal (CMC) joint is perhaps the major determinant of effective thumb mobility, with less importance placed on the metacarpophalangeal (MCP) and interphalangeal (IP) joints. In principle, mobility may be sacrificed for stability at these levels, which might then translate into improved strength.

Classical thumb hypoplasia, as part of a radial longitudinal deficiency, is a specific entity. It may accompany varying degrees of forearm radial hypoplasia or absence or may occur alone. This latter circumstance is uncommon, as a close clinical and radiological examination will nearly always reveal some proximal hypoplasia, even if subtle. In the OMT system, thumb hypoplasia is classified as a "failure of axis formation/differentiation – affecting the radial-ulnar axis of the entire upper limb" or the "radial-ulnar axis of the hand plate" when the thumb alone is affected [1, 2].

Thumb hypoplasia is often bilateral, although mild grades may be overlooked. Associations, syndromic and non-syndromic, are not uncommon (Table 9.1) [3]. Assessment of cardiac, gastrointestinal, renal, vertebral and other musculoskeletal anomalies and investigation for possible blood disorders, such as those associated with thrombocytopenic absent radius (TAR) and

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Fanconi's anaemia, are routine and have generally been performed by the referring paediatrician, although this should always be verified. Genetic counselling may be warranted.

Table 9.1 Associations of thumb hypoplasia, aplasia and triphalangism[a]

Frequent in:
Aase S.
Baller-Gerold S.
Congenital microgastria-limb reduction complex
Deletion 13q S.
Fanconi pancytopenia S.
Holt-Oram S.
Levy-Hollister S.
Nager S.
Oculo-auriculo-vertebral spectrum
Radial aplasia-thrombocytopenia S.
Roberts-SC phocomelia
Rothmund-Thomson S.
Townes-Brocks S.
VATER association
Yunis-Varon S.
Occasional in:
De Lange S.
Fetal aminopterin/methotrexate S.
Fetal valproate S.
Fibrodysplasia ossificans progressiva S.
Fraser S.
Fryns S.
Hypomelanosis of Ito
Lenz microphthalmia S.
Miller S.
Monozygotic (MZ) twinning and structural defects – general
MURCS association
Popliteal pterygium S.
Trisomy 18 S.

[a]Reprinted from Jones [3]

Classification

Müller, in 1937, introduced the concept of a teratogenic sequence resulting in increasing severity of thumb hypoplasia [4]. He did not specify the precise anomalies associated with a particular grade of severity, although many subsequent reviews have attributed four grades of hypoplasia to his name. In 1967 Blauth refined Müller's concept, defining five grades of thumb hypoplasia (Fig. 9.1) [5, 6]. A number of modifications to this classification have been suggested. That of Manske is most commonly quoted in the literature, but does involve significant changes to the definitions of Blauth [7, 8]. Blauth viewed the hypoplastic thumb according to grades of severity, with increasing bone and joint hypoplasia accompanied by increasing soft tissue hypoplasia. He distinguished Grade 2 from Grade 3 according to the presence or absence of a CMC joint, retaining the thumb in the former case but advising reconstruction of an alternative CMC joint in the latter. Manske moved this distinction into a subclassification of Grade 3, in which Grade 3A has a CMC joint and Grade 3B does not. Buck-Gramcko added a 3C in which only the distal one-third of the metacarpal remained (Fig. 9.2) [9]. The Manske classification distinguishes between Grades 2 and 3A by the absence or presence of extrinsic musculotendinous anomalies. Such a subclassification suggests that extrinsic anomalies develop with more severe grades of hypoplasia but are not present in less severe grades (Grades 1 and 2) and that these occur after the insult to intrinsic musculotendi-

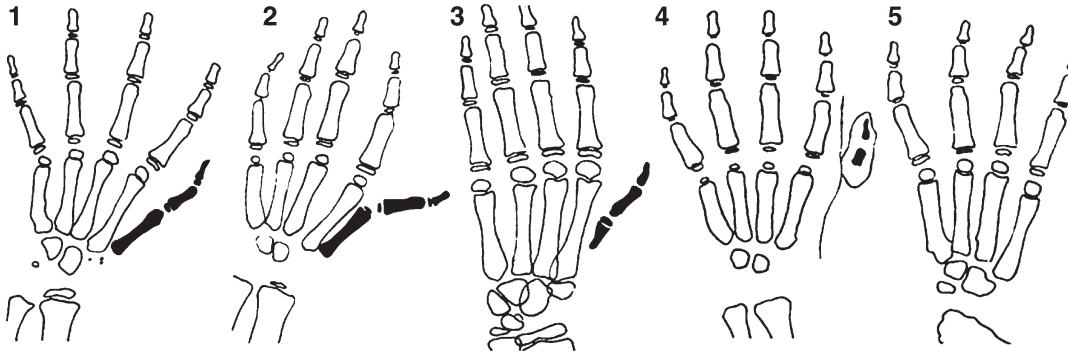

Fig. 9.1 Blauth grades of thumb hypoplasia 1–5. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

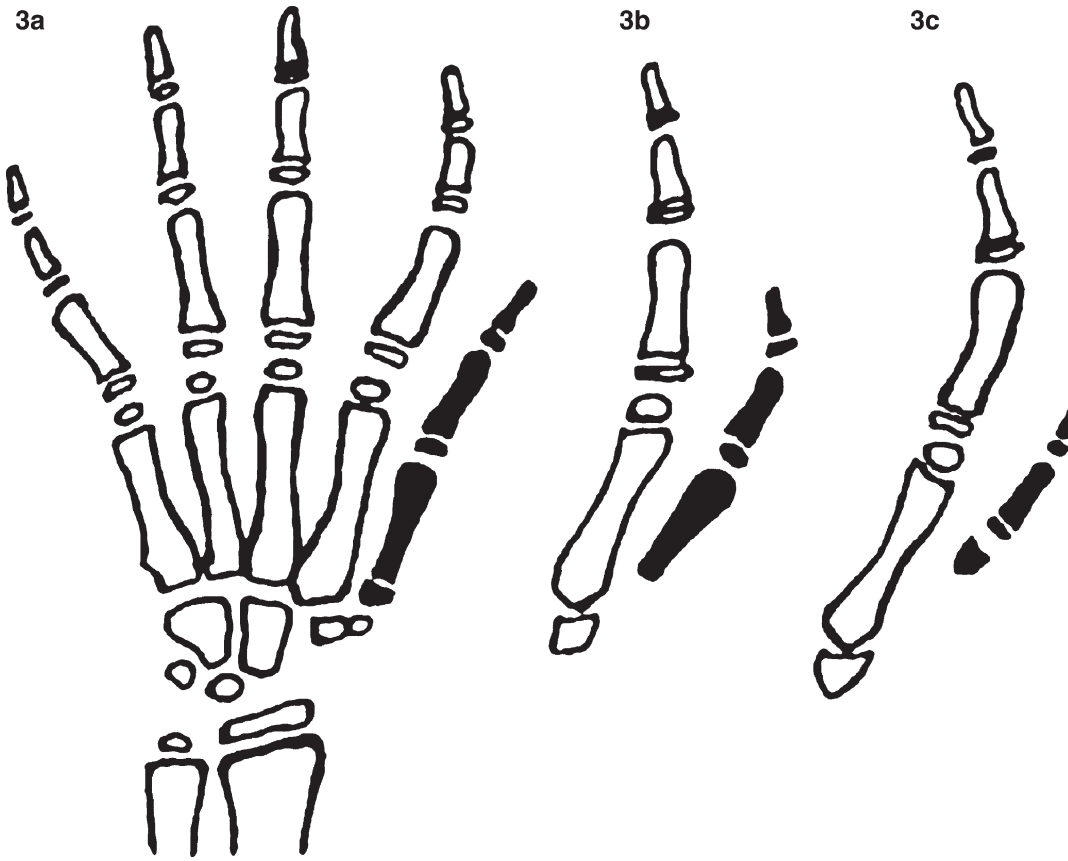

Fig. 9.2 Classification of thumb hypoplasia as modified by Manske (Grades 3A and 3B) and Buck-Gramcko (Grade 3C). (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

nous units. In our experience, if surgical reconstructions of thumb intrinsic muscles, MCP joint instability and first web hypoplasia are indicated, there are invariably some extrinsic muscle anomalies. These may or may not merit reconstruction. It is of interest that neither the classification of Blauth nor Manske considered the stability or mobility of the CMC joint in those grades in which the proximal metacarpal is present (Blauth Grade 2, Manske Grades 2 and 3A). Manske specifically equated the presence of the proximal metacarpal with a stable CMC joint and proximal metacarpal absence with an unstable joint. Buck-Gramcko defined the 3A thumb as having an unstable CMC joint and described significant extrinsic anomalies within Grade 2.

We favour Müller's concept of increasing hypoplasia of all thumb elements, of soft tissues, bones and joints, occurring concurrently, and prefer Blauth's distinction between Grades 2 and 3 according to the presence or absence of the proximal metacarpal. In its original form, the Blauth classification also provides logical guidelines for treatment by grade. Traditionally, Grade 2 thumbs are reconstructed; Grade 3 thumbs are removed and the index finger is pollicized. Manske and Buck-Gramcko moved these alternative treatment recommendations to within Grade 3, distinguishing between 3A and 3B.

Some who are classification "splitters" may choose to subclassify Grade 2 according to which components of the thumb would be improved by surgical reconstruction and the techniques whereby this is achieved. Smith advised a Grade 2A or 2B on the basis of uniaxial or global MCP joint instability [10, 11]. This could be extended to specify differences in other aspects of Grade 2 hypoplasia. The classification "lumpers" may

prefer to designate the classification of Grade 2 to all such thumbs, regardless of the reconstructive techniques utilized. However, as Buck-Gramcko states "the assessment of results is difficult, especially because the outcome depends on the preoperative condition in the severity of the deformity" [9]. It is clear that the surgical reconstruction of a thumb with uniaxial MCP joint instability, intrinsic hypoplasia and a mildly hypoplastic first web, when accompanied by minor extrinsic anomalies not requiring reconstruction, is quite different from the reconstruction of a thumb with global MCP joint instability, severe hypoplasia of the first web and intrinsic absence, in association with a pollex abductus anomaly and/or hypoplasia or aplasia of the extrinsic flexors and extensors and/or abnormal alignment and insertion of these.

The following classification has been introduced by Tonkin [12] in 2014 as one maintaining the integrity of Blauth's skeletal classification and the teratological sequence of increasing severity of hypoplasia proposed by Müller, Blauth and others (Fig. 9.3). The sub-divisions

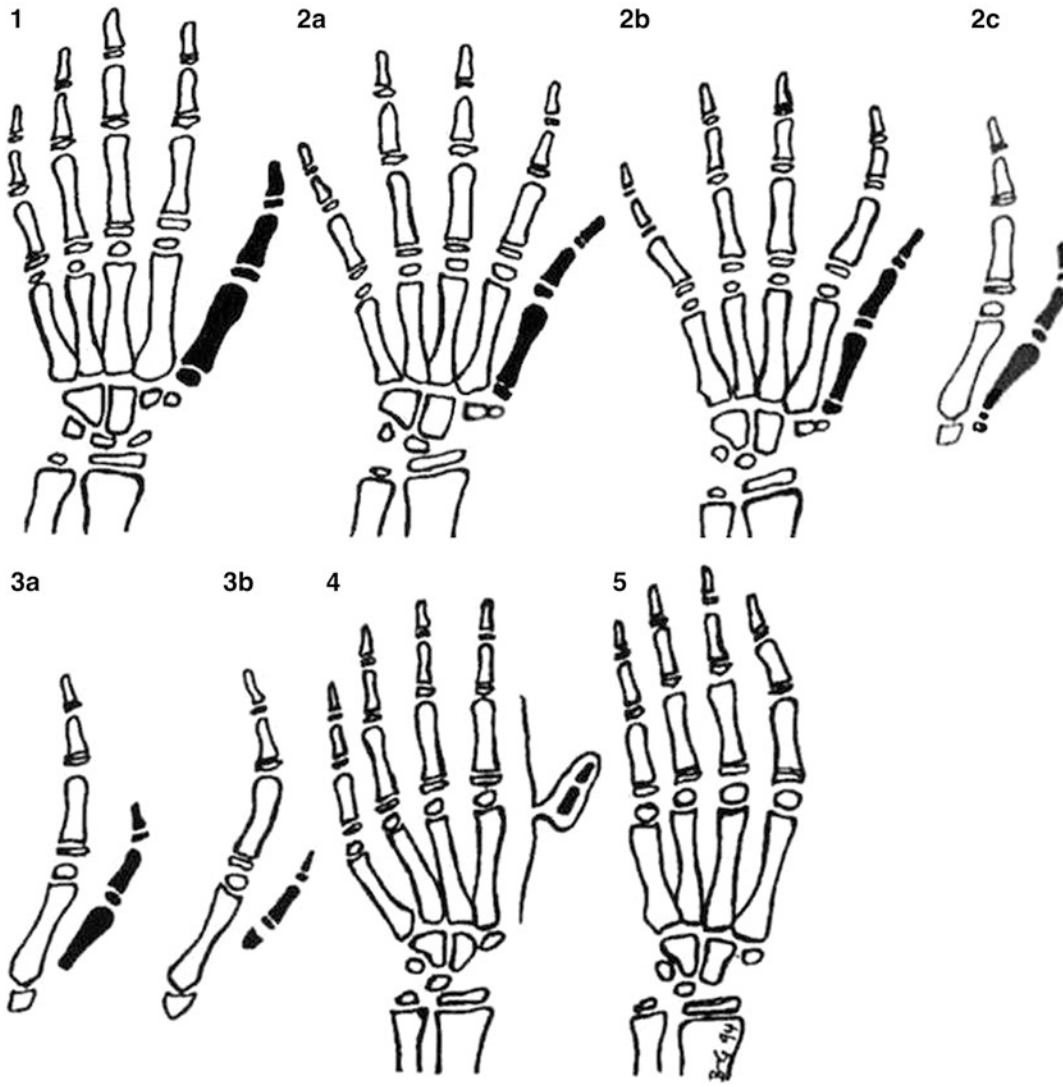

Fig. 9.3 Proposed modified Blauth classification. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

within grades do not create separate categories for each anatomical anomaly and its treatment, but allow the results of surgical reconstructions to be compared for "similar" thumbs:

- *Grade 1:* The thumb is small, there is some hypoplasia of the thenar musculature and there may be mild extrinsic anomalies. However, the joints are stable and mobile. No surgery is indicated.
- *Grade 2:* Thumb hypoplasia is more severe and would benefit from reconstruction. The CMC joint is present. Intrinsic and extrinsic anomalies are more significant, and there is MCP joint instability and first web underdevelopment. An increasing severity of hypoplasia is recognized according to the clinical and radiological examinations:
  - *2A:* Mild. Hypoplasia of intrinsic muscles; uniaxial MCP joint instability; and adduction of the first metacarpal with first web deficiency. Management includes release of the first web, MCP joint ulnar collateral ligament (UCL) reconstruction and an opposition transfer as appropriate. Mild extrinsic anomalies do not demand attention.
  - *2B:* Moderate. The intrinsic hypoplasia and first web insufficiency are more severe. MCP joint instability is multiplanar, requiring reconstruction of soft tissues other than the UCL alone. Chondrodesis or formal fusion may be necessary in a minority. Extrinsic anomalies demand reconstruction for optimal thumb function and prevention of recurrence of deformity. CMC joint stability and mobility are adequate as indicated by radiological evidence of a proximal flare at the 1st metacarpal base (Fig. 9.4).
  - *2C:* Severe. Increasing hypoplasia of all structures, with severe global MCP joint instability, gross extrinsic hypoplasia and an inadequate CMC joint – clinically unstable or immobile. These thumbs may also be identified by the radiological appearance of loss of the proximal metacarpal base flare, which tapers proximally (the "pencil sign") (Fig. 9.5). The thumb requires a more significant 1st web release and skin transposition, an opposition transfer and extrinsic reconstruction. A chondrodesis or fusion of the MCP joint and reconstruction of the CMC joint through stabilization or mobilization creates a satisfactory albeit compromised thumb ray. Rarely, pollicization may be considered to provide a superior result for the most severe of these Grade 2C hypoplasias.
- *Grade 3:* Increasing hypoplasia of all structures. The CMC joint is absent (Fig. 9.6).
  - *3a:* Absence of the proximal metacarpal.
  - *3b:* A distal metacarpal remnant is the only remaining metacarpal component.

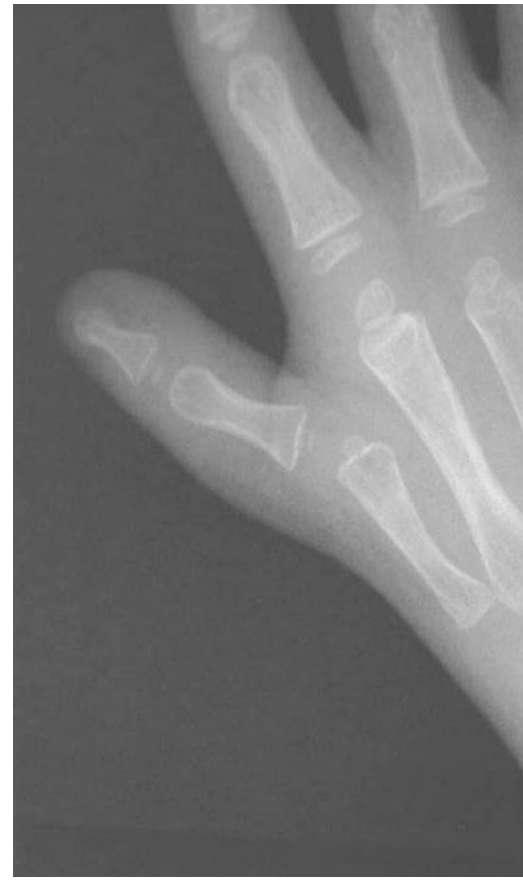

Fig. 9.4 Blauth Grade 2B thumb hypoplasia with proximal metacarpal flare. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

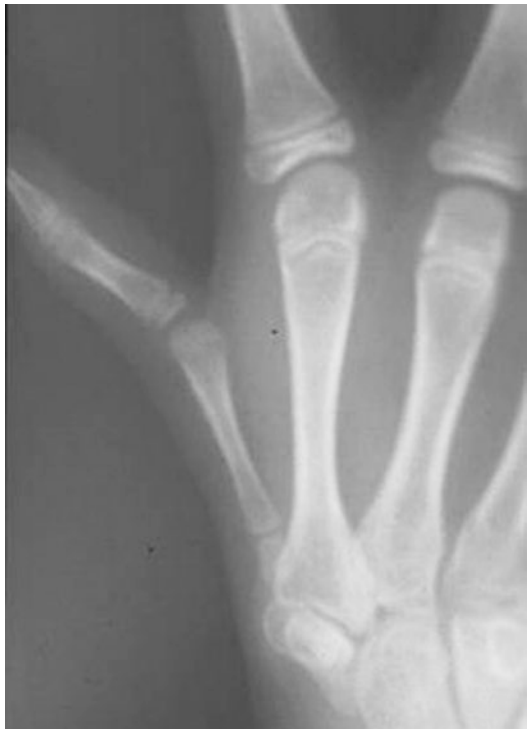

Fig. 9.5 Blauth Grade 2C thumb hypoplasia with an inadequate CMC joint. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

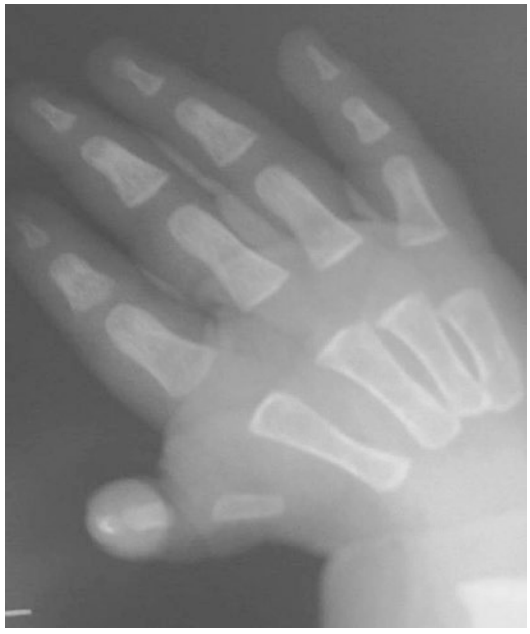

Fig. 9.6 Grade 3A – absent proximal metacarpal. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

- *Grade 4:* Metacarpal absence. The floating thumb with phalanges is connected by a skin bridge to the index finger ray.
- *Grade 5:* Thumb absence.

Pollicization is usually considered the optimal surgical reconstruction for Grades 3, 4 and 5, but more recently, alternative methods of construction of a CMC joint, through transfer of vascularized and non-vascularized joints and/or bone, have shown some encouraging results and may be indicated when the need to retain five digits is paramount [13–29].

The precise reconstructive procedure may be tailored to the degree of hypoplasia and the amount of bone available within the thumb to be retained. The surgical techniques are easier to perform, and the results of such surgery are likely to be better for Grade 3A thumbs than for those of Grade 3B or 4. In Grade 5 hypoplasia, a vascularized toe transfer is perhaps the only feasible method of creating five digits.

Surgery

When the child is under anaesthesia, a further pre-operative examination assists decision-making. CMC joint stability and mobility, or the lack thereof, MCP joint instability and the passive range of IP joint motion can be confirmed at this time (Fig. 9.7a–c). Final decisions await the detail of anomalous anatomy revealed at surgical exploration.

Surgical Techniques

First Web Insufficiency

A four- or a five-flap web-plasty is the most common technique of first web deepening (Fig. 9.8a–d). Rotation and advancement of tissue from the dorsum of the hand may be indicated for more severe first web deficiency. It is very uncommon to require tissue from distant sources, such as a pedicle posterior interosseous artery flap or radial forearm flap, or even a free tissue transfer. They may be considered if reconstruction in Grades 3, 4 and 5 is undertaken.

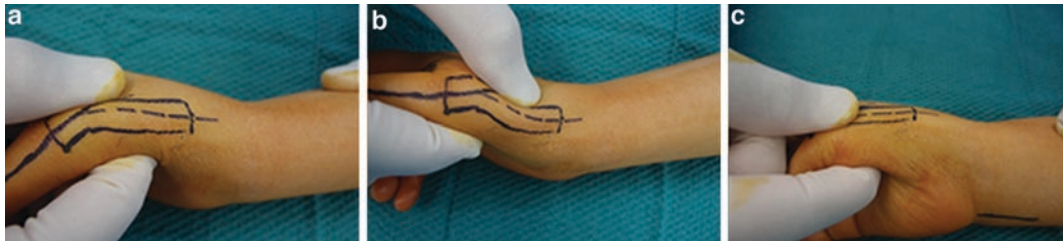

Fig. 9.7 Assessment of CMC joint stability/motion at surgery (**a**–**c**). (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

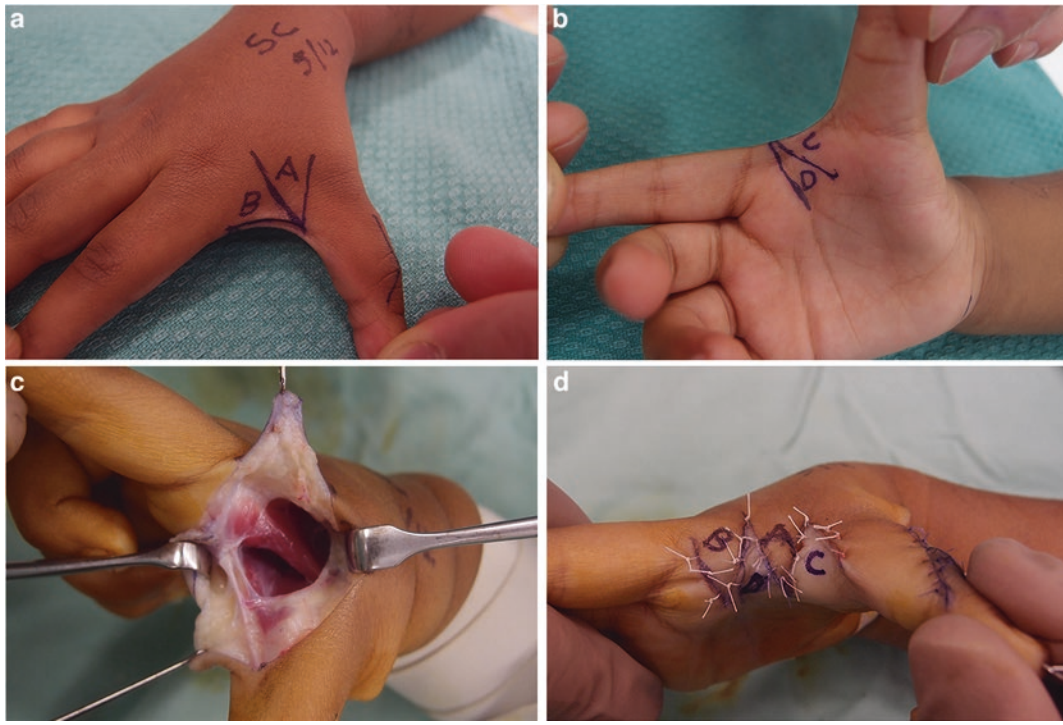

Fig. 9.8 Four flap first web plasties (**a**–**d**). (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

The adductor pollicis and first dorsal interosseous muscles, both supplied by the ulnar nerve, are intact but play a role in the adduction of the first metacarpal and first web insufficiency. The thumb is weak and too aggressive a release of these muscles may position the thumb better but weaken it further. The fascia over each muscle should be divided (see Fig. 9.8c). Some gentle recession of the first dorsal interosseous from the thumb metacarpal or of the transverse component of the adductor pollicis may be indicated, but tenotomy should be avoided.

Metacarpophalangeal Joint Instability

In determining the optimal stabilization procedure, consideration must be given as to whether the instability is predominantly a loss of UCL integrity (Grade 2A) or whether the instability is biplanar (or even multiplanar) or of severe global nature (Grades 2B and 2C, respectively), requiring a more extensive reconstruction or even a chondrodesis or fusion of the joint (Fig. 9.9).

There are two common methods for reconstruction of the UCL. One is to use available local tissue, imbricating capsule and ligamentous

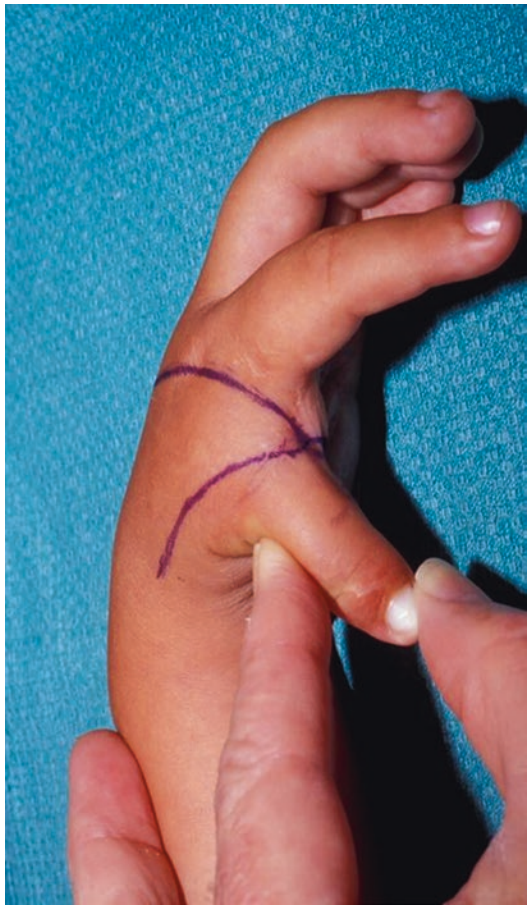

Fig. 9.9 Assessment of MCP joint instability at surgery. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

structures, such as they are, on the ulnar side of the joint. The other is to introduce tissue which is extrinsic to the joint, to cater for the deficiencies of the local structures. The terminal part of a flexor digitorum superficialis (FDS) tendon used for an opposition transfer is a popular source.

Whichever reconstruction of the UCL is performed, it will fail if there is an abnormal abduction force crossing the MCP joint on its radial side, most commonly in association with a pollex abductus anomaly in which there is a flexor to extensor connection [30]. Attention must be directed to this if the joint forces are to be balanced and the UCL reconstruction protected.

The quality of the MCP joint ulnar soft tissues should be evaluated at the time of surgery by direct inspection. If the tissues are satisfactory, one may proceed to a double-breasting of these structures and protect the joint with a fine Kirschner wire (K-wire). A strip of palmar plate can supplement this reconstruction. A 2- to 3-mm width may be mobilized, maintaining its insertion at the proximal phalanx base, transferring its proximal origin dorsally to the metacarpal head-neck junction. A similar technique may be applied for radial collateral ligament instability. However, stability of the MCP joint is one of the key determinants in the creation of a satisfactory thumb, and several authors have found that imbrication of local tissue alone tends to stretch and fail with time [31, 32], which we find a valid observation; this implies that the surgeon should be prepared to augment local tissues if they are found to be unsatisfactory at surgery.

If local tissue is adequate for collateral ligament reconstruction, the abductor digiti minimi (ADM) is used as an opposition transfer as described below. If the soft tissues are inadequate, proceeding to an FDS opposition transfer is preferable. One slip of the terminal part of the FDS is passed through a drill hole at the head-neck junction of the metacarpal, from radial to ulnar side, and is sutured to the base of the proximal phalanx and to soft tissues attached to this. Lister and subsequently Smith have advocated placing drill holes through the proximal phalanx, but we prefer to avoid this in the child because of the proximity of the growth plate and the small size of the bone.

One alternative for moderate global instability (Grade 2B) is to use two slips of FDS to reconstruct ulnar and radial collateral ligaments (Fig. 9.10). For MCP joint hyperextension instability, the whole of the palmar plate may be advanced proximally and fixed at the head-neck junction of the metacarpal, creating a check rein (Fig. 9.11a, b). This complex combination of soft tissue reconstructions may be preferred to chondrodesis or fusion, unless the underdevelopment of articular surfaces is profound indeed. Intraoperatively, the "elephant's trunk sign" is indicative of severe global instability (Fig. 9.12a, b). The condyles of the head of the metacarpal are severely underdeveloped on the palmar

aspects, with the shape of the metacarpal head, viewed end-on, triangular in appearance, curving palmar in the manner of an elephant's trunk. The base of the proximal phalanx is of small diameter

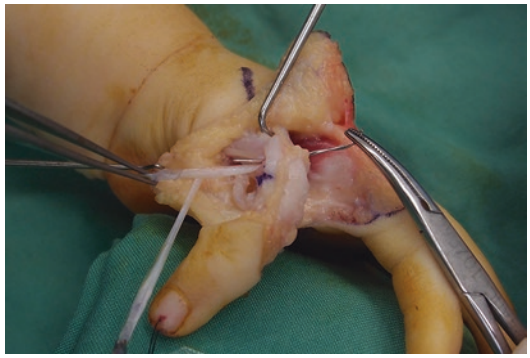

Fig. 9.10 Use of an FDS slip to create an MCP joint ulnar collateral ligament. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

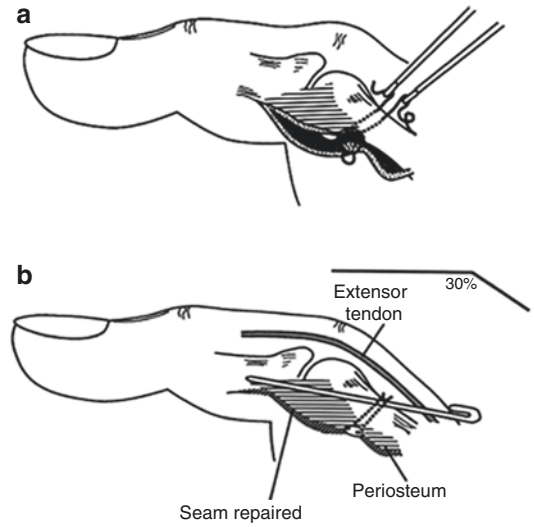

Fig. 9.11 Advancement of the palmar plate proximally to prevent hyperextension instability of the MCP joint (**a**, **b**). (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

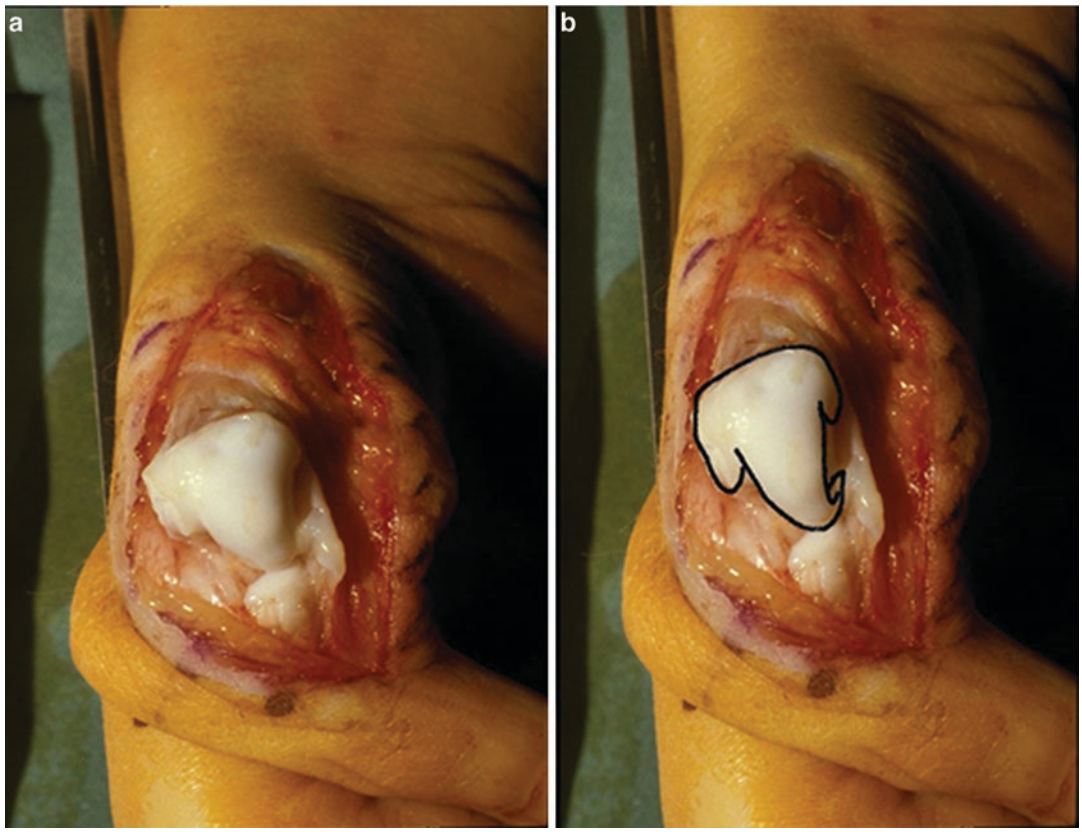

Fig. 9.12 The "elephant's trunk" sign of global MCP joint instability (**a**, **b**). Note also the hypoplastic base of proximal phalanx. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

and is planar with no concavity. A formal arthrodesis can be performed, but this does shorten the thumb and is only possible if there is epiphyseal ossification. A chondrodesis, fixing the cartilaginous surfaces with one or two fine wires, will stabilize the joint, at least temporarily. This is necessary for the degree of underdevelopment present in Grade 2C thumbs.

Correction of MCP joint instability is vital to the protection of the underdeveloped CMC joint. Radial deviation at the MCP joint results in adduction of the metacarpal and basal subluxation at the CMC joint – a zigzag deformity. If an MCP joint fusion or chondrodesis is necessary, this lengthens the lever arm, which places increased stress across the CMC joint and may further compromise an unstable CMC joint. In this instance, one must consider the necessity of a soft tissue stabilization at the CMC joint level, a relatively difficult reconstruction using free tendon graft in a figure of eight fashion. A soft tissue release for an immobile CMC joint is possible but may create instability and is therefore rarely undertaken. In circumstances of severe MCP joint instability and significant proximal hypoplasia, in spite of the presence of a CMC joint, alternative methods of CMC joint reconstruction such as pollicization may be considered.

Opposition Transfers

The main alternatives are an ADM (Huber) transfer and an FDS transfer. There are proponents of both, but there is no clear evidence of the superiority of one over the other [33]. The use of the ADM diminishes the power of abduction of the little finger but provides some thenar bulk. It is a better pronator of the thumb ray. The FDS transfer removes a flexor from the usually more mobile ulnar digits (ring finger), perhaps decreasing grip strength, and fails to provide any bulk to the thenar eminence. The FDS is superior in providing palmar abduction but pronates less effectively. When additional tissue is needed to stabilize the MCP joint, the FDS can provide this as described above.

Abductor Digiti Minimi Transfer The incisions are shown in Fig. 9.13. The ulnar incision at the junction of glabrous skin and dorsal skin provides a very pleasing cosmetic result (Fig. 9.14). Proximally, the incision should curve around the wrist crease at the level of the pisiform so that the origin of the ADM may be mobilized, if neces-

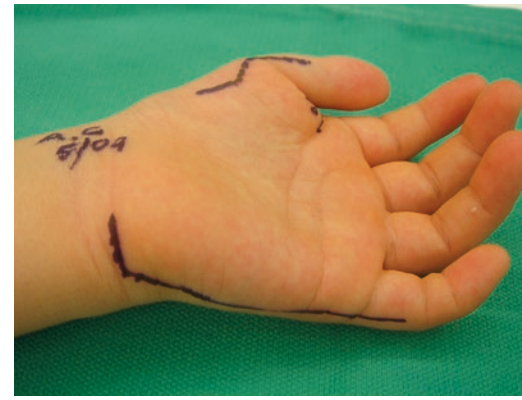

Fig. 9.13 Medial incision for ADM transfer. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

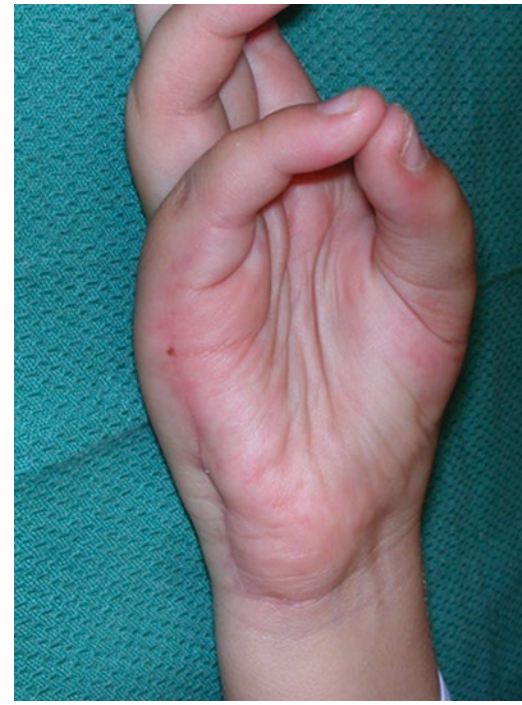

Fig. 9.14 Scar from medial incision following ADM transfer; note opposition and thenar bulk. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

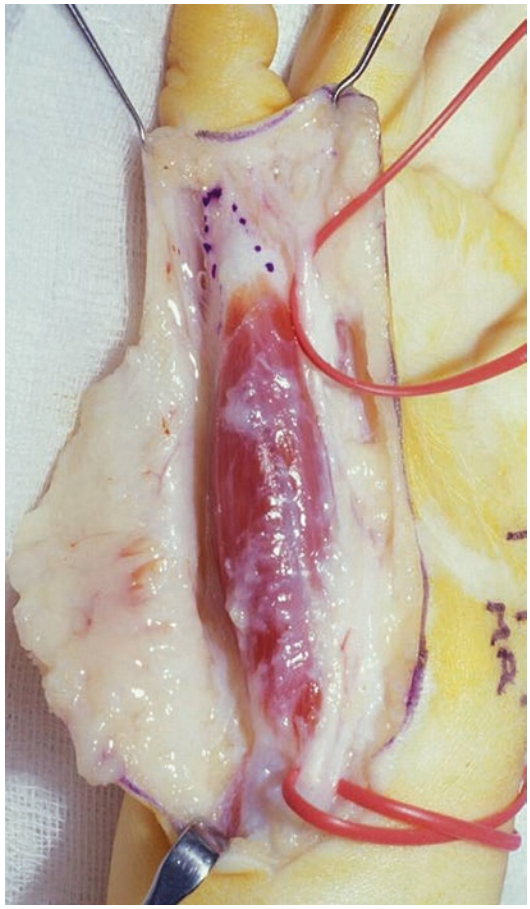

Fig. 9.15 Dissection for ADM transfer with distal extension to gain tendon length. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

sary, for length. Distally, the insertion of the abductor should be incised from the base of the proximal phalanx, but the tendon contribution to the extensor mechanism dorsally should also be harvested to provide adequate length (Fig. 9.15). This tissue is not of adequate quality to be extended to the ulnar side of the joint for ligament construction. We do not transfer the origin of the ADM to the flexor retinaculum as suggested by some for fear of interference with the neurovascular pedicle. Its origin may be mobilized fairly aggressively, maintaining some attachment to both the flexor carpi ulnaris (FCU) and the pisiform proximally. Tunnelling of the muscle is a little more difficult with the ulnar incision than with a para-hypothenar incision. It is necessary to make certain that no retinacular fibres of the aponeurosis impede its passage and that the neurovascular bundle is not kinked during its transfer. Insertion at the thumb is into the abductor pollicis brevis (APB) remnant if it is present. Otherwise it is better to attach the transfer to the head-neck junction of the metacarpal rather than to the proximal phalanx, as the latter insertion tends to create a radial deviating force which may challenge the UCL reconstruction.

Flexor Digitorum Superficialis Transfer Incisions are shown in Fig. 9.16. The FDS transfer is sutured to the periosteum at the head-neck junction with one slip passed through the metacarpal to be used for UCL reconstruction (see Fig. 9.10).

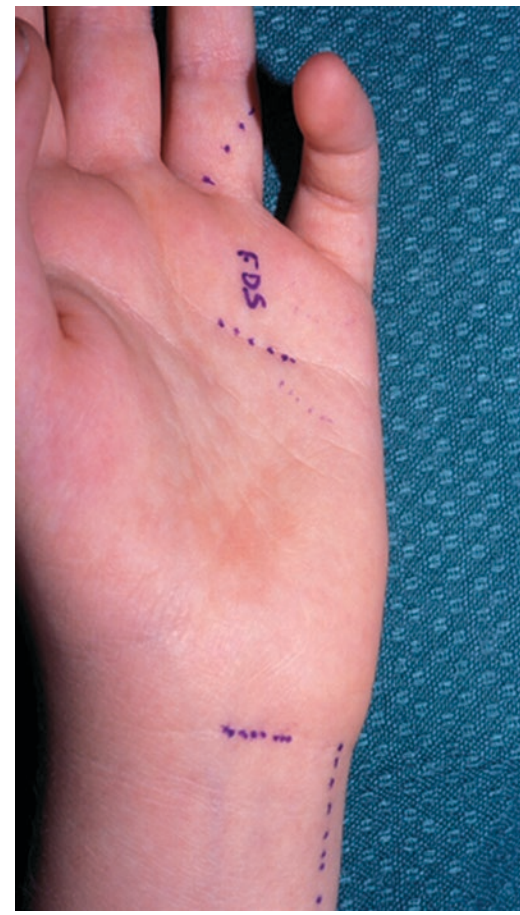

Fig. 9.16 Incisions for FDS transfer. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

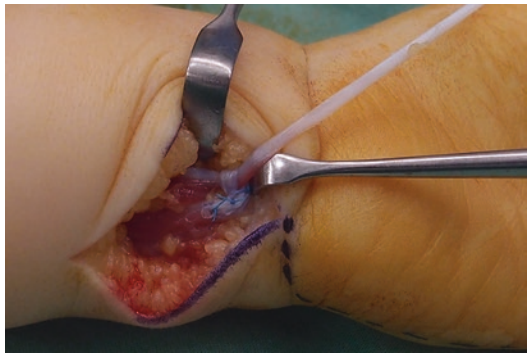

Fig. 9.17 FDS opposition transfer through an FCU pulley. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

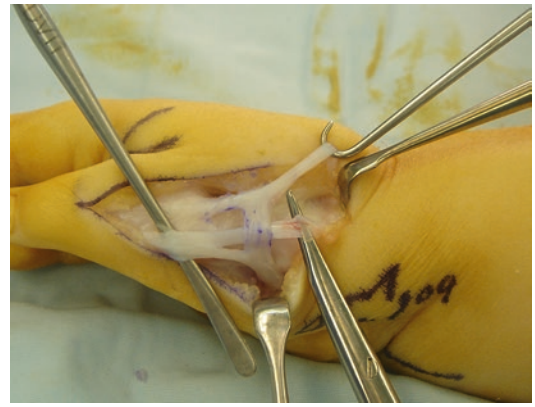

Fig. 9.18 Pollex-abductus connection between extrinsic extensors and flexor. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

The FDS transfer requires the reconstruction of a pulley to allow an optimal direction of pull so that pronation of the thumb ray is possible. This can be achieved with a distally based slip of FCU (Fig. 9.17). The palmar aponeurosis [34] and the transverse carpal ligament [35] are alternative pulleys. A more distal pulley (palmar aponeurosis or flexor retinaculum) potentially acts more as an adducting force, and a more proximal pulley (FCU pulley) tends to provide greater pronation [34], although Vuillermin et al. [36] found no significant difference between the FCU and the transverse carpal ligament pulleys in either Kapandji score or in strength of pinch and grip. It is possible to also prolong a radial slip to assist in reconstruction of the radial collateral ligament for global instability, sometimes in association with a proximal advancement of the palmar plate, as described previously. This aggressive soft tissue reconstruction at the MCP joint reduces the necessity to consider a primary MCP joint chondrodesis or a fusion or at least allows delay of such a procedure until a later stage if failure of the soft tissue reconstruction demands a more permanent solution.

Extrinsic Tendon Reconstruction

Failure to correct a pollex abductus anomaly (flexor to extensor connection) will lead to a recurrence of MCP joint UCL instability, metacarpal adduction and possible CMC joint instability. Flexor pollicis longus (FPL) anomalies are common. Traction on the FPL at the level of the MCP joint will alert the surgeon to eccentric distal insertions and abnormal origins. In the former, deviation of the IP joint or lack of full flexion is evident. In the latter, there is minimal excursion of the musculotendinous unit with proximal traction. Any connection between the flexor and extensor mechanism must be divided (Fig. 9.18). In these instances, the pulley system is often incompetent. This may be reconstructed at proximal phalangeal level with a strip of extensor retinaculum or a strip of local tendon (Fig. 9.19). Sometimes, particularly following release of a pollex abductus anomaly, the FPL tendon will continue to bowstring across the radial aspect of the MCP joint, placing at risk the efficacy of both the UCL reconstruction and the opposition transfer, as the deviating force will tend to recreate the radial deviation deformity at the MCP joint. We believe that, just as in reconstruction for thumb duplications, axial malalignment of extrinsic tendons is one of the main causes of surgical failure. It is possible that axial realignment of FPL following the first web release and MCP joint stabilization may well compromise gliding of the tendon and, if it is present passively, active IP joint flexion. This loss is less important than the presence of a deforming force postoperatively. The radialmost aspect of the tendinous insertion of flexor pollicis brevis (FPB), or perhaps the adductor pollicis, may be elevated from its insertion,

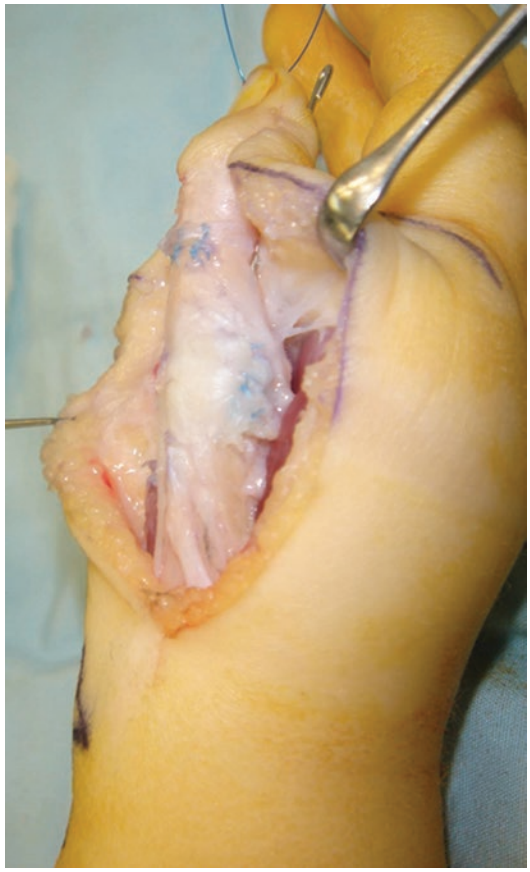

Fig. 9.19 Realignment of flexor pollicis longus and pulley reconstruction. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

allowing transposition of FPL ulnar. The intrinsic muscles, sutured distally, create a pulley and prevent subluxation of FPL radially. Rarely, the FPL needs to be divided in a Z fashion, either proximal to the wrist or distal to the carpal tunnel, to allow realignment and stabilization in the longitudinal axis of the thumb. The tendon ends are sutured, side to side (Fig. 9.20a–d).

If there is minimal passive IP joint motion, it is preferable not to proceed to sophisticated extrinsic flexor reconstruction. A superficialis transfer to a well-formed FPL tendon without an adequate proximal muscle belly is a possibility when there is a satisfactory passive range of motion. A staged flexor tendon reconstruction with preliminary insertion of a silastic rod, pulley reconstruction and subsequent superficialis transfer is rarely necessary but may be considered in certain circumstances. Eccentric extensor and flexor insertions should be centralized. An extensor indicis proprius (EIP) transfer may replace extensor pollicis longus (EPL) or extensor pollicis brevis (EPB) function, when occasionally indicated.

Pollicization

We believe that pollicization provides optimal thumb function and a very satisfactory appearance when the CMC joint is absent in Grades 3, 4 and 5 hypoplasia. Such a procedure may also be considered, uncommonly, in cases of Grade 2C hypoplasia in which, in spite of the presence of a proximal metacarpal, the global hypoplasia is so severe that reconstruction would provide an inferior thumb to that achieved by pollicization (positive "elephant's trunk" and "pencil" signs). The necessity to retain five digits for social, racial or religious reasons must not be underestimated. In these instances, the alternative reconstructions outlined below are considered.

The surgical technique of pollicization has been refined over the past 100 years [37–44] and is still subject to modifications today. The technique of Buck-Gramcko is probably still that followed by most surgeons [37]. A number of modifications have been offered, with alterations in placement of incisions and specific techniques of CMC joint and tendon reconstruction. However, the younger surgeon might find a reliable friend if he/she adheres to Buck-Gramcko's method.

Incisions The surgery is performed under tourniquet. Some prefer not to utilize a Martin or Esmarch bandage to exsanguinate the limb, so that venous and arterial vasculature patterns are more obvious. Our preference is to use a bandage to exsanguinate the limb. Over a relatively short period of time, the vessels fill with blood allowing identification, and we believe this to be preferable to the excessive bleeding which may occur as the tourniquet time progresses. The surgeon may move from palmar to dorsal dissection sites whilst this phenomenon evolves.

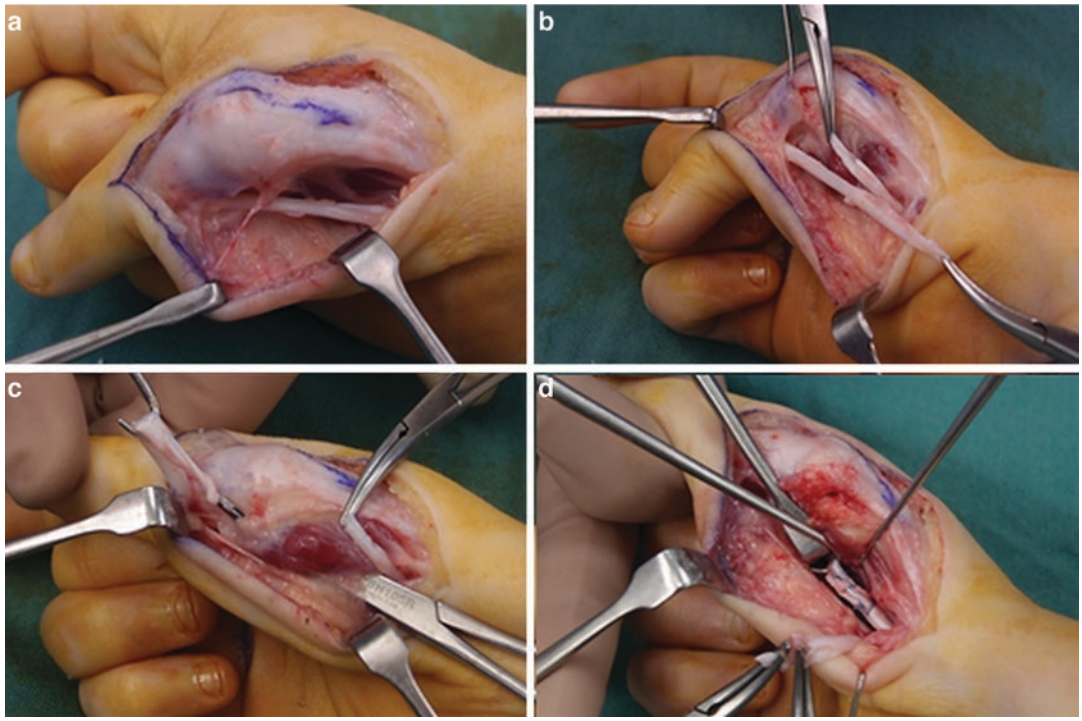

Fig. 9.20 Z-division and realignment of FPL in the correct longitudinal axis (**a**–**d**). (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

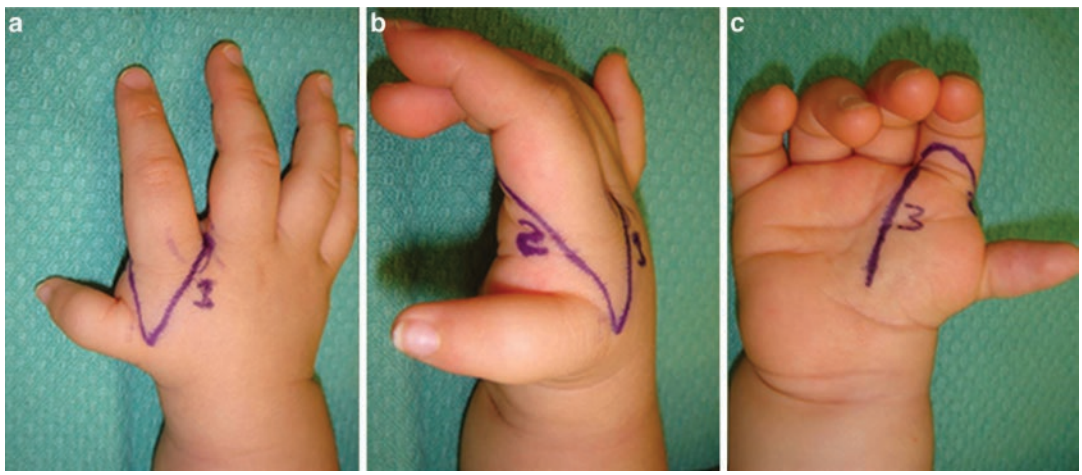

Fig. 9.21 Z concept of pollicization skin incision with the three limbs marked (**a**–**c**). (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

The skin incision must provide sufficient exposure and allow index finger transposition as well as creation of an adequate first web space. For Buck-Gramcko's technique, understanding of the concept of the incisions forming a modified z-plasty may be helpful (Fig. 9.21a–c). The first limb begins dorsally and distally at the index-middle web and extends proximally and obliquely to the radial border of the hand proximal to the index finger MCP joint. The second

limb extends from the proximal point of the first limb onto the palmar aspect of the proximal phalanx to meet the origin of the first limb in the index-middle web space. The third limb extends proximally from the palmar limb, in the line of the index-middle intermetacarpal space. These flaps are transposed when the index finger is rotated and recessed proximally. The standard incisions may be modified to cater for specific demands. The palmar incision in the digit should be extended to just proximal to the proximal interphalangeal (PIP) joint when the index finger is well-developed and mobile (see Fig. 9.21c); this mimics the skin draping seen in a normal thumb and first web. A longer thumb is preferable if there is significant index finger stiffness as greater length compensates for lack of mobility. In this instance the palmar incision is moved proximally towards the basal finger crease. A longitudinal incision extended distally from the dorsal limb incision to the PIP joint allows access to the extensor mechanism and its lateral bands for construction of thumb intrinsic mechanisms and the extrinsic muscles, EPB and abductor pollicis longus (APL) (Fig. 9.22). The third palmar limb may be moved radially to incorporate excision of a Grade 3 or Grade 4 thumb (Fig. 9.23). Alternatively, the excision of such may be incorporated into the second, more radial limb (Figs. 9.22 and 9.24). Alternative skin incisions include those popularized by Ezaki and Carter [41] and Upton [43] or modifications of these.

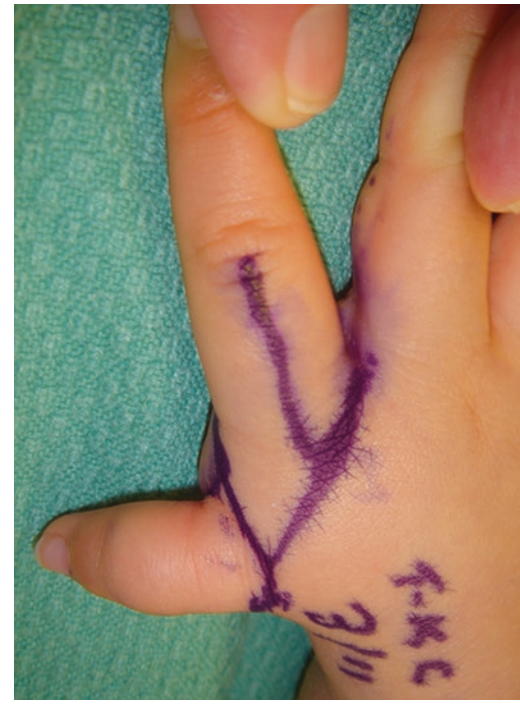

Fig. 9.22 Dorsal incision for intrinsic reconstruction. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

Palmar Dissection We prefer to begin with the palmar dissection. The neurovascular bundle of the index-middle web is identified. A radial neurovascular bundle is usually present. However, the radial digital artery to the index finger may be very small, perhaps even absent, in Grade 5 hypoplasia which is accompanied by index finger hypoplasia. The neurovascular bundles on either side of the digit are mobilized using microsurgical instruments and magnification. Inspection of the second common digital artery will determine the level of bifurcation into digital arteries to the adjacent sides of the index and middle fingers. The radial digital artery to the middle finger is tied off (Fig. 9.25). The neurovascular pedicle is dissected proximally. A neural ring is relatively common but can usually be attended to by intraneural dissection of the common digital nerve (Fig. 9.26). An awareness of the possibility of arterial compromise with proximal recession of the digit, either due to a neural ring or fascial structures, should prevent this complication.

Rarely, anomalies of the common digital artery demand an alteration in strategy. The vessel may arise from the deep palmar arch. In this instance the artery is short and may not allow proximal recession of the digit without compromising its arterial supply. It may be necessary to divide the deep arch, following preliminary clamping and assessment of any compromise in vascularity to the hand, to gain length. In one instance, we have found absence of a palmar common digital artery but with a large dorsal metacarpal artery connecting to the palmar sys-

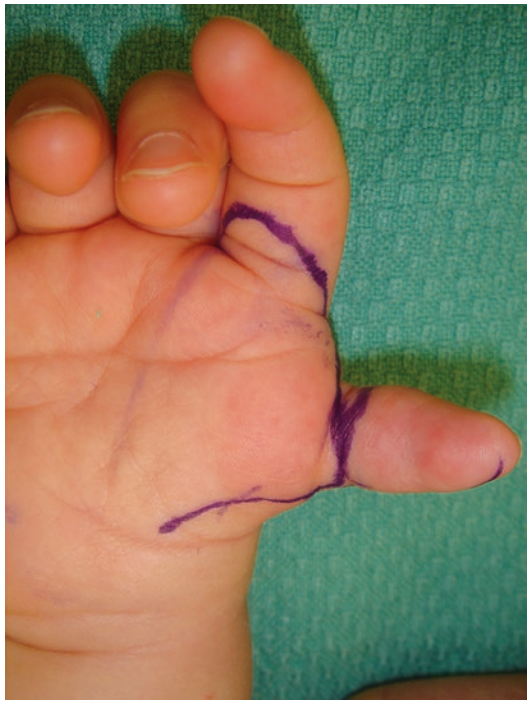

Fig. 9.23 Incorporation of Grade 3 thumb to be excised into third limb of pollicization incisions. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

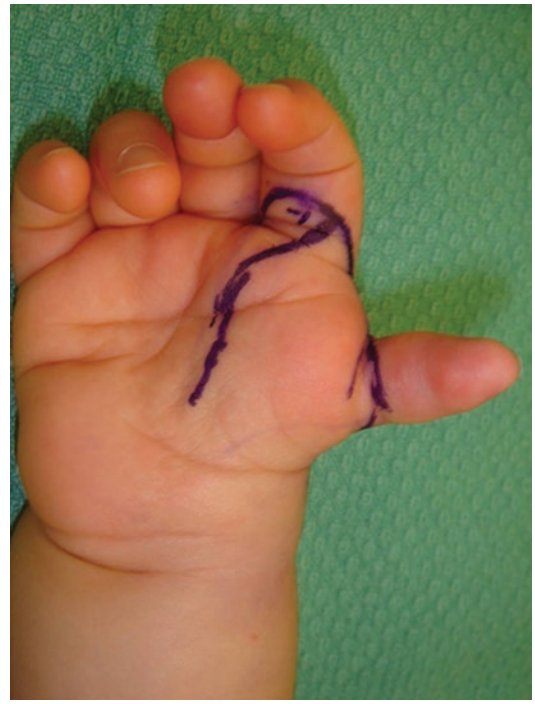

Fig. 9.24 Incorporation of Grade 3 thumb to be excised into second limb of pollicization incisions. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

tem at the head-neck junction (Fig. 9.27). Pollicization was performed with the digit nourished by this vascular pedicle.

The A1 and A2 pulleys are divided (Fig. 9.28). The A3, A4 and A5 pulleys become the thumb A1, oblique and A2 pulleys, respectively. Some routinely shorten the flexor digitorum profundus (FDP) [45], but we have not found this necessary unless pollicization is performed at greater than 5 years of age. A z-shortening can be performed proximal to the wrist to avoid increasing the possibility of adhesions within the dissected area of the palm. The neurovascular structures and flexor tendons can then be delineated and protected with a vessel loop; note that if a loop is used care must be taken to avoid excessive traction on the neurovascular structures. The intermetacarpal ligament is divided after attending to the pulley system.

The dissection of the intrinsic muscles, the first dorsal and first palmar interossei, begins on the palmar side, mobilizing the musculotendinous units to the MCP joint level, but protecting the neural supply of each.

Dorsal Dissection Thin dorsal flaps are elevated until the dorsal venous architecture is identified so that one or two veins, along with superficial dorsal nerves, can be mobilized separately from the flaps and the underlying digit (Fig. 9.29). This prevents kinking of vessels, compromising venous return, when the digit is recessed proximally. Capturing these vessels and nerves (protected by maintaining some surrounding fat) in a vessel loop is useful to allow subsequent gentle retraction when it comes to securing the metacarpal head to the metacarpal base.

The extensor mechanism is inspected to assess the presence or absence of EIP and the quality of extensor digitorum communis (EDC) (Fig. 9.30). Excursion is often poor when radial deficiency accompanies thumb hypoplasia. Subsequent dissection of the extrinsic extensors and the intrinsic

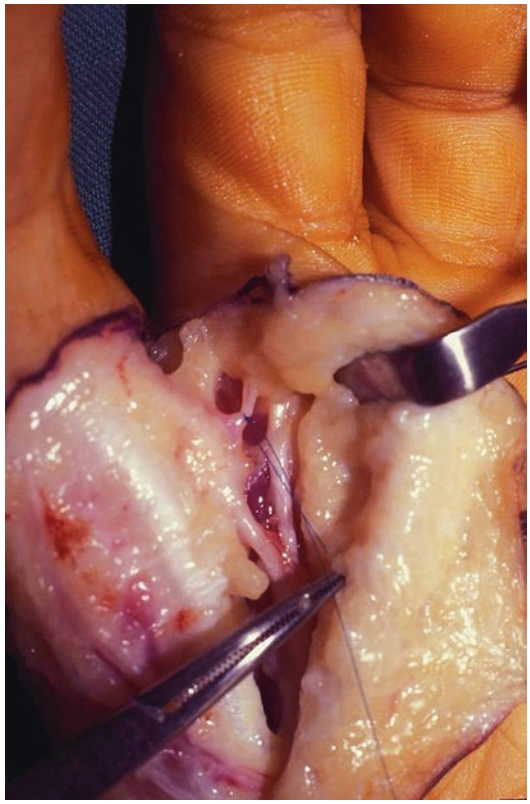

Fig. 9.25 The radial digital artery to the middle finger is tied off. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

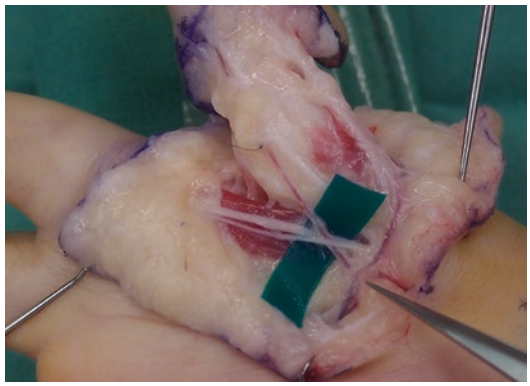

Fig. 9.26 Dissection of a neural ring to prevent common digital artery compromise. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

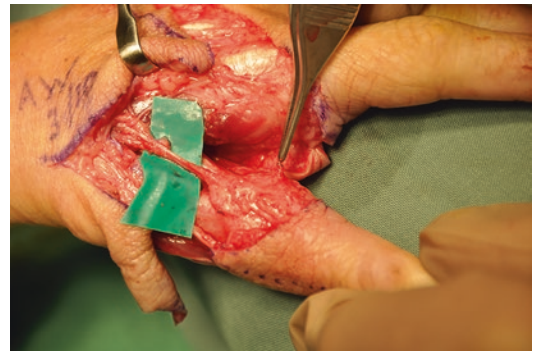

Fig. 9.27 Dorsal metacarpal artery connecting with palmar digital system. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

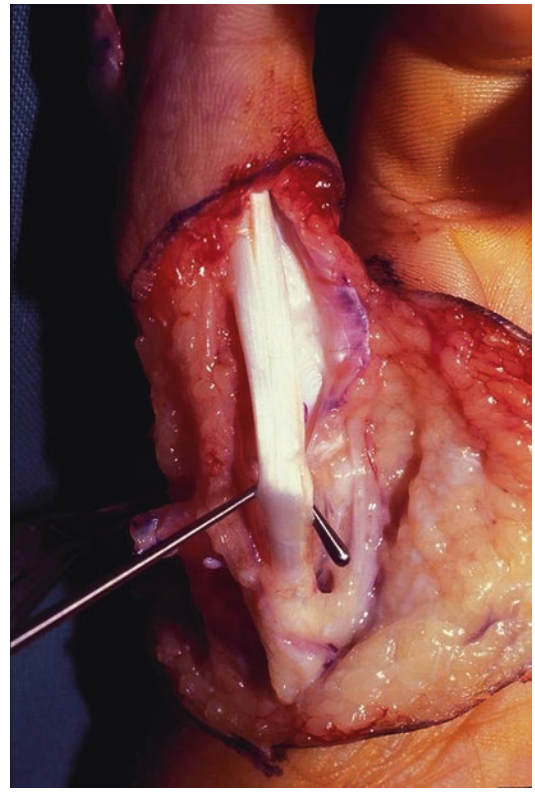

Fig. 9.28 Release of A1 and A2 pulleys. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

contributions to the extensor mechanism are performed before division of the extensors and with the skeleton intact. This allows distal mobilization of the extensor mechanism to the level of the PIP joint, separating the lateral band contributions to this level, but maintaining continuity with the first dorsal interosseous and the first palmar interosseous muscles on radial and ulnar sides, respectively (Fig. 9.31). Release of the

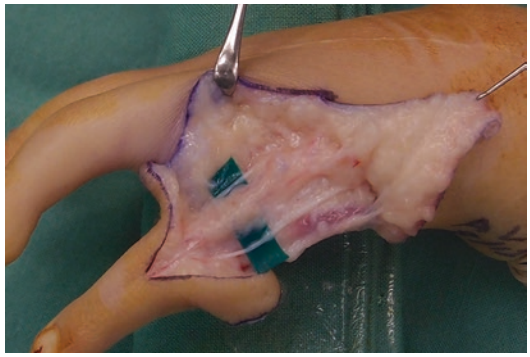

Fig. 9.29 Dorsal veins and nerves. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

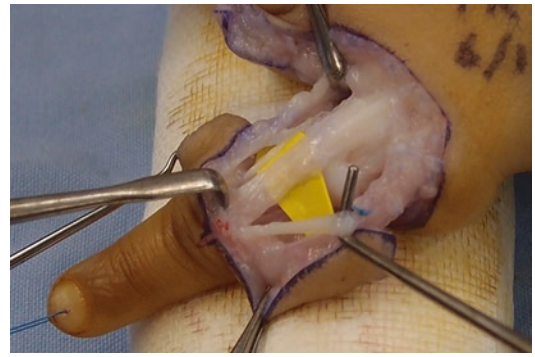

Fig. 9.31 Dissection of radial and ulnar lateral bands without division. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

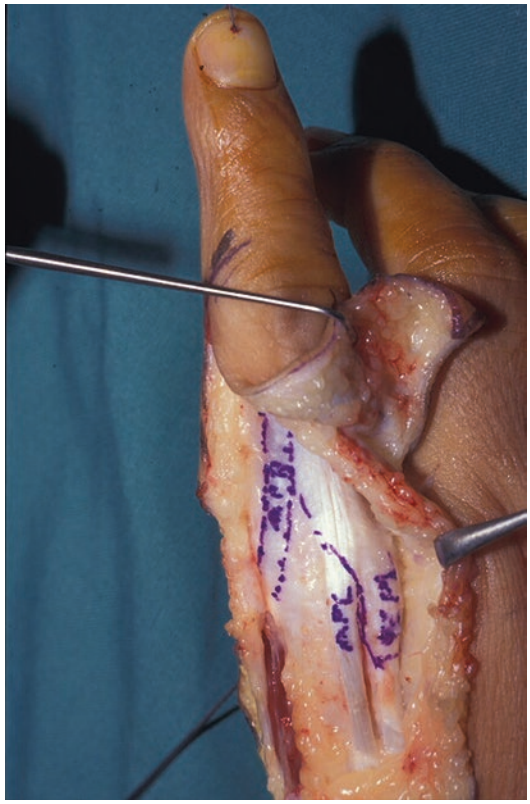

Fig. 9.30 Intrinsic and extrinsic tendons outlined prior to reconstruction. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

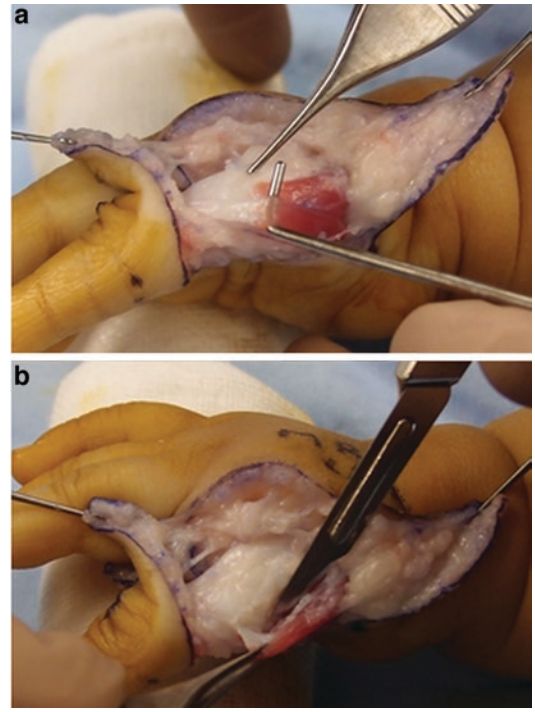

Fig. 9.32 Dissection of first dorsal interosseous from capsule of MCP joint (**a**, **b**). (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

intrinsic attachments to either side of the base of the proximal phalanx must respect the integrity of the capsule and ligaments of what will become the new CMC joint (Fig. 9.32a, b). Although some recommend ablation of the blood supply to the physis of the metacarpal, others prefer not to interfere with any contribution which may maintain the integrity of the physis of the proximal phalanx. Ezaki has suggested that searching for and preserving the small arterial branch to the palmar aspect of the index MCP joint, which usu-

ally arises from the deep anterior metacarpal artery, may be important in minimizing the risk of developing premature physeal closure of the transferred proximal phalanx and a resultant short first metacarpal [46].

At this point, the EIP and EDC may be divided at the level of the MCP joint. Any remaining attachments of the intrinsic musculature are then dissected in a sub-muscular extra-periosteal manner from the metacarpal diaphysis. Retractors are then placed around the head-neck junction of the metacarpal, protecting all other structures, particularly the palmar neurovascular bundles, whilst an osteotomy is performed at the head-neck junction of the metacarpal. In the young child, a Beaver blade or small osteotome is most satisfactory for the purpose. Some bone nibblers can be used to flower the metaphyseal perimeter of the head of the metacarpal by simply breaking bone fragments, which remain attached to the periosteum. This leaves the bone with osteogenic potential to assist in bone union of the new trapezium to the metacarpal base (see below). The physis is removed using a fine curette and Beaver blade so that the new trapezium will not grow longitudinally. If ossification has occurred in the head of the metacarpal, it is easy to establish that the growth plate has been adequately removed. Care needs to be taken when ossification has not occurred, so that the articular surface of the metacarpal head is not breached.

CMC Joint Reconstruction An integral part of the success of a pollicization is the creation of a new CMC joint, and there are a number of principles in reconstruction which are important:

- Optimal positioning of the new thumb ray in palmar abduction, radial abduction and appropriate rotation.
- Placement of the thumb ray in an anterior plane to that of the finger CMC joints.
- Hyperextension of the index finger MCP joint via flexion of the metacarpal head to prevent hyperextension deformity of the new CMC joint. This will result in orientation of the raw cancellous bone of the neck of the metacarpal dorsally rather than proximally.

It is difficult to satisfy all of the above parameters and obtain bony apposition between the index finger metacarpal head and base. Buck-Gramcko initially suggested retention of the metacarpal base to be necessary only in cases with relatively short phalanges. In these cases, the metacarpal head was fixed to the base using one or two K-wires. If the phalanges were of normal length, his original description did not retain the metacarpal base, and the metacarpal head was sutured to the joint capsule and carpal bones. Subsequently, most, including Buck-Gramcko, have preferred to retain the base. The suggested plane of osteotomy through the base of the metacarpal has varied, with both a transverse osteotomy at the metacarpal base and an oblique osteotomy in either coronal or sagittal planes described. Some prefer K-wire fixation to promote head to base union as described by Buck-Gramcko [37, 39, 41, 47] whilst others eschew this [43]. Manske wrote of the importance of a fibrous union rather than a bony union between the retained base and head [48, 49], creating a pseudoarthrosis at this articulation. He proposed that using sutures rather than K-wires for fixation permitted increased mobility of the new thumb.

A concern is one of possible instability of the new trapezium. However, the effect on functional outcomes according to the presence or absence of bone union between the metacarpal head (new trapezium) and the metacarpal base has not been determined. Our preference is to aim for bone union whilst satisfying the above criteria of positioning.

An oblique osteotomy leaving the bone longer dorsally and radially provides a satisfactory compromise between positioning the thumb optimally and maintaining some bone to bone contact (Fig. 9.33). A fine K-wire can be placed antegrade through the flexed metacarpal head and phalanges of the index finger and then driven retrograde into the carpus with the thumb in the desired position, removing the wire at 5 weeks (Fig. 9.34). Before fixing the thumb to the carpus in this manner, two gauge 2-0 Ti-Cron sutures are placed through the base of the metacarpal and into the metacarpal head, to be tightened following wire fixation of the thumb to the carpus. This

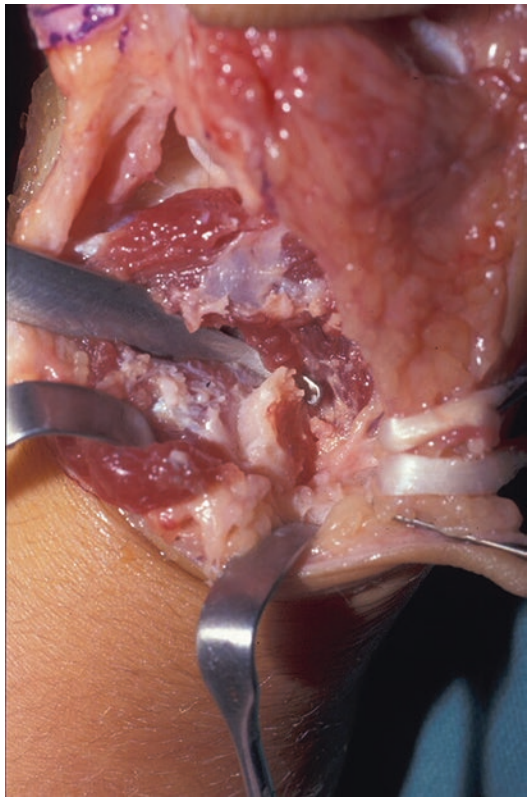

Fig. 9.33 Oblique osteotomy at base of index finger metacarpal. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

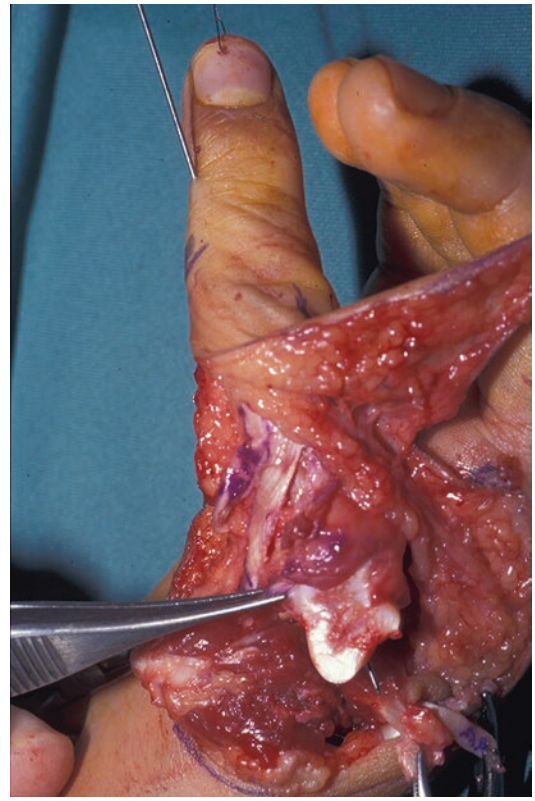

Fig. 9.34 K-wire placement through index finger with metacarpal head flexed. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

method compromises the position of pronation, as 90° only is possible if one is to maintain an anterior lie of the new trapezium in relationship to the metacarpal base and some bone to bone apposition. Thirty degrees of radial abduction and 40° of palmar abduction is ideal. The less mobile digit may be fixed at lesser angles of radial and palmar abduction. Passive joint motion and the quality of the extrinsic and intrinsic motors play a role in this decision. Mennen [44] suggested that pollicization without creation of a neo-trapezium, but with complete resection of the metacarpal, not only simplifies the procedure but also can create sufficient stability at the base of the thumb, prevent mal-growth and lead to a more thumb-like appearance in terms of length.

Tendon Reconstruction The EIP, if present, is shortened and re-sutured to the central extensor mechanism to the proximal interphalangeal joint of the index finger. Most refer to this as a construction of EPL function. However, the insertion of the central slip into the middle phalangeal base of the index finger mimics EPB anatomy of the thumb, rather than EPL anatomy. The new tendon does simulate the adduction-retropulsion action of EPL. The tension of repair should be firm but less than full. Too tight a repair will result in retropulsion of the pollicized digit, particularly if a balance is not achieved following the reconstruction of APB. EDC helps stabilize the position of the new thumb metacarpal, more so if its route and positioning are modified to better mimic the function of APL. It is attached to the periosteum at the dorso-radial aspect of the index proximal phalanx, avoiding the growth plate. If EIP is absent, EDC is used for EPB construction.

Although Buck-Gramcko advises dividing the lateral bands, shortening and suturing them to create an APB and an adductor from the first dorsal interosseous and the first palmar interosseous respectively, we usually concertina these tendons without dividing them and suture them together under as firm a tension as is possible. It is necessary to mobilize both lateral bands to beyond the PIP joint of the index finger, particularly that from the first dorsal interosseous so that its ability to abduct and rotate is optimal. This also decreases a tendency of the lateral bands to hyperextend the new MCP joint of the thumb. A gauge 5-0 Ti-Cron suture is used to secure the tendon reconstructions.

When thumb hypoplasia is accompanied by radial hypoplasia, there is often a camptodactyly of the index finger. It may be preferable to deal with any significant flexion deformity of the new thumb MCP joint at a second procedure, in order not to interfere with the viability of the pollicized digit.

The tourniquet is released to check the vascularity of the thumb. Flaps are then refashioned so that they may be sutured into position with a pleasing contour. The skin tension within the flaps will assist the musculotendinous reconstruction in maintaining the position of the thumb once the wire is removed (Fig. 9.35).

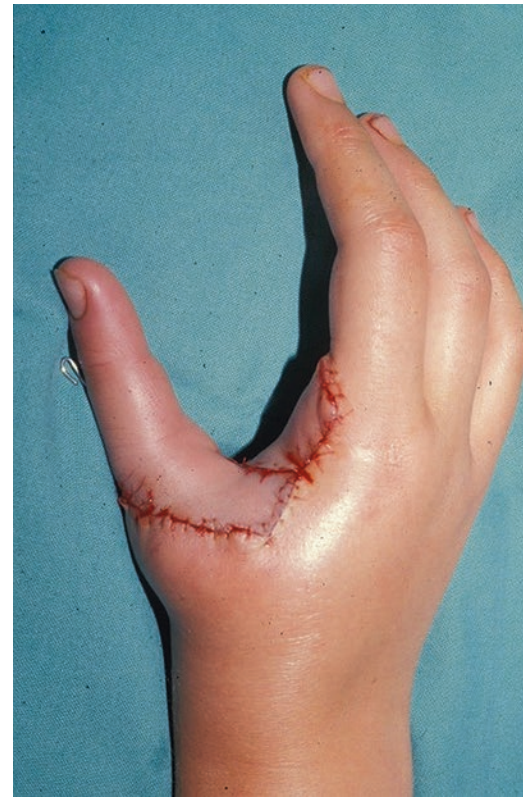

Fig. 9.35 Position of reconstructed thumb. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

Reconstruction of Grades 3, 4 and 5 Thumb Hypoplasia

When pollicization is unacceptable to parents and/or patient, reconstruction of Grades 3, 4 and 5 thumbs is possible [13–16], and alternative methods to reconstruct the CMC joint and hypoplastic or missing metacarpal can be considered. Non-vascularized transfer of toe phalanges can be used for different indications in reconstruction of the hand [17–19]. Gilbert [50] reported using one or two non-vascularized toe phalanges in 38 reconstructions of thumb hypoplasia grade 3B, 3C and 4 at the 2018 World Symposium of Congenital Malformations of Hand and Upper Limb. An alternative is to transfer the distal two-thirds of the fourth metatarsal bone (non-vascularized), reversing this and using the metatarsal head as the new joint [20]. The shaft is fixed distally to the remnant of the metacarpal or proximal phalanx of the Grade 3 or 4 thumb [21]. In order to reduce donor site morbidity at the foot, Chow et al. [21] used a non-vascularized hemi-longitudinal 3rd or 4th metatarsal graft in six cases.

Although continued growth of transferred non-vascularized metatarsal bone has been reported [51], microsurgical reconstruction is more likely to provide growth than those reconstructions relying on non-vascularized bone grafts, and there is an increasing number of reports of encouraging results.

Free vascularized transfer of metatarsal bone [13, 22–24, 27], metatarsophalangeal (MTP) joint [14–16, 25, 26], reversed MTP joint [27], or free vascularized use of spare parts such as an

accessory great toe [28] or a contralateral duplicated thumb [29] may be used for reconstruction in thumb hypoplasia. The vascularized MTP joint may be transferred to the carpus and to the base of the shaft of the second metacarpal. The metatarsal head becomes the new trapezium, and the proximal phalanx becomes the thumb metacarpal. Wang [52] presented the reconstruction of hypoplastic thumbs using free vascularized hemimetarsal composite tissue transfer to reduce donor site morbidity at the 2018 World Symposium of Congenital Malformations of Hand and Upper Limb. An extrinsic extensor can be reconstructed using EIP from the index finger. A superficialis tendon can be transferred as a flexor, and an opposition transfer is created in the manner described for Grade 2 hypoplasia.

Flaps are necessary to re-create the first web in all such cases.

Multiple surgeries are often necessary to create a stable thumb with some mobility. Ultimately, the patient has five digits, and the width of the hand is maintained, which assists grip. However, the problems are many: scarring is significant; the "new" thumb remains small and may require lengthening; joints are often unstable, requiring fusion subsequently; and mobility is poor. The results remain inferior to those obtained from a well-performed pollicization.

Full toe transfers have been utilized by some for Grade 5 hypoplasia. However, the lack of normal proximal tissues and the lack of cortical representation render the function of such transfers less than satisfactory. Skin transfer through pedicle or free flaps is necessary for first web construction.

It is not our practice to apply these reconstructive procedures to young children. If pollicization is refused, some of the above techniques may be indicated at a later age if the child is using the thumb. Carefully selected surgery may stabilize a joint or even provide a joint through an MTP transfer. An opposition tendon transfer may improve function. Such reconstructions should be limited to those who have not excluded the rudimentary thumb but used it for some activities.

Postoperative Management

Following reconstructive surgery of Grade 2 thumbs and pollicization procedures, we immobilize the forearm and hand in an inclusive plaster for 5 weeks. Occasionally the child escapes from the plaster, but the technique taught by Foucher is effective. Two U-slabs of plaster cover the hand and forearm to elbow. Three-inch Elastoplast tape is used as a stirrup around the elbow to prevent the plaster cast from slipping (Fig. 9.36); the tape can be prolonged past the hand to allow elevation from a drip stand. When performing a pollicization, we prefer to leave the new thumb exposed overnight for inspection before completing the plaster the next day.

Wires are removed in the clinic at 5 weeks. A soft dressing is used for 1 or 2 weeks with twice daily bathing and massage of scars. A low-profile

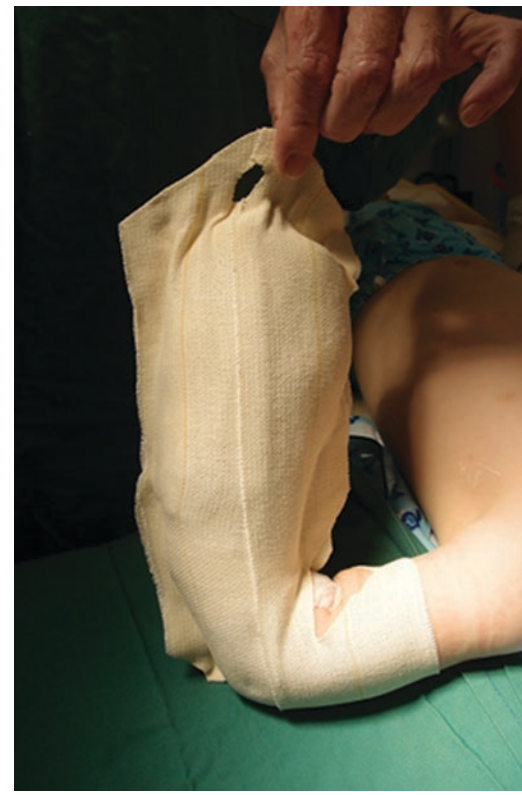

Fig. 9.36 Postoperative dressing. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

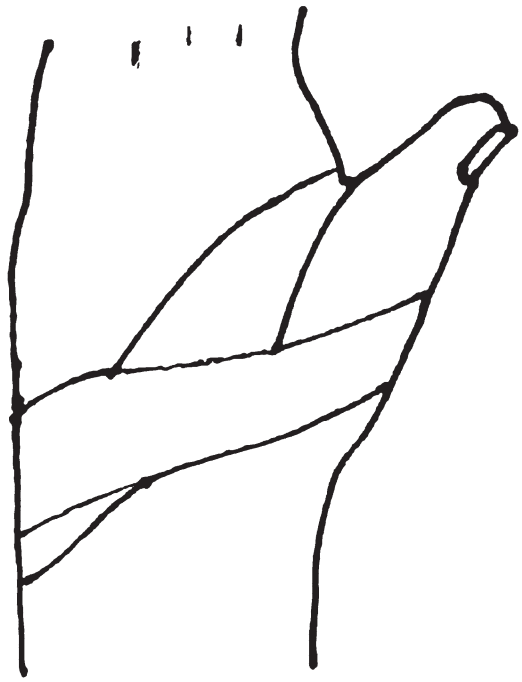

Fig. 9.37 Soft tissue splint. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

elastic splint, as practised by Manske and others, helps maintain opposition without interfering greatly with mobilization (Fig. 9.37) [48]. A deviating force should not be applied beyond the MCP joint. Radial deviation may simulate opposition but is a false friend. Buddy strapping of the two radial fingers discourages side-to-side use of these for pinch and encourages use of the new thumb. The therapists may assist in retraining by introducing the child to games which utilize desired thumb activities. In the main, the child is his/her best therapist. FPL function usually returns from 3 months or thereabouts.

Results and Complications

Functional results following pollicization are entirely dependent upon the pre-operative status. Those with a significant radial longitudinal deficiency are severely disadvantaged. The wrist may be unstable, in spite of the best attempts to stabilize the carpus on the end of the ulna. Extrinsic musculotendinous units to the index finger, in particular, have poor excursion; joints tend to be stiff with camptodactyly of the index finger a common finding. The index finger is hypoplastic. As a consequence, the thumb function and appearance are compromised. Nevertheless, it is our experience and that of others that in nearly all instances the child will use the pollicized digit for certain activities. Side-to-side pinch utilizing the more mobile ulnar digits may be preferred for smaller diameter objects. Strength and motion are significantly diminished in comparison to age-related normal values. These results contrast with those following pollicization of a near-normal index finger in a limb with minimal, if any, discernible radial longitudinal deficiency.

Kozin [53] found a grip strength of 67% of the opposite side and Clark [47] reported 43% of the opposite side. Tonkin's [54] review of 42 pollicizations found results very similar to those of Manske [49]. Grip strength was reduced to 40% of age-related normal values when the pre-operative status of the limb and index finger was normal or near normal, in comparison to Manske's 31%. These values decreased alarmingly with significant radial longitudinal deficiency when the index finger was of poor quality, with values of 6% and 15% in the Tonkin and Manske series, respectively. Strength of pinch was similar in the two studies and with the same significant decrease in those with poor quality limbs and index fingers. In the latter instance, lateral pinch measured 9% (Manske 14%) of age-related normal values. This improved to 30% (Manske 38%) in those children not disadvantaged by the accompanying deficiencies. These trends are also apparent for measurements of total active motion of the digit, with an average of 26 degrees of motion at the MCP joint when combining all patients undergoing pollicization (Manske 42 degrees) and 26 degrees at the IP joint (Manske 25 degrees). Radial abduction averaged 44 degrees. Sixty percent of patients could oppose the pulp of the little finger, 17% to the ring finger and 23% to the middle finger only, again with motion being significantly improved in those without concomitant deformities. The Jebsen timed test for functional tasks found an increased time as a percentage of published nor-

mal values, 200% for those patients with concomitant deficiency and 130% in those with good pre-operative status. These figures were a little poorer than those of Manske.

The results in both studies were not significantly altered by the age of the patient at the time of the operation. In Tonkin's [54] group, 14 patients repeated the study 3 years apart. The strength measurements and time to completion of Jebsen tasks improved with age, but they remained the same relative to age-related normal values.

These results are consistent with those published by others [37, 39, 41, 43, 47–49, 53, 55–61].

Percival introduced a scale to measure function incorporating strength, motion, ability to perform certain tasks, sensibility and appearance [55]. In his 30 pollicizations, 73% were graded good or excellent, 17% fair and 10% poor. Vekris and others found similar results in 21 pollicizations, with 75% excellent, 19% good and 6% poor [60].

Goldfarb, in conjunction with Manske and others, evaluated the objective features and aesthetic outcomes of 31 pollicized digits, comparing these with normal thumbs [62]. They found the average length of the pollicized digit relative to the long finger proximal phalanx to be 90% compared to an age-matched normal average of 71%. The girth of the pollicized digit relative to the long finger was 92% compared to an age-matched normal average of 132%. The nail width of the pollicized digit relative to the nail width of the long finger was 96% compared with an age-matched normal thumb average of 104%. The visual analogue scale for subjective aesthetic analysis of these pollicized digits averaged 7.3 for the caregiver, 6 for the therapist and 6.4 for the surgeon. They concluded that pollicized digits are longer, but have reduced girth and nail width compared with age-matched normal thumbs.

Intraoperative complications are associated with vascular compromise, arterial and/or venous; denervation of the dorsal and/or palmar interossei during mobilization; and poor position of the digit – often in association with inadequate motors or inappropriate tension in musculotendinous reconstructions and skin suture. Failure to flex the MC head may create a radial abduction (hyperextension) deformity of the metacarpal. Partial flap necrosis is uncommon, but is reported. Secondary surgery is not uncommon with some reports of a high incidence of opposition transfers to better position and move the digit. Instability of both the new trapezium and the new CMC joint may follow a failure to adequately stabilize the MC head to the MC base or capsule or from loss of structural integrity of the index finger MCP joint collateral ligaments during harvest (Figs. 9.38a, b and 9.39). Flexion contractures of the MCP joint may be secondary to excessive CMC joint radial abduction or to the pre-operative status of the index finger.

In Tonkin's series of 96 pollicizations, a mobile trapezium has been stabilized in two cases, two webs which were too deep and v-shaped have been revised, one tendon transfer to increase radial abduction was performed, one metacarpal osteotomy was used to better position the thumb and three MCP joint fusions for flexion contractures have been carried out.

Complications of reconstructions of Grade 2 thumbs relate to continuing or recurrent MCP joint instability and poor function of the opposition transfer – denervation of ADM or adhesion formation impairing FDS gliding. Both problems tend to result in a recurrence of first metacarpal adduction and radial deviation at the MCP joint. Malalignment of extrinsic tendons plays a significant role in this deformation.

It is generally considered that reconstruction of Grade 3 and 4 thumbs provides poorer results than those obtained by pollicization. The first web space often remains deficient. Mobility is poor and strength is compromised in comparison to a pollicized index finger.

Functional results of reconstruction of Grade 2 hypoplastic thumbs may be assessed utilizing the same parameters as those used to assess the results of pollicization. The reconstructed thumb is usually weaker and has less motion than the thumbs of the unaffected hand and age-related

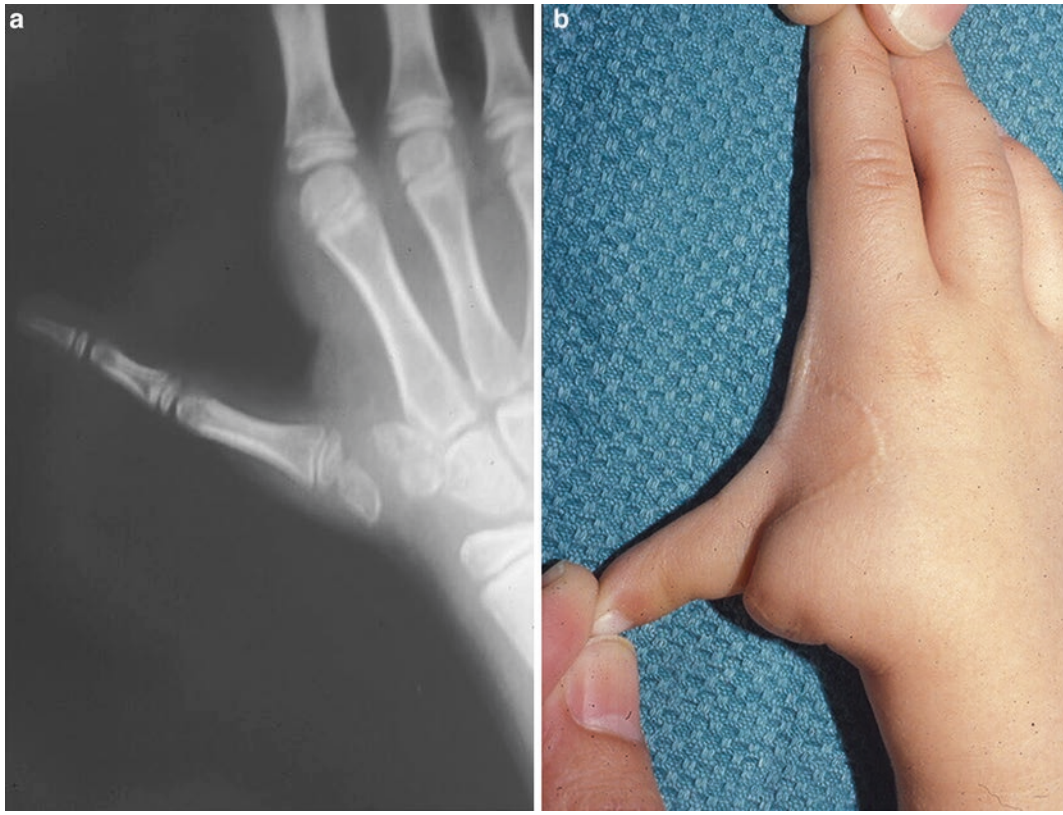

Fig. 9.38 Instability of the new trapezium (**a**, **b**). (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

normative values [31, 36, 63]. However, the disparate anomalies within this grade of thumb hypoplasia render comparisons difficult.

A systematic review that evaluated the existing literature for the different techniques and outcome measures utilized in thumb hypoplasia identified low quality of the available studies and inconsistent use of grading systems, assessment methods and reporting outcomes [33]. Although a high postoperative patient satisfaction can be expected based on the reports in the literature, there is no current agreement on a standard set of objective and subjective outcome measures on the basis of which surgical results in thumb hypoplasia could be evaluated. As discussed under the sub-heading of Classification, different definitions of characteristics according to grade and, consequently, the alternative reconstructions, which have been performed, do not allow comparison of like with like. Subclassification along the lines that have been suggested in this article would assist in addressing this difficulty. However, this grading classification, although more detailed than those previously proposed, describes anatomical deficiencies alone. All existing classifications are descriptive in nature and are not indicative of function or appearance, although they might provide guidelines for surgical treatment and allow some comparison between pre-operative and postoperative grading. Additionally, one of the greatest problems of outcome assessments in congenital hand conditions is the difficulty in measurement of parameters that reliably describe the status and function of a very young child's hand, particularly pre-operatively.

We therefore propose the establishment of a specific thumb hypoplasia assessment as part of a functional score, analogous to the severity grading for radial dysplasia described by Vilkki [64].

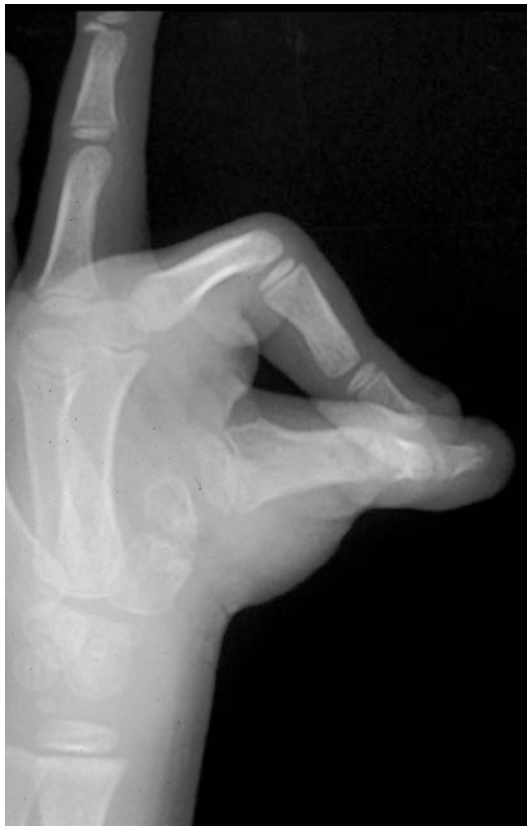

Fig. 9.39 Instability of the "new" CMC joint. (Published with kind permission of Michael A. Tonkin ©2014. All rights reserved)

The outcome measures chosen address the components of thumb hypoplasia and reflect the distinct anatomical anomalies potentially undergoing reconstruction. They are intended to be applicable to all age groups and to pre- and postoperative assessments.

The basic score would therefore assess the following five categories which can be encompassed by the acronym "WIMEC": (1) the first web opening (W); (2) intrinsic function, which is mainly the ability to oppose (I); (3) the stability of the MCP joint (M_1); (4) extrinsic function and anomalies €; and (5) stability and mobility of the CMC joint (C). Alternative variables are given if the young age or non-cooperation of the patient does not allow direct measurements. To these anatomical variations are added three further functional assessment categories – MCP joint mobility (M_2), strength of pinch (S_1) and strength of grip (S_2). The full acronym becomes "WIMMECSS" (Fig. 9.40).

In detail, the first web (W) receives a score based on the width of the first web: 5 points for a normal web, with a decreasing number of points allocated for a decrease in web width and depth and, finally, 0 points for no web (an absent thumb – Blauth grade 5). To measure first web opening, the angle between the first and second metacarpals (passive radial abduction) can be assessed using goniometry and can then be compared to the contralateral side (if normal) or age-related normative data [65]. Kuroiwa et al. [66] recently concluded that CMC joint pronation and palmar abduction, as the main components of opposition, effectively plateau at Kapandji score 6. Therefore, the Kapandji score as an indication of intrinsic function (I) is scored from 5 (normal thumb, Kapandji 6) to 0 (absent thumb). If active opposition cannot be evaluated, the visible and palpable thenar muscle bulk could be assessed as an indicator. Similarly, a score is given according to the degree of MCP joint stability (M_1). Extrinsic function (E) considers IP joint range of motion (ROM) and MCP and IP joint alignment. Deviation in these joints – as opposed to radial polydactyly – is mainly the result of aberrant extrinsic flexor and extensor tendons. Although active IP joint motion might be a better indication of extrinsic muscle function, passive ROM is perhaps more practical and provides useful data. Again, these measurements can be compared to the contralateral side if that is normally developed or alternatively to age-related normative data [65]. If ROM of the IP joint cannot be determined because of the patient's age or lack of cooperation, the presence or absence of IP joint creases can be considered as an indirect measure. Similarly, the degree of CMC joint stability (C) receives a score. Additionally, tip and key pinch strength (S1), grip strength (S2) and ROM of the MCP joint (M2), which are the results of multiple factors and do not strictly fall into one of these five categories, can be considered in the older and cooperative patient and compared to a healthy contralateral hand or age-related normative data [65] (see Fig. 9.40).

			Normal 5	Mild 4	Moderate 3	Severe 2	Floating Thumb 1	No thumb 0	Basic Score (WIMEC)	Extended Score* (WIMMECSS)
W	First Web Opening	Radial abduction relative to normal***	> 3/4	1/2 - 3/4	1/4 - 1/2	< 1/4	-	-		
I	Thumb intrinsic activity/ ability to oppose	Kapandji score or Thenar muscle bulk**	≥ 6 or Normal thenar muscle bulk	4 to 5 or Slightly reduced thenar muscle bulk, but functional	3 or Marked reduction of thenar muscle bulk	1 to 2 or No thenar muscle bulk	-	-		
M_1	MCP Joint stability	Clinical testing of collateral ligaments and palmar plate	Normal	Unidirectional (UCL only)	Bidirectional (UCL and RCL +/- hyperextension)	Severe global (UCL, RCL, palmar plate, inadequate joint, Elephant trunk sign intraoperatively)	-	-		
M_2	MCP Joint mobility*	ROM flexion-extension relative to normal***	> 3/4	1/2 - 3/4	1/4 - 1/2	< 1/4	-	-		
E	Thumb extrinsic activity and structure Score = mean of the two subcategory scores	ROM IP joint flexion-extension relative to normal*** or Presence of joint creases**	> 3/4 or Normal creases	1/2 - 3/4 or Slightly reduced creases	1/4 - 1/2 or Minimal creases	< 1/4 or No creases	-	-		
		Alignment MCP/ IP joints	Normal alignment and/ or intraoperatively no extrinsic anomalies.	Mild IP and/ or MCP joint deviation each ≤5° and/ or intraoperatively mild extrinsic anomalies not interfering with function and not contributing to deformity.	Moderate IP and/ or MCP joint deviation each 6-20° and/ or intraoperatively markedly hypoplastic tendons and/or aberrant connections, insertions or origins, interfering with function, pollex abductus.	Severe IP and/ or MCP joint deviation each >20° and/ or intraoperatively severe hypoplasia or absence of tendons and/ or pulleys.	-	-		
C	Thumb CMC joint	CMC joint stability, mobility and radiographic appearance	Normal CMC joint	Mild hypoplasia but proximal flare on X-ray still present. Stable in dorsal shift test, mobile.	Severe hypoplasia , Pencil sign. Unstable in dorsal shift test or immobile.	Absent proximal < 1/3 metacarpal	Absent proximal < 2/3 metacarpal	-		
S_1	Strength (pinch)* Score = mean of the two subcategory scores	Tip pinch strength relative to normal***	> 3/4	1/2 - 3/4	1/4 - 1/2	< 1/4	-	-		
		Key pinch strength relative to normal***	> 3/4	1/2 - 3/4	1/4 - 1/2	< 1/4	-	-		
S_2	Strength (grip)*	Grip strength relative to normal***	> 3/4	1/2 - 3/4	1/4 - 1/2	< 1/4	-	-		
									Total score (basic) (max. 25 points)	Total score (extended)* (max. 40 points)

*Use only when measurable
**Use as alternative, indirect measure when primary measure are not available
***Contra-lateral side if normal or normative, age-related data
ROM = range of motion, IP = interphalangeal, MCP = metacarpophalangeal, CMC = carpometacarpal
UCL = ulnar collateral ligament, RCL = radial collateral ligament

Fig. 9.40 The thumb hypoplasia score as proposed by Mende. A basic five-category score of maximum 25 points (WIMEC) can be evaluated in all patients regardless their age. An extended eight-category (WIMMECSS) score with a maximum of 40 points can be assessed if age and cooperation of the patient are adequate. (Published with kind permission of Konrad Mende ©2020. All rights reserved)

Each category score is summed up to a total value. A normal thumb scores 40 WIMMECSS points. An absent thumb scores 0 WIMMECSS points. If the full (WIMMECSS) score cannot be determined for lack of patient cooperation, which is usually the case in the very young, preoperative child, a basic (WIMEC) score of up to 25 points can be evaluated. This allows us to compare the score of a pre-operative hypoplastic thumb with that of a postoperative hypoplastic thumb to provide an objective measurement of the improvement gained from surgery. The thumb hypoplasia score also allows a comparison of the results of different techniques, for instance, in assessment of two types of opposition plasty: abductor digiti minimi (ADM) and flexor digitorum superficialis (FDS). The score allows a comparison of results from different surgical units. Additionally, in the context of the current expansion of indications for reconstruction of more severely underdeveloped and absent thumbs (Grades 3, 4 and 5) rather than pollicization of the index finger, such a score would potentially allow surgeons to compare the functional out-

comes of reconstruction of these severe grades with the results of pollicization. These objective measurements would ideally be completed by a standard set of functional tests, patient and/or caregiver reported outcomes and subjective assessments, yet to be determined. We present this system of a specific thumb hypoplasia score for consideration. It is clear that if the score is accepted, it will need to be subjected to validity assessment.

In all, results of surgical treatment of the hypoplastic thumb are dependent on the state of the digit to be reconstructed or to be pollicized and the presence or absence of accompanying limb deformities. Attention to technical details brings beneficial outcomes for patients and is rewarding for surgeons. Valid assessments and comparisons of results could be achieved by general acceptance and use of the thumb hypoplasia score, which incorporates the pre- and intraoperative status of the digit to be reconstructed or pollicized and allows for evaluation of the improvement achieved by surgery and comparison of the outcomes of different groups and techniques (including pollicization). A multicentre trial is needed to determine validity and any alterations in weighting of the parameters.

References

1. Oberg KC, Feenstra JM, Manske PR, Tonkin MA. Developmental biology and classification of congenital anomalies of the hand and upper extremity. J Hand Surg Am. 2010;35(12):2066–76.
2. Tonkin MA, Tolerton SK, Quick TJ, Harvey I, Lawson RD, Smith NC, et al. Classification of congenital anomalies of the hand and upper limb: development and assessment of a new system. J Hand Surg Am. 2013;38(9):1845–53.
3. Jones KL. Smith's recognizable patterns of human malformation. 6th ed. Philadelphia: Elsevier Saunders; 2006. p. 908.
4. Müller W. Die angeborenen Fehlbildungen der menschlichen Hand. Leipzig: Thieme; 1937.
5. Blauth W. The hypoplastic thumb. Arch Orthop Unfallchir. 1967;62(3):225–46.
6. Blauth W, Schneider-Sickert F. Congenital deformities of the hand. An atlas of their surgical treatment. Translated by UH Weil. Berlin: Springer; 1981.
7. Manske PR, McCarroll HR. Reconstruction of the congenitally deficient thumb. Hand Clin. 1992;8(1):177–96.
8. Manske PR, McCarroll HR, James M. Type III-A hypoplastic thumb. J Hand Surg Am. 1995;20(2):246–53.
9. Buck-Gramcko D. Congenital malformations of the hand and forearm. State of the art part III. Eur Med Bibliogr Hand Surg. 1993;3(4):15–21.
10. Smith P. Lister's the hand. Diagnosis and indications. 4th ed. London: Churchill Livingstone; 2002.
11. Smith P, Sivakumar B, Hall R, Fleming A. Blauth II thumb hypoplasia: a management algorithm for the unstable metacarpophalangeal joint. J Hand Surg Eur Vol. 2012;37(8):745–50.
12. Tonkin MA. On the classification of congenital thumb hypoplasia. J Hand Surg Eur Vol. 2014;39(9):948–55.
13. Yamauchi Y, Fujimaki A, Yanagihara Y, Yoshizaki K. Reconstruction of floating thumb. Especially on the use of metatarsophalangeal joint grafting. Seikeigeka (Orthop Surg). 1979;30:1645–8.
14. Foucher G, Medina J, Navarro R. Microsurgical reconstruction of the hypoplastic thumb, type IIIB. J Reconstr Microsurg. 2001;17(1):9–15.
15. Shibata M, Yoshizu T, Seki T, Goto M, Saito H, Tajima T. Reconstruction of a congenital hypoplastic thumb with use of a free vascularized metatarsophalangeal joint. J Bone Joint Surg Am. 1998;80(10):1469–76.
16. Matsuzaki H, Toishi S, Yoshizu T. A Blauth IIIB hypoplastic thumb reconstructed with a vascularised metatarso-phalangeal joint transfer: a case report with 28 years of follow up. Hand Surg. 2009;14(1):63–8.
17. Buck-Gramcko D. The role of nonvascularized toe phalanx transplantation. Hand Clin. 1990;6(4):643–59.
18. Goldberg NH, Watson HK. Composite toe (phalanx and epiphysis) transfers in the reconstruction of the aphalangic hand. J Hand Surg Am. 1982;7(5):454–9.
19. Tonkin MA, Deva AK, Filan SL. Long term follow-up of composite non-vascularized toe phalanx transfers for aphalangia. J Hand Surg Br. 2005;30(5):452–8.
20. Tsujino A, Itoh Y, Hayashi K. Reconstruction of floating thumb by transplanting the fourth metatarsal. J Bone Joint Surg Br. 1994;76(4):551–4.
21. Chow CS, Ho PC, Tse WL, Hung LK. Reconstruction of hypoplastic thumb using hemi-longitudinal metatarsal transfer. J Hand Surg Eur Vol. 2012;37(8):738–44.
22. Schneider W, Reichert B, Pallua N, Meyer H. Correction of hypoplastic thumb by free transfer of metatarsal bone: a case report. Microsurgery. 1993;14(7):468–71.
23. Tan JS, Tu YK. Comparative study of outcomes between pollicization and microsurgical second toe-metatarsal bone transfer for congenital radial deficiency with hypoplastic thumb. J Reconstr Microsurg. 2013;29(9):587–92.
24. Tu YK, Yeh WL, Sananpanich K, Ueng SW, Chou YC, Ma CH, et al. Microsurgical second toe-metatarsal bone transfer for reconstructing congenital radial defi-

ciency with hypoplastic thumb. J Reconstr Microsurg. 2004;20(3):215–25.
25. Ozols D, Butnere MM, Petersons A. Methods for congenital thumb hypoplasia reconstruction. A review of the outcomes for ten years of surgical treatment. Medicina (Kaunas). 2019;55(10):610.
26. Ozols D, Butnere MM, Petersons A. The second toe-to-hand transfer for full-length thumb reconstruction in congenital thumb's grade IIIb to V hypoplasia: MTPJ arthrodesis instead of tendon rebalansing. Tech Hand Up Extrem Surg. 2020;24:13–9.
27. Tong DD, Wu LH, Li PC, Rong YB, Liu B, Lee W, et al. Reversed vascularized second metatarsal flap for reconstruction of Manske type IIIB and IV thumb hypoplasia with reduced donor site morbidity. Chin Med J (Engl). 2019;132(21):2565–71.
28. Harashina T, Inoue T, Fujino T, Uchinishi K, Itoh Y. Reconstruction of a floating thumb with an excess big toe. J Reconstr Microsurg. 1994;10(1):11–5.
29. Kakinoki R, Ikeguchi R, Ohta S, Duncan SF, Fujita S, Noguchi T. Treatment of a type 3B hypoplastic thumb using extra phalanges from the contralateral duplicated thumb: case report. J Hand Surg Am. 2011;36(9):1492–6.
30. Tupper JW. Pollex abductus due to congenital malposition of the flexor pollicis longus. J Bone Surg Am. 1969;51(7):1285–90.
31. de Kraker M, Selles RW, Zuidam JM, Molenaar HM, Stam HJ, Hovius SE. Outcome of flexor digitorum superficialis opponensplasty for type II and IIIA thumb hypoplasia. J Hand Surg Eur Vol. 2016;41(3):258–64.
32. Hovius SE, Versnel S, Zuidam J. Tendon transfers in reconstructive hand surgery. Tendon transfer in the congenital hand. London: Informa Healthcare; 2005. p. 121–32.
33. Suurmeijer A, Mende K, Tonkin M. Reconstruction for congenital thumb hypoplasia. In: Evidence based data in hand surgery and therapy. Federation of European Societies for Surgery of the Hand. Budapest, Hungary; 2017. p. 139–161.
34. Light TR, Gaffey JL. Reconstruction of the hypoplastic thumb. J Hand Surg Am. 2010;35(3):474–9.
35. Snow J, Fink G. Use of a transverse carpal ligament window for the pulley in tendon transfers for median nerve palsy. Plast Reconstr Surg. 1971;48(3):238–40.
36. Vuillermin C, Butler L, Lake A, Ezaki M, Oishi S. Flexor digitorum superficialis opposition transfer for augmenting function in types II and IIIA thumb hypoplasia. J Hand Surg Am. 2016;41(2):244–9; quiz 50.
37. Buck-Gramcko D. Pollicization of the index finger. Method and results in aplasia and hypoplasia of the thumb. J Bone Joint Surg Am. 1971;53(8):1605–17.
38. Buck-Gramcko D. Congenital malformations of the hand and forearm. Chir Main. 2002;21(2):70–101.
39. Egloff DV, Verdan C. Pollicization of the index finger for reconstruction of the congenitally hypoplastic or absent thumb. J Hand Surg Am. 1983;8(6):839–48.
40. Foucher G, Medina J, Lorea P, Pivato G. Principalization of pollicization of the index finger in congenital absence of the thumb. Tech Hand Up Extrem Surg. 2005;9(2):96–104.
41. Kozin SH. Pollicization: the concept, technical details, and outcome. Clin Orthop Surg. 2012;4(1):18–35.
42. Littler JW. On making a thumb: one hundred years of surgical effort. J Hand Surg Am. 1976;1(1):35–51.
43. Taghinia AH, Upton J. Index finger pollicization. J Hand Surg Am. 2011;36(2):333–9.
44. Mennen U. Pollicisation: the myth about creating a pseudo-trapezium. J Hand Surg Asian Pac Vol. 2018;23(2):302–5.
45. Bartlett GR, Coombs CJ, Johnstone BR. Primary shortening of the pollicized long flexor tendon in congenital pollicization. J Hand Surg Am. 2001;26(4):595–8.
46. Lochner HV, Oishi S, Ezaki M, Malungpaishrope K, Moore RB. The fate of the index metacarpophalangeal joint following pollicization. J Hand Surg Am. 2012;37(8):1672–6.
47. Clark DI, Chell J, Davis TR. Pollicisation of the index finger. A 27-year follow-up study. J Bone Joint Surg Br. 1998;80(4):631–5.
48. Manske PR. Index pollicization for thumb deficiency. Tech Hand Up Extrem Surg. 2010;14(1):22–32.
49. Manske PR, Rotman MB, Dailey LA. Long-term functional results after pollicization for the congenitally deficient thumb. J Hand Surg Am. 1992;17(6):1064–72.
50. Gilbert A. Hypoplastic thumb IIIB-C and IV: reconstruction without pollicization. World symposium of congenital malformations of hand and upper limb; Hong Kong; 2018. p. 50.
51. Nakada M, Tada K, Nakajima T, Matsuta M, Tsuchiya H. A case of a 5-year-old boy with a Blauth type IIIB hypoplastic thumb reconstructed with a nonvascularized, hemilongitudinal metatarsal transfer. Case Rep Orthop. 2018;2018:8205285.
52. Wang B. Reconstruction of hypoplastic thumb using hemi-metatarsal composite tissue transfer. World symposium of congenital malformations of hand and upper limb; Hong Kong; 2018. p. 53.
53. Kozin SH, Weiss AA, Webber JB, Betz RR, Clancy M, Steel HH. Index finger pollicization for congenital aplasia or hypoplasia of the thumb. J Hand Surg Am. 1992;17(5):880–4.
54. Tonkin MA, Boyce DE, Fleming PP, Filan SL, Vigna N. The results of pollicization for congenital thumb hypoplasia. J Hand Surg Eur. 2015;40(6):620–4.
55. Percival NJ, Sykes PJ, Chandraprakasam T. A method of assessment of pollicisation. J Hand Surg Br. 1991;16(2):141–3.
56. Staines KG, Majzoub R, Thornby J, Netscher DT. Functional outcome for children with thumb aplasia undergoing pollicization. Plast Reconstr Surg. 2005;116(5):1314–23; discussion 24–5.

57. Netscher DT, Aliu O, Sandvall BK, Staines KG, Hamilton KL, Salazar-Reyes H, et al. Functional outcomes of children with index pollicizations for thumb deficiency. J Hand Surg Am. 2013;38(2):250–7.
58. Ceulemans L, Degreef I, Debeer P, De Smet L. Outcome of index finger pollicisation for the congenital absent or severely hypoplastic thumb. Acta Orthop Belg. 2009;75(2):175–80.
59. Foucher G, Medina J, Lorea P, Pivato G, Szabó Z. Pollicization in congenital differences. Handchir Mikrochir Plast Chir. 2004;36(2–3):146–51.
60. Vekris MD, Beris AE, Lykissas MG, Soucacos PN. Index finger pollicization in the treatment of congenitally deficient thumb. Ann Plast Surg. 2011;66(2):137–42.
61. Sykes PJ, Chandraprakasam T, Percival NJ. Pollicisation of the index finger in congenital anomalies. A retrospective analysis. J Hand Surg Br. 1991;16(2):144–7.
62. Goldfarb CA, Deardorff V, Chia B, Meander A, Manske PR. Objective features and aesthetic outcome of pollicized digits compared with normal thumbs. J Hand Surg Am. 2007;32(7):1031–6.
63. Christen T, Dautel G. Type II and IIIA thumb hypoplasia reconstruction. J Hand Surg Am. 2013;38(10):2009–15.
64. Vilkki SK. Severity grading in radial dysplasia. J Hand Surg Eur Vol. 2014;39(9):977–83.
65. Da Paz SN, Stalder A, Berger S, Ziebarth K. Range of motion of the upper extremity in a healthy pediatric population: introduction to normative data. Eur J Pediatr Surg. 2016;26(5):454–61.
66. Kuroiwa T, Nimura A, Suzuki S, Sasaki T, Okawa A, Fujita K. Measurement of thumb pronation and palmar abduction angles with a small motion sensor: a comparison with Kapandji scores. J Hand Surg Eur. 2019;44(7):728–33.

Congenital Radioulnar Synostosis

10

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Introduction

Congenital radioulnar synostosis is a rare congenital anomaly due to a failure of segmentation resulting in restricted forearm rotation. The forearm is fixed in a position ranging from neutral to severe pronation [1]. Sandifort originally described the condition in 1793 in *Museum Anatomicus* [2]. When the deformity is mild, a child can compensate using the ipsilateral shoulder and wrist, and the deformity may hardly be noticed [1, 3]. A severe pronation deformity can cause disabilities and difficulty in performing ordinary everyday tasks such as eating, washing, turning a door knob, accepting objects in the palm, and similar activities.

Embryology

Congenital radioulnar synostosis results from an anomaly of longitudinal segmentation. The upper limb bud arises at about 26 days of embryonic development. The segmentation begins distally. The proximal ends of the radius and ulna share a common perichondrium for some time, and genetic or teratogenic factors can lead to disruption in the formation of the radioulnar joint. During the phase of intrauterine development, the forearm is anatomically placed in varying degrees of pronation [4]. A failure of segmentation leading to disruption in the formation of the proximal radioulnar joint will leave the forearm in its fetal position of pronation. This is consistent with the clinical picture seen in children, where the synostosis invariably results in a pronated position of the forearm [4].

Epidemiology and Natural History

The condition is usually sporadic, though positive family history has been identified in cases [1, 5, 6]. Some authors have identified a dominant inheritance pattern [6]. Radioulnar synostosis has also been found to be a feature of chromosomal abnormalities, in particular the X chromosome [7–9]. About 60–80% of cases are bilateral. It is more common in males with a male/female ratio of 3:2. It can be associated with other conditions

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such as Apert syndrome, Klinefelter's syndrome, acropolysyndactyly (Carpenter syndrome), arthrogryposis, Holt-Oram syndrome, microcephaly, fetal alcohol syndrome, Crouzon syndrome, William syndrome, Treacher Collins syndrome, and amegakaryocytic thrombocytopenia [10–13].

There can be associated clinical anomalies affecting the cardiovascular, musculoskeletal, renal, gastrointestinal, and thoracic and central nervous systems. Musculoskeletal anomalies found include clubfeet, dislocated hips, syndactyly, polydactyly, and Madelung deformity [14–16]. Cardiac anomalies include ventricular septal defect and tetralogy of Fallot. Associated thoracic abnormalities include hypoplasia of the pectoralis musculature and the first and second ribs. Central nervous system anomalies include hydrocephalus, microcephaly, and encephalocoele.

Presentation and Clinical Features

These children will often present when a parent or teacher notes their functional deficit. Children with bilateral involvement and a more severe pronation deformity tend to present earlier. The age at presentation can vary between 2.5 and 5 years and most children would have presented by school age. However, the condition can go unnoticed into adolescence in unilateral cases.

The complaints often relate to difficulty in being able to accept objects in the palm and holding a small object such as a pencil. Dressing might be a problem, including being unable to manipulate buttons. Feeding might present problems due to the pronation deformity. Other problems include participating in certain sports that require skilled use of upper limbs and backhanded positioning when holding objects.

On physical examination, there is often a minimal flexion contracture at the elbow with a decreased carrying angle. The forearm shortening is more obvious in unilateral cases. The forearm is fixed in varying degrees of pronation ranging from 15° to 150°. In Ramachandran et al.'s study, the mean pronation deformity was 68° [17]. In the study by Simmons et al., 40% of patients had a pronation deformity of more than 60°, 20% had deformities ranging from 30° to 60°, while 40% had a deformity of less than 30° [15]. The loss of rotation is often compensated to an extent by rotational hypermobility at the wrist [1, 3].

Imaging

There may be a wide anatomical spectrum of deformities ranging from simply a radial head deformity, synostosis of just the proximal forearm to complete synostosis for the forearm bones (Fig. 10.1) [14]. There may be shortening of the forearm and there is usually an anterior bowing of the radius. Part of the synostosis may be cartilaginous and is best demonstrated on an MRI scan. Occasionally, a fibrous tether may become obvious on the MRI [16].

Classification

Wilkie, Tachdjian, and Cleary and Omer have proposed various classification systems.

Wilkie [2] described two types of congenital synostosis, based on the proximal radioulnar junction. Type 1 is a complete synostosis, with the radius and ulna fused proximally for a variable distance. Type 2 is a partial synostosis involving the region just distal to the proximal radial epiphysis and is associated with radial head dislocation.

Classification according to *Tachdjian's criteria* [18]:

- Type 1: The radial head may be fused to the ulna or may be completely absent (known as the "headless type").
- Type 2: The radial head is malformed and often dislocated.

Cleary and Omer [1] proposed a four-part radiological classification:

- Type 1: Synostosis did not involve the bone and was associated with an abnormal-looking radial head.

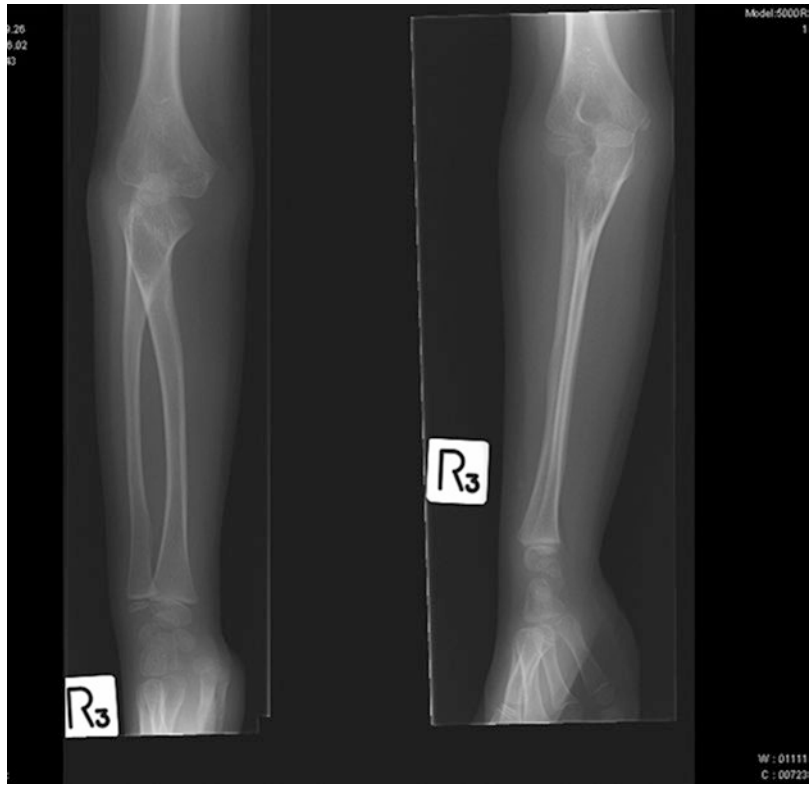

Fig. 10.1 Plain radiographs showing complete radioulnar synostosis

- Type 2: A visible osseous synostosis was present, otherwise normal findings.
- Type 3: Osseous synostosis with hypoplastic and posteriorly dislocated radial head.
- Type 4: Short osseous synostosis with anteriorly dislocated radial head, which is usually mushroom-shaped.

Cleary and Omer type 3 is the most common type reported in various studies. In Ramachandran et al.'s study [17], out of the six cases in their series, five forearms were classified as Cleary and Omer type 3 (with a posteriorly dislocated radial head), while one was classified as type 2. In the paper by Rubin et al., all cases were classified as Cleary and Omer type 3 [19]. Since there is not much functional difference between the different types and the appearances may change with time, the classifications may have not much role in deciding the management and are thus of limited clinical significance [17].

Management

Many children with forearm synostosis will not have much functional limitation and they can be treated conservatively. These children will often have mild pronation deformities less than 60°, unilateral disease and are able to compensate with radiocarpal and intercarpal wrist rotation. Often these children will present to clinic when their parents or schoolteachers have noticed that they perform routine tasks differently from their peers.

Indication for Surgery

Most authors suggest a pronation deformity of 60° to be significant enough to merit operative intervention. In the paper by Ramachandran et al., all of the patients had a mean pronation deformity of 68° [17]. Simmons et al. consid-

ered pronation of 60° as definite indication for osteotomy, while 15–60° was considered a relative indication depending on individual need of that patient [15]. Ogino and Hikino proposed that a pronation deformity of 60° created disability which needed surgery, whereas patients with a mean deformity of 20° did not complain of significant disability [3]. Van Heest et al. published a case series of Cleary and Omer type 4 cases ($n = 4$), which were initially treated non-operatively but developed restricted elbow flexion due to anterior dislocation of the radial head [20]. They were treated by excision of the radial head which resulted in pain relief and return of baseline range of motion [20]. These figures have varied in different studies, and some papers have considered ethnic and cultural factors that could influence decision-making.

Age at Surgery

Most children will present at school going age. There is some variation in literature about the age at surgery for these children. In the study by Ramachandran et al., the mean age of the patients was 4.9 years (3.5–8.5 years) [17]. In the study by Rubin et al., the average age at surgery was 11 years (range 9–13 years) [19]. Hung et al. performed surgery at an average age of 6 years 3 months [21]. There were a total of 34 patients and 52 forearms in this series. Eighteen patients (52.9%) had bilateral deformities. They considered the ideal age for surgery to be between 3 and 6 years as it is easy to perform an osteotomy and there is significant potential for remodeling left at this age. Griffet et al. considered an average age of 4–10 years as appropriate for surgery [22]. In the study by Kanaya et al. the average age was 8 years and 2 months (range 6 years 4 months to 11 years 10 months) [23]. However, surgical correction in adulthood is not unheard of. Garg et al. published a series of four cases of mean age 20.25 where they excised the proximal radius up to the distal extent of the synostosis and secured the distal radius with a tensor fascia late graft. Preoperatively, the patients were locked in pronation (mean 51.6°). Postoperatively, mean supination improved to 15° active and 24.8° passive, and mean pronation was 58.5° active and 64.16° passive [24].

Operative Management

Various types of surgeries have been described. The two broad categories include either operative mobilization to restore forearm rotation or to perform an osteotomy to place the forearm in a position appropriate for day-to-day activities of the child.

Resection of the synostosis to restore forearm rotation has generally produced unsatisfactory results with subsequent loss of correction and vascular complications [23, 25]. Interposition of a free vascularized fascial flap between the separated bones has been attempted to reduce the risk of reformation of the synostosis [23, 26, 27]. Joint replacement using metallic swivel prostheses in the intramedullary canal of the radius between the supinator and pronator teres did not show good results [28].

The second group of procedures involves an osteotomy. Three types have been described to correct the deformity. The first is an osteotomy at the site of the synostosis followed by an acute correction. As the rotation here takes place over a narrow space, this may lead to excessive soft tissue tightness, loss of correction, vascular complications, and neurological deficit including posterior interosseus nerve palsy [15, 29]. The second type is an osteotomy at a single site at the distal radius diaphysis [30]. The third type involves osteotomy of the diaphysis of both the radius and ulna [21, 31]. Nakasone et al. conducted a three-dimensional analysis of the deformities of the radius and ulna in CRUS [32]. They studied 38 forearms in 25 patients based on CT images. They found that average ulnar/radial deviation, flexion, and internal rotation deformities for the radius and ulna were 6°/3°, 3°/4°, and 18°/30°. The flexion deformity of the radius and internal rotation deformity of the radius and ulna were significantly correlated with the degree of fixed pronation. This defor-

mity might impede forearm rotation after corrective surgery in the proximal part of the forearm [32].

Other authors have used circular external fixators such as Ilizarov to gradually correct the deformity [33]. Other techniques included osteotomies followed by derotation 10 days later and bone shortening by resection of the bone from the synostosis [3, 33, 34].

Satake et al. published the long-term (average >10 years) follow-up results of a simple rotational osteotomy of the radius in nine patients of average age 13.6 [10–19]. Preoperatively, they were fixed in pronation, mean of 51.3°. Postoperatively, they were fixed at 4.2° of supination. At final follow-up, the average range of motion was from 26° of pronation to 62° of supination [35].

Murase et al. performed osteotomies in the distal third of the radius and proximal third of the ulna in patients with deformities more than 70° of pronation [31]. They achieved good correction and only lost about 20° of correction in one case. Ramachandran et al. performed a distal radius osteotomy achieving correction in all their cases [17]. Hung et al. performed a shortening by resection of 1.5 cm of the bone. They measured the length of the synostosis mass in their cases and found the average length to between 15 and 18 mm [21]. Yammine et al. recommended shortening the forearm by <2 cm [36].

Various authors have attempted separation of the synostosis with mixed results. Miura et al. interposed the anconeus after synostosis separation but could not prevent recurrence with this technique [25]. Most authors have used some sort of interposition graft after separation of the synostosis. Gill et al. noted that free fat grafts worked well to prevent recurrence and performed better than Gelfoam in dogs [37]. They also noted that pedicle fat graft was superior to free fat graft for this purpose. Langenskiold and Valle demonstrated the viability of free fat grafts transplanted onto the dura up to 18 years later in four patients [38]. Kanaya et al. reported excellent results with the use of a free vascularized fascio-fat graft with no recurrence in their seven cases [23]. They chose the lateral aspect of the ipsilateral arm as the donor site for their fascio-fat graft to ensure that surgery was confined to one limb only. This case series was followed up for an average of 10 years. The authors found that while the average flexion, extension, and pronation ranges were well maintained, the average supination range decreased by 16° over the course of follow-up [39].

The Ilizarov technique has been successfully used for this deformity. Rubin et al. performed an osteotomy followed by gradual correction of deformity using the Ilizarov frame achieving excellent results [19]. They pointed out that correction should be achieved gradually as two of their patients did develop radial nerve neurapraxia when they attempted acute corrections. Bolano et al. also used the Ilizarov frame but performed an immediate acute correction of 60° followed by a gradual derotation [40]. Because of the complications encountered by Rubin et al. using this technique of acute correction, they did not recommend it [19].

Operative Technique from Ramachandran et al. [17]

The patient is positioned supine and a well-padded tourniquet applied. An osteotomy is performed in the ulna at the mid-shaft level through a subcutaneous posterior approach. A 1.8-mm Ilizarov wire is passed retrograde from the osteotomy to exit through the olecranon and then antegrade across the osteotomy into the distal ulna. A second osteotomy is then performed in the radius at the distal diaphyseal-metaphyseal junction through a volar approach using an oscillating saw. The tourniquet is released and the forearm rotated to a position of 10° of supination. The deep fascia of the forearm is incised proximally and distally at the osteotomy sites to allow for expansion of the muscle bellies. The Ilizarov wire is bent and left proud of the skin. An above-elbow plaster cast is applied with the elbow flexed to 90° and the forearm in the corrected position (Fig. 10.2). The patient is observed postoperatively for any evidence of compartment syndrome and neurovascular deficit.

The wire is removed 3 weeks postoperatively in theater under general anesthesia. The plaster is changed to a below elbow cast. A plain radiograph is performed to confirm callus at the osteotomy sites, and the patients are then allowed to mobilize the elbow. At a further 3 weeks, if the radiographs confirm bony union, the cast is removed. In case of delayed healing, the cast is retained till bony union is achieved.

Postoperative Correction

In the study by Ramachandran et al., all patients achieved a postoperative correction of 10° of supination [17]. Green and Mital proposed that one should be aiming for a position of 30–45° of pronation in the dominant forearm and 20–35° of supination in the nondominant arm in bilateral cases [4]. In unilateral cases they considered 10–20° of supination as the ideal position. Simmons et al. proposed that the dominant arm be corrected to 10–20° of pronation and the nondominant arm to neutral rotation in bilateral cases [15]. In unilateral cases they considered 0–15 of pronation to be the ideal position. Rubin et al. proposed that in right-handed patients with bilateral involvement, the left forearm be corrected to 15° (0–30°) of supination [19]. They considered this to be a good functional position that would help in holding objects and for use in activities of daily living. Hung et al. considered 0–30° of pronation for the dominant arm and neutral for the nondominant limb [21]. Their best end position was 70–100° of pronation.

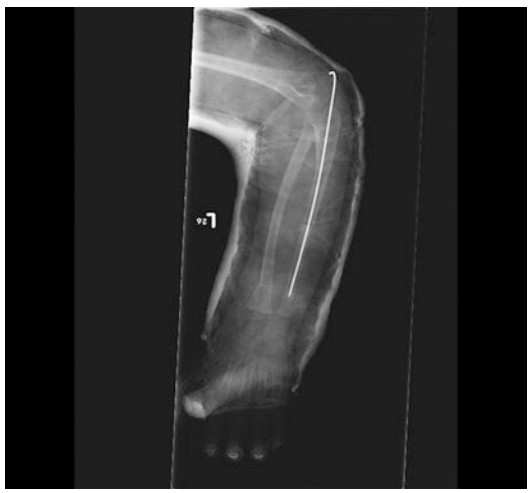

Fig. 10.2 Plain radiographs showing the ulna osteotomy fixed with a wire and a separate distal radial osteotomy

Complications

The most significant complication of the corrective procedures is compartment syndrome. It is related to changes in the vascularity and volume of the forearm compartments with significant derotation osteotomies in the range of 60– 90° [15]. Prophylactic fasciotomies or resection of a segment of the synostotic bone will reduce the incidence of this complication.

In children, high levels of anxiety and increasing analgesic requirements are the most diagnostic signs for compartment syndrome [41]. Green and Mital reported one case of Volkmann's ischemic contracture out of a total of 13 cases [4]. Simmons et al. reported a single case of Volkmann's ischemia out of 33 cases [15]. Other complications include neurological deficit. To shorten the time spent in the Ilizarov frame, Rubin et al. performed a trial of partial immediate correction of deformity by 30° at the end of the operation in two patients [19]. They noticed neurapraxia of the radial nerve in both patients in the in the recovery room. They returned the forearm to the original position in the recovery room under sedation. This led to complete neurological recovery. Ramachandran et al. reported a delayed union in one case (bilateral staged forearm case) [17]. No loss of correction was noted in any case. There was one case of hematoma collection resulting in compartment syndrome requiring fasciotomy. No neurovascular complications were noted at follow-up. One of their patients developed a pin tract infection.

Hung et al. reported slight loss of correction (15–20°) during cast immobilization in five forearms [21].

In Kanaya et al.'s [23] series, the patients in whom a radial osteotomy was not performed

developed a radial head dislocation. The arc of motion in this subgroup was less (40°) in comparison to the group in which a radial osteotomy was performed (83°).

With regard to separation of synostosis and interposition of fat or muscle, several authors have reported recurrence of the ankylosis. Miura et al. reported recurrence in all of their series of eight patients after they had used the anconeus muscle as an interposition graft [25]. Kanaya et al. did not report any recurrence with their technique of using a free vascularized fascio-fat graft [23].

References

1. Cleary JE, Omer GE. Congenital proximal radio-ulnar synostosis. Natural history and functional assessment. J Bone Joint Surg Am. 1985;67(4):539–45.
2. Wilkie D. Congenital radio-ulnar synostosis. Br J Surg. 1914;1:366–75.
3. Ogino T, Hikino K. Congenital radio-ulnar synostosis: compensatory rotation around the wrist and rotation osteotomy. J Hand Surg Br. 1987;12(2):173–8.
4. Green WT, Mital MA. Congenital radio-ulnar synostosis: surgical treatment. J Bone Joint Surg Am. 1979;61(5):738–43.
5. Bergsma D, editor. Birth defects compendium. For The National Foundation, March of Dimes. 2nd ed. New York: Alan R. Liss; 1979.
6. Hansen OH, Andersen NO. Congenital radio-ulnar synostosis. Report of 37 cases. Acta Orthop Scand. 1970;41(3):225–30.
7. Burgemeister AL, Daumiller E, du Bois G. Clinical report of 8 patients with 49,XXXXY syndrome: Delineation of the facial gestalt and depiction of the clinical spectrum. Eur J Med Genet. 2019;62(3):210–6.
8. James C, Robson L, Jackson J, Smith A. 46,XY/47,XYY/48,XYYY karyotype in a 3-year-old boy ascertained because of radioulnar synostosis. Am J Med Genet. 1995;56(4):389–92.
9. Townes PL, Ziegler NA, Lenhard LW. A patient with 48 chromosomes (XYYY). Lancet. 1965;1(7394):1041–3.
10. Dawson HG. A congenital deformity of the forearm and its operative treatment. Br Med J. 1912;2(2701):833–5.
11. Germeshausen M, Ancliff P, Estrada J, Metzler M, Ponstingl E, Rütschle H, et al. MECOM-associated syndrome: a heterogeneous inherited bone marrow failure syndrome with amegakaryocytic thrombocytopenia. Blood Adv. 2018;2(6):586–96.
12. Giuffrè L, Corsello G, Giuffrè M, Piccione M, Albanese A. New syndrome: autosomal dominant microcephaly and radio-ulnar synostosis. Am J Med Genet. 1994;51(3):266–9.
13. Jaffer Z, Nelson M, Beighton P. Bone fusion in the foetal alcohol syndrome. J Bone Joint Surg Br. 1981;63B(4):569–71.
14. Mital MA. Congenital radioulnar synostosis and congenital dislocation of the radial head. Orthop Clin North Am. 1976;7(2):375–83.
15. Simmons BP, Southmayd WW, Riseborough EJ. Congenital radioulnar synostosis. J Hand Surg Am. 1983;8(6):829–38.
16. Waters P, Simmons B. Congenital abnormalities: elbow region. In: Peimer CA, editor. Surgery of the hand and upper extremity. New York: McGraw Hill; 1996.
17. Ramachandran M, Lau K, Jones DHA. Rotational osteotomies for congenital radioulnar synostosis. J Bone Joint Surg Br. 2005;87(10):1406–10.
18. Tachdjian's pediatric orthopaedics: from the Texas Scottish Rite Hospital for Children – 5th edition [Internet]. [cited 2019 Jul 8]. Available from: https://www.elsevier.com/books/tachdjians-pediatric-orthopaedics-from-the-texas-scottish-rite-hospital-for-children/herring/978-1-4377-1549-1.
19. Rubin G, Rozen N, Bor N. Gradual correction of congenital radioulnar synostosis by an osteotomy and Ilizarov external fixation. J Hand Surg Am. 2013;38(3):447–52.
20. VanHeest AE, Lin TE, Bohn D. Treatment of blocked elbow flexion in congenital radioulnar synostosis with radial head excision: a case series. J Pediatr Orthop. 2013;33(5):540–3.
21. Hung NN. Derotational osteotomy of the proximal radius and the distal ulna for congenital radioulnar synostosis. J Child Orthop. 2008;2(6):481–9.
22. Griffet J, Berard J, Caton J, Michel C. Les synostoses congenital radio- cubitales supeiurse. Int Orthop. 1986;10:265–9.
23. Kanaya F, Ibaraki K. Mobilization of a congenital proximal radioulnar synostosis with use of a free vascularized fascio-fat graft. J Bone Joint Surg Am. 1998;80(8):1186–92.
24. Garg G, Gupta SP. Surgical outcome of delayed presentation of congenital proximal radioulnar synostosis. SICOT J. 2015;1:33.
25. Miura T, Nakamura R, Suzuki M, Kanie J. Congenital radio-ulnar synostosis. J Hand Surg Br. 1984;9(2):153–5.
26. Funakoshi T, Kato H, Minami A, Suenaga N, Iwasaki N. The use of pedicled posterior interosseous fat graft for mobilization of congenital radioulnar synostosis: a case report. J Shoulder Elbow Surg. 2004;13(2):230–4.
27. Kawaguchi S, Kitamura M, Usui M. Proximal radioulnar synostosis treated with a free vascularised fascio-fat graft – report of two cases. Hand Surg. 2000;5(2):161–4.
28. Kelikian H. Congenital deformities of the hand and forearm. Philadelphia: WB Saunders Company; 1974.
29. Hankin FM, Smith PA, Kling TF, Louis DS. Ulnar nerve palsy following rotational osteotomy of con-

genital radioulnar synostosis. J Pediatr Orthop. 1987;7(1):103–6.
30. Fujimoto M, Kato H, Minami A. Rotational osteotomy at the diaphysis of the radius in the treatment of congenital radioulnar synostosis. J Pediatr Orthop. 2005;25(5):676–9.
31. Murase T, Tada K, Yoshida T, Moritomo H. Derotational osteotomy at the shafts of the radius and ulna for congenital radioulnar synostosis. J Hand Surg Am. 2003;28(1):133–7.
32. Nakasone M, Nakasone S, Kinjo M, Murase T, Kanaya F. Three-dimensional analysis of deformities of the radius and ulna in congenital proximal radioulnar synostosis. J Hand Surg Eur Vol. 2018;43(7):739–43.
33. Manske PR, McCarroll HR, Hale R. Biceps tendon rerouting and percutaneous osteoclasis in the treatment of supination deformity in obstetrical palsy. J Hand Surg Am. 1980;5(2):153–9.
34. Lin HH, Strecker WB, Manske PR, Schoenecker PL, Seyer DM. A surgical technique of radioulnar osteoclasis to correct severe forearm rotation deformities. J Pediatr Orthop. 1995;15(1):53–8.
35. Satake H, Kanauchi Y, Kashiwa H, Ishigaki D, Takahara M, Takagi M. Long-term results after simple rotational osteotomy of the radius shaft for congenital radioulnar synostosis. J Shoulder Elbow Surg. 2018;27(8):1373–9.
36. Yammine K, Salon A, Pouliquen JC. Congenital radioulnar synostosis: study of a series of 37 children and adolescents. Ann Chir Main Memb Super. 1998;17(4):300–8.
37. Gill GG, Sakovich L, Thompson E. Pedicle fat grafts for the prevention of scar formation after laminectomy. An experimental study in dogs. Spine. 1979;4(2):176–86.
38. Langenskiöld A, Valle M. Epidurally placed free fat grafts visualized by CT scanning 15-18 years after discectomy. Spine. 1985;10(1):97–8.
39. Kanaya K, Iba K, Yamashita T. Long-term results after a free vascularized adipofascial graft for congenital proximal radioulnar synostosis with an average follow-up of 10 years: a series of four cases. J Shoulder Elbow Surg. 2016;25(8):1258–67.
40. Bolano LE. Congenital proximal radioulnar synostosis: treatment with the Ilizarov method. J Hand Surg Am. 1994;19(6):977–8.
41. Kadiyala RK, Waters PM. Upper extremity pediatric compartment syndromes. Hand Clin. 1998;14(3):467–75.

Ulnar Longitudinal Deficiency

11

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Introduction

Ulnar longitudinal deficiency (ULD) is a rare condition that usually affects the entire upper limb, including the elbow, forearm, and hand. It has been reported to occur in 1:25,000 live births. ULD is most commonly unilateral [1, 2]. It is a sporadic, non-inherited condition, but can be associated with other musculoskeletal anomalies, such as proximal femoral focal deficiency, fibular and tibial deficiency, scoliosis, and finger differences [1, 2].

Embryology

To better understand the clinical appearance and variation in the spectrum of ULD, one must first review the development of the upper limb. Starting around days 26 to 52 after fertilization, the limb bud develops around three axes: proximal-distal, dorsal-ventral, and radial-ulnar [1, 3–5]. Each axis has its own signaling center:

1. Apical ectodermal ridge (AER) coordinates the proximal-distal outgrowth
2. Zone of polarizing activity (ZPA) controls radial-ulnar asymmetry
3. Progress zone (PZ) for dorsal-ventral differentiation [3, 6]

Integral to these specialized zones are several signaling molecules. They include fibroblast growth factors, sonic hedgehog, and bone morphogenic proteins. These molecules affect each other through feedback loops [3]. In regard to ULD, sonic hedgehog is responsible for development of ulnar-sided forearm structures as well as the four ulnar-sided digits [1]. The thumb abnormalities occasionally seen in ulnar dysplasia can be explained by the sonic hedgehog-fibroblast growth factor feedback loop [6].

Classification and Clinical Picture

The spectrum of clinical presentation of children with ULD is variable. A majority will have involvement in their entire upper limb. Classification systems focus on the elbow/forearm abnormalities [7–11], hand [12], and more specifically the thumb and first web space [13].

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The commonly used Bayne classification [7] describes the progression of deficiency noted at the elbow and forearm. Its original description had four types and was later modified by Havenhill et al. [8]. This modified classification of ULD is as follows:

I. Normal length ulna with ulnar-sided hand anomalies
II. Hypoplasia of the ulna (presence of distal and proximal ulnar epiphysis)
III. Partial aplasia of the ulna (absence of the distal or middle one-third of the ulna)
IV. Total aplasia of the ulna (complete absence of the ulna)
V. Complete absence of the ulna with radiohumeral synostosis (fusion of the radius to the humerus)

Goldfarb et al. [14] proposed a type V ulnar longitudinal dysplasia incorporating cases of severe radiohumeral synostosis with humeral bifurcation or a large medial epicondyle. Given the rarity of the disease along with variable presentation, Buck-Gramcko [15] stated that the pathological findings in ulnar deficiency are so different in their involvement and distribution that it was impossible for him to divide them into any classification system. Although Bayne and others describe the elbow and forearm abnormalities, treatment has really been focused more on the hand and digits. Cole and Manske [13] presented a classification system based upon the characteristics of the thumb and first web:

A. Normal first web space and thumb
B. Mild first web and thumb deficiency
C. Moderate to severe first web and thumb deficiency; potential loss of opposition; malrotation of the thumb into the plane of the other digits; thumb-index syndactyly; absent extrinsic tendon function
D. Absent thumb

The authors of this classification scheme point out that it is the complexity of the radial-sided problems that requires the majority of surgical procedures, so their classification will focus the surgeon's attention on those deficiencies most important for the restoration of function. Their conclusion was that ULD is best classified by an elbow/forearm system, supplemented by hand classification [13].

Associated Anomalies

Unlike patients with radial longitudinal deficiency, children with ULD rarely have heart or hematopoietic anomalies. However, these children may have associated musculoskeletal anomalies such as proximal femoral focal deficiency, additional hip pathology (coxa vara), tibial or fibular ray deficiency, phocomelia, scoliosis, clubfeet, and spina bifida [1, 16].

Upper Arm and Shoulder

Patients with ULD may have hypoplasia of their proximal humerus and shoulder region. Despite this abnormality, most patients do not have restricted motion [15].

Elbow

There is quite a bit of variation in the clinical presentation of children with ULD. They may have an elbow that is stable, unstable, or fused. Their affected joints may have normal, hypoplastic, or severely deformed articular surfaces. Patients may present with congenital dislocation of the radial head, which may cause subsequent deformity to the distal end of the humerus [15]. El Hassan et al. [17] reported that 12% of the children they treated with ULD had a radiohumeral synostosis. In their series, they described patients' elbows in 20–90° of flexion and no elbows in full extension [17]. Others have described patients having elbows fixed in full extension [11] or with severe flexion and rotation, so that the hand is positioned behind the child and away from the opposite, uninvolved hand. This creates the so-called hand on flank deformity [18].

Forearm

Buck-Gramcko [15] reported that patients with different types of ulna defect showed no correlation to the severity of the involvement of other parts of the arm. He described patients presenting with ULD expressing all variations of other hand and elbow anomalies. Most patients with ULD will have a shorter than normal forearm (Fig. 11.1). Havenhill et al. [8] described a variation of patients with a normal forearm but deficiencies isolated to the ulnar side of the hand—a type 0 ulnar longitudinal deficiency.

In ULD, ulnar hypoplasia is most common (60%) with partial absence of the ulna reported in 22.5% and complete absence in 18% of patients [15]. Some patients with ULD will have a fibrocartilaginous mass, possibly representing the anlage of the absent portion of the ulna [16]. This is commonly seen in Bayne types II and IV and may be the cause for radial bowing and wrist deviation, although this point has been debated [16–22].

Wrist

Children may present with angulation of their wrist, but it is typically not as severe as that seen in radial longitudinal deficiency (see Fig. 11.1c). El Hassan et al. [17] reported that patients with ULD had wrists that were positioned in neutral in 71% of patients, with the remaining having wrists resting in 5–40° of ulnar deviation. Those patients with the wrist in neutral position had essentially normal wrist range of motion. However, when their wrists were in ulnar deviation, patients had limitations of radial deviation, wrist flexion, and extension [17]. Controversy over the role of the ulnar anlage and its relationship to wrist deviation

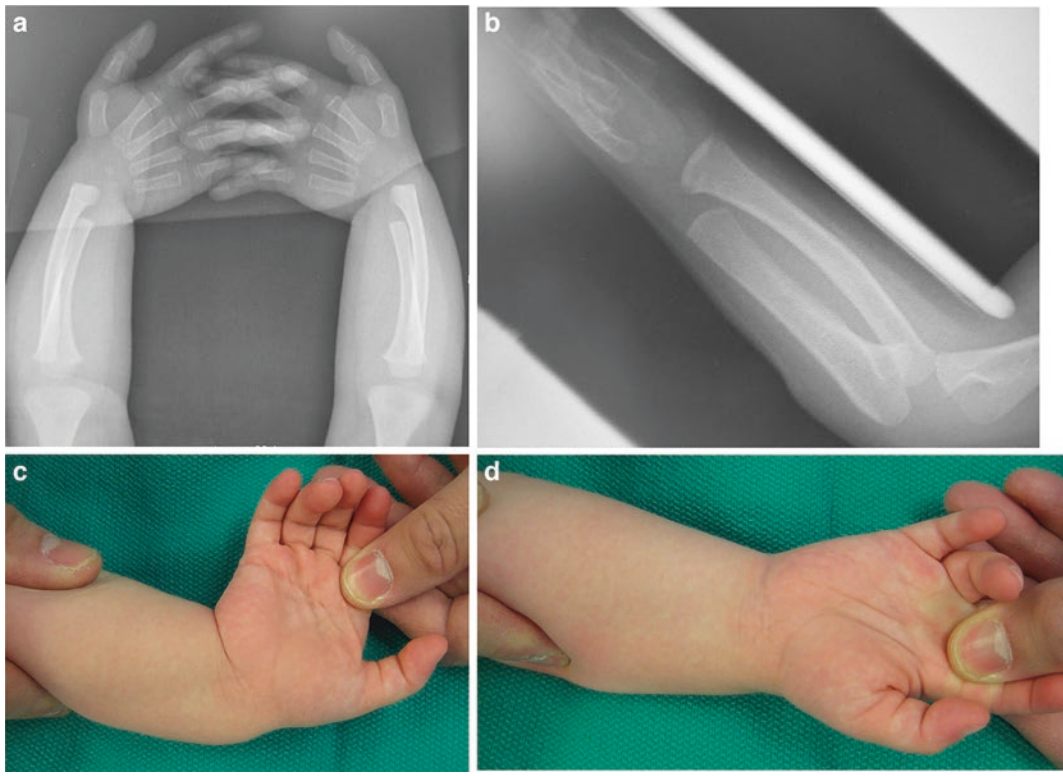

Fig. 11.1 (**a**) Anteroposterior and (**b**) lateral radiographs of a 2-year-old boy with bilateral ulnar longitudinal deficiency type II/A. (**c**) Clinical photograph showing excessive wrist ulnar deviation. (**d**) The wrist position rests in neutral

continues [15–17]. Patients may present with absent carpal bones in correlation with missing digital rays, and synostoses occur in 30% to 40% of cases [15].

Hand

Approximately 90% of patients with ULD have missing digits and 30% have syndactyly [1]. Multiple digital anomalies can be seen in the patients with ULD, ranging from a full complement of digits to just one digit. Ectrodactyly has been well documented in patients with ULD [1, 13, 15, 17]. Often, the patient's existing digits are not normal, with variations of hypoplasia, missing phalanges or metacarpals, syndactyly, and synostoses between phalanges and metacarpals [15].

Seventy percent of patients with ULD have abnormalities related to the thumb [1]. El Hassan et al. [17] reported that 11 of 17 limbs with ULD had digital anomalies, with four of those limbs having absent thumbs. Swanson et al. [11] and Broudy and Smith [21] reported that 68% and 100% of their patients with ULD had radial-sided hand abnormalities, respectively. Cole and Manske [13] reported that 73% of the 55 patients evaluated had an abnormal thumb or first web space. Their classification system describes the spectrum of thumb and first web space involvement from normal all the way to aplastic [13]. Evaluating a patient's thumb and first web space deficiencies is important, as surgical intervention to alter the radial-sided abnormalities in the hand may provide more substantial gains for a patient's function than operations elsewhere along their arm [1, 13, 15–17].

Treatment

Treatment of patients with ULD depends on the function of the limb. Nonoperative intervention typically consists of early stretching and splinting starting at a young age. Depending on the function of the hand, surgical intervention may be warranted. Tissue distraction is a more invasive method of stretching and may be an adjunct to surgical management. The majority of surgical interventions in patients with ULD are performed on the hand, including syndactyly releases, deepening of the first web space, and first metacarpal rotational osteotomies [1, 13, 15, 16]. In special circumstances, other procedures, including excision of an ulnar anlage, humeral rotational osteotomy, and creation of a one-bone forearm, may be indicated.

Hand

Hand function can be improved with syndactyly releases, reconstruction of the thumb (opponensplasty, pollicization), and deepening of the first web space [1, 16, 23]. Ezaki and Carter [16] recommend delaying hand surgery until the child's second year of life. The reconstruction procedures of a child's hand are very important in improving their function; waiting for the child's hands to get larger allows for a more precise surgery and thus a better result [16].

First metacarpal rotational osteotomy is indicated when a child's hands has digits that all lie in the same plane. The goal of this rotation is to allow for prehension with the pulp of the digits. Rotation of other metacarpals and even phalanges to achieve this goal should also be considered. Ezaki and Carter [16] report that there is a tendency for a slow loss of rotation after surgical intervention, and they recommend concomitant realignment of muscle power with tendon transfers to help prevent derotation.

Wrist

Controversy over excision of the ulnar anlage continues to be debated within the literature [11, 15–17, 21, 22]. However, there is some agreement as to which patients may benefit from early anlage excision. Indications for ulnar anlage excision [1, 15–17, 22] include the following:

1. Greater than 30° of fixed ulnar deviation
2. Clinically documented progression of ulnar deviation

It is recommended that excision of the ulnar anlage be performed at age 6 months. Proponents of early excision state it may improve both the function and appearance of a patient's arm [1, 7, 22]. The anlage acts as a tether and will restrict radial growth and increase deformity of the forearm. In addition, the forearm will double in length by age 3 years, and resection of the anlage will provide the best possibility for unrestricted growth of the limb [16, 22].

To excise the ulnar anlage, either a longitudinal or lazy "S" incision is used over the ulnar border of the forearm and wrist. Usually the flexor carpi ulnaris is absent, and the neurovascular bundle (if present) is directly under the skin and will need to be protected. Distally, it is crucial to dissect the anlage off of the carpus and radius completely. Following distal resection, the patient's wrist should be passively corrected to a neutral position. Resection of the entire fibrous anlage proximally is not required; usually resection of the distal third is adequate [16]. If excessive bowing of the radius is present, then an osteotomy can be performed at the same time. Postoperative management includes immobilization of the patient's wrist in a neutral position for 6 weeks followed by stretching and splinting for at least 6 months. Some authors have recommended nighttime splinting with a short arm orthosis until patients reach skeletal maturity [23].

Forearm

The forearm of patients with ULD can be challenging to treat. Multiple procedures have been described: creation of a one-bone forearm [1, 15, 23, 24], radial osteotomies [18–20], and forearm lengthening [25, 26].

Several authors [1, 16, 27, 28] have advocated that the only indication for creating a one-bone forearm is in the presence of forearm instability that is disabling to the patient. Thus, this procedure should rarely be done, knowing that any possible improvement in cosmetic appearance will be offset by the loss of function.

Radial osteotomies have been described [18–20] and may be performed at the same time as excision of the ulnar anlage if excessive bowing exists [16]. Although the forearm may be malrotated, most children do not require a forearm rotational osteotomy to improve their function [1].

Chen et al. [26] describe a case using an external fixator distraction osteogenesis of the ulna in a child with a Bayne type II deformity. They reported an 81-mm lengthening over 7 months, with gradual reduction of a dislocated radial head. Elbow range of motion increased and preservation of preoperative forearm rotation was documented.

Schachinger et al. described the use of soft tissue distraction in two children with Bayne type II deformities prior to definitive one-bone forearm surgery [29]. This seems to be an option in this very specific subset of patients.

Elbow/Humerus

When a child's hand is positioned behind the body, the "hand-on-flank deformity," a rotational osteotomy near their elbow may be useful [1, 16–18, 23]. These patients typically have a radiohumeral synostosis with a hyperpronated forearm, bowing of the radius, and flexion and rotation of the elbow [17, 18]. The procedure can be performed at the level of the distal humerus through a lateral incision. Careful dissection is used to expose the humerus. Kirshner wires are placed distal and proximal to the proposed osteotomy site in a parallel fashion. The distal skeletal fragment is rotated so that the patient's hand is now positioned in front of the trunk. Care must be taken in this rotation surgery, as the patient's vessels and nerve are at risk for serious damage. If needed, it may be useful to shorten the patient's humerus as well. The osteotomy can be fixed with either transverse wires or plate and screws depending on the size of the patient. Their arm can then be treated postoperatively in a long arm cast for 4–6 weeks.

References

1. Bauer AS, Bednar MS, James MA. Disruption of the radial/ulnar axis-congenital longitudinal deficiencies. J Hand Surg Am. 2013;38(11):2293–302.
2. Koskimies E, Lindfors N, Gissler M, Peltonen J, Nietosvaara Y. Congenital upper limb deficiencies and associated malformations in Finland: a population-based study. J Hand Surg Am. 2011;36A:1058–65.
3. Oberg KC, Feenstra JM, Manske PR, Tonkin MA. Developmental biology and classification of congenital anomalies of the hand and upper extremity. J Hand Surg Am. 2010;35A:2066–76.
4. Tickle C, Summerbell D, Wolpert L. Positional signaling and specification of digits in chick limb morphogenesis. Nature. 1975;254:199–202.
5. Tickle C. Experimental embryology as applied to the upper limb. J Hand Surg Am. 1987;12B:294–300.
6. Yang Y, Kozin SH. Cell signaling regulation of vertebrate limb growth and patterning. J Bone Joint Surg. 2009;91A(Suppl 4):76–80.
7. Bayne LG. Ulnar club hand (ulnar deficiencies). In: Green DP, Hotchkiss RN, Pederson WC, editors. Operative hand surgery. 3rd ed. New York: Churchill Livingstone; 1993. p. 288–303.
8. Havenhill TG, Manske PR, Patel A, Goldfarb CA. Type 0 ulnar longitudinal deficiency. J Hand Surg Am. 2005;30A:1288–93.
9. Kummel W. Die missbildungen der extremitaeten durch defect, verwachsung und ueberzahl. Bibliotheca Medica (Casse). 1895;Heft 3:1–83.
10. Ogden JA, Watson HK, Bohne W. Ulnar dysmelia. J Bone Joint Surg. 1976;58A:467–75.
11. Swanson AB, Tada K, Yonenobu K. Ulnar ray deficiency: its various manifestations. J Hand Surg Am. 1984;9A:658–64.
12. Ogino T, Kato H. Clinical and experimental studies on ulnar ray deficiency. J Pediatr Orthop. 1983;3:37–40.
13. Cole RJ, Manske PR. Classification of ulnar deficiency according to the thumb and first web. J Hand Surg Am. 1997;22A:479–88.
14. Goldfarb CA, Manske PR, Busa R, Mills J, Carter P, Ezaki M. Upper-extremity phocomelia reexamined: a longitudinal dysplasia. J Bone Joint Surg. 2005;87A:2639–48.
15. Buck-Gramcko D. Congenital malformations of the hand and forearm. Chir Main. 2002;21:70–101.
16. Carter PR, Ezaki M, Oishi S, Herring JA. Disorders of the upper extremity. In: Herring JA, editor. Tachdjian's pediatric orthopaedics, vol. 4. 1st ed. Philadelphia: Saunders; 2008. p. 536–9.
17. El Hassan B, Biafora S, Light T. Clinical manifestations of type IV ulna longitudinal dysplasia. J Hand Surg Am. 2007;32A:1024–30.
18. Miller JK, Wenner SM, Kruger LM. Ulnar deficiency. J Hand Surg Am. 1986;11A:822–9.
19. Carroll RE, Bowers WH. Congenital deficiency of the ulna. J Hand Surg Am. 1977;2:169–74.
20. Straub LR. Congenital absence of the ulna. Am J Surg. 1965;109:300–5.
21. Broudy AS, Smith RJ. Deformities of the hand and wrist with ulnar deficiency. J Hand Surg Am. 1979;4A:304.
22. Flatt AE. The care of congenital hand anomalies. St Louis: Quality Medical Publishers; 1994.
23. James MA, Bednar M. Deformities of the wrist and forearm. In: Green DP, Hotchkiss RN, Pederson WC, Wolfe SW, editors. Green's operative hand surgery. 5th ed. New York: Churchill Livingstone; 2005. p. 1479–83.
24. Vitale CC. Reconstructive surgery for defects in the shaft of the ulna in children. J Bone Joint Surg. 1952;34A:804–10.
25. Smith AA, Greene TL. Preliminary soft tissue distraction in congenital forearm deficiency. J Hand Surg Am. 1995;20A:420–4.
26. Chen GX, Zhou ZA, Yang L. Ulnar lengthening using a half ring sulcated external fixator for ulnar longitudinal deficiency: a case report. Cell Biochem Biophys. 2013;67(2):809–12.
27. Laurin CA, Farmer AW. Congenital absence of the ulna. Can J Surg. 1959;2:204–7.
28. Blair WF, Shurr DG, Buckwalter JA. Functional status in ulnar deficiency. J Pediatr Orthop. 1983;3:37–40.
29. Schachinger F, Girsch W, Farr S. Soft tissue distraction prior to single bone forearm surgery in ulnar longitudinal deficiency: a report of two cases. J Hand Surg Asian Pac. 2018;23(1):153–7.

Symbrachydactyly

12

William J. Dahl and Neil F. Jones

Definition

Symbrachydactyly is a congenital hand difference that can present with a variety of findings including brachydactyly, syndactyly, and hypoplasia of the hand. The condition is typically unilateral and may be associated with absence of the pectoralis major muscle in some cases. The fingers in symbrachydactyly are shortened and stiff with varying degrees of bone loss depending on the size of the middle phalanx [1].

Classification

Swanson [2] and the International Federation of Societies for Surgery of the Hand [3] classify symbrachydactyly as a deformity resulting from a failure of formation. Manske and Oberg in 2009 [4] modified this classification system based on increased knowledge about the molecular basis of congenital hand differences. Symbrachydactyly was placed in the transverse deficiency subset under the group I failure of axis formation and/or differentiation. In 2010, Oberg further modified the 2009 classification system creating the Oberg-Manske-Tonkin (OMT) classification system [5]. It placed symbrachydactyly under the malformations' group and the subgroup of failure of axis formation/differentiation involving the entire upper limb. The OMT classification system was further modified in 2013 [6]. Symbrachydactyly continued to be grouped under the malformations' group and the subgroup of failure of axis formation/differentiation involving the entire upper limb, but this subgroup was further subdivided into three divisions: proximal distal outgrowth, radial-ulnar axis, and dorsal-ventral axis. Symbrachydactyly was placed into the proximal distal outgrowth division. In 2015, the OMT classification system was used to classify congenital hand differences in 641 patients with 653 congenital anomalies. Symbrachydactyly was found to be the second most common anomaly within the subgroup of anomalies affecting only the hand plate [7].

Several classification systems have been proposed to better characterize the often-wide spectrum of involvement seen in symbrachydactyly patients. The original classification of symbrachydactyly was introduced by Pol in 1921 [8] and modified by Blauth and Gekeler in 1971, based on an analysis of 19 of their cases and 179 cases in the literature [9]. They divided symbrachydactyly into four types based mainly on morphological characteristics. The first category

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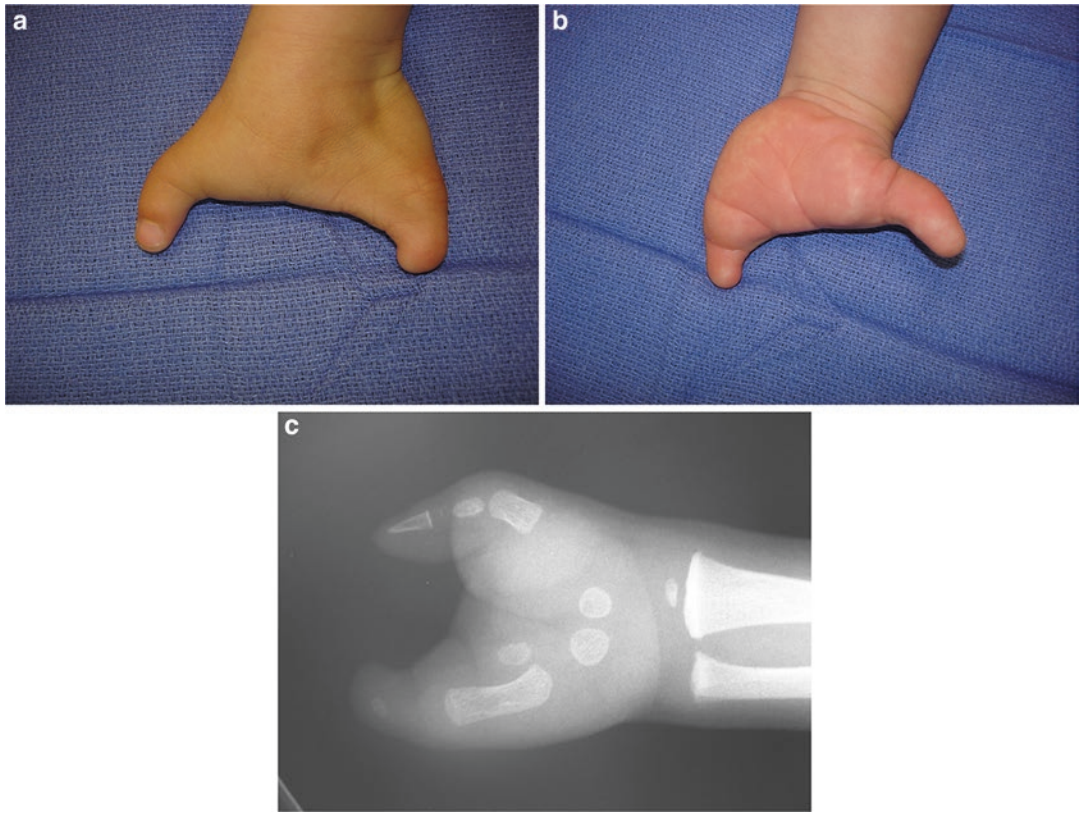

Fig. 12.1 (**a**–**c**) Dorsal and palmar photographs and radiograph of an "atypical" cleft hand in a 4-year-old boy. This would now be classified as a central absence or oligodactylic type II symbrachydactyly or as a C3R1U1 hand. (Published with kind permission of Neil F. Jones ©2014. All rights reserved)

in their teratologic sequence is brachymesophalangia or short finger type I. The fingers in this group are often missing middle phalanges and display incomplete syndactyly. Functionally, fingers in this group tend to be stiff with limited flexion and unstable proximal interphalangeal joints. The second group in their classification system is the oligodactylic or "atypical cleft hand" type II, in which the hand is missing some or all of the central three fingers (Fig. 12.1) as well as partial loss of the small finger. The third or monodactylic group consists of hands missing all four fingers except the thumb (Fig. 12.2). The finger metacarpals may also be partially or completely absent. The most involved group in their teratologic sequence is the peromelic or adactylic group IV, in which the hand is missing all

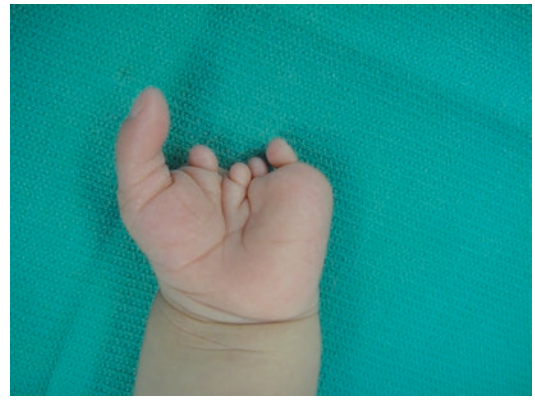

Fig. 12.2 Monodactylic type III symbrachydactyly of the left hand in a 2-year-old girl. The four fingers are represented by nubbins and this would be classified as a U4R1 hand. (Published with kind permission of Neil F. Jones ©2014. All rights reserved)

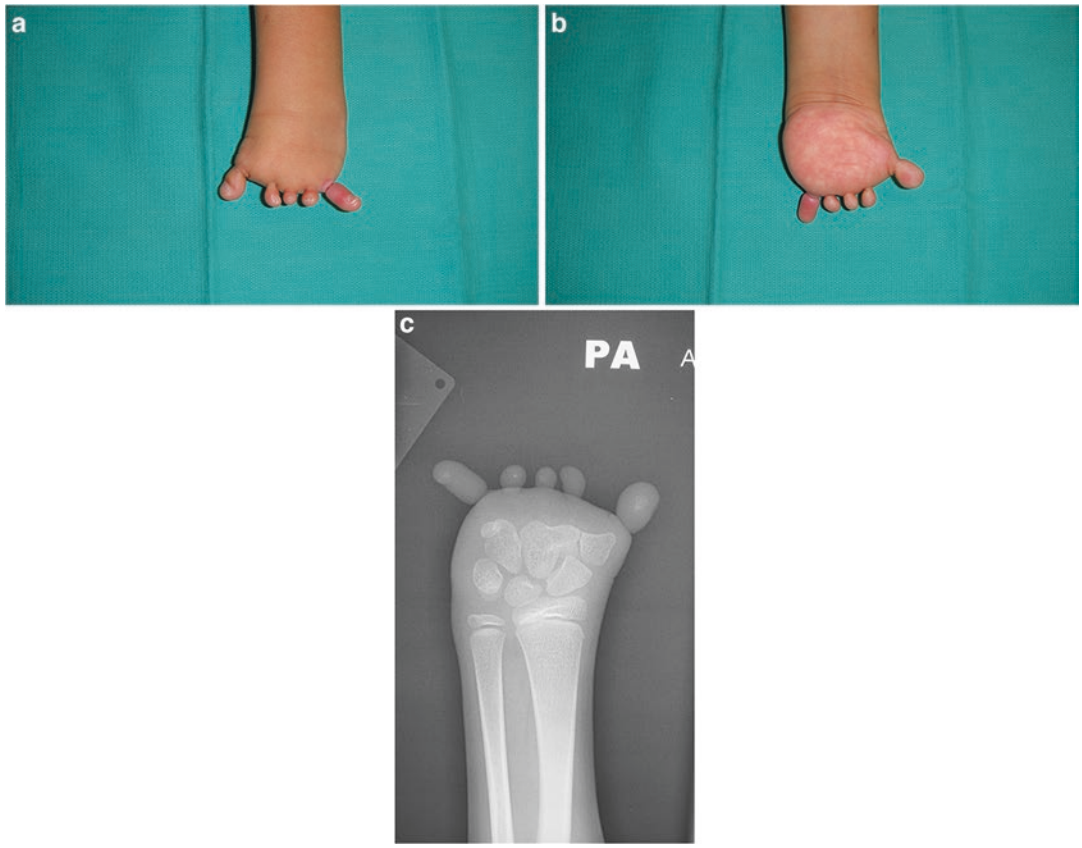

Fig. 12.3 (**a**–**c**) Dorsal and palmar photographs and radiograph of a 2-year-old girl with adactylic type IV symbrachydactyly of her left hand. All five digits are represented just by nubbins and are missing from the level of the carpometacarpal joints. This would be classified as an R5 hand. (Published with kind permission of Neil F. Jones ©2014. All rights reserved)

five digital rays, with only nubbins or nail remnants (Fig. 12.3).

Suguira refined the Blauth and Gekeler classification in 1976 [10]. He further subclassified the type one or short-fingered hands based on the number of phalanges in each digit. The least involved digits were the triphalangeal type. Diphalangeal and monophalangeal types have two phalanges and one phalanx, respectively.

Ogino et al. analyzed 76 children with symbrachydactyly [11]. All were unilateral; 48 were classified as type I, nine were type II, eight were type III, and 11 were type IV. Ogino argued that type I symbrachydactyly is a mild form of an intercalary transverse deficiency, whereas types II through IV represent terminal transverse deficiencies.

Yamauchi further divided the classification of symbrachydactyly into seven types [12]. In type 1 or triphalangia type, the hand has its full complement of bony structures although the middle phalanges are usually short. Type 2 or diphalangia type hands have one phalanx, usually the middle phalanx, missing. Type 3 or monophalangia type hands have a digit or digits containing only one phalanx. Type 4 or aphalangia type hands have a digit or digits that are missing all three phalanges. Type 5 or ametacarpia type hands have absence of the metacarpal and all three phalanges in one digit or several digits.

Type 6 or acarpia hands have absence of all the digits and a partial or complete absence of the carpus. Type 7 or forearm amputation has absence of the distal part of the forearm.

All of the classification systems have inherent weaknesses. In particular, the IFSSH classification originally placed the two transverse abnormalities in two different categories, with transverse arrest being placed in category I failure of formation and symbrachydactyly under category V undergrowth. Swanson wrote in his original paper "failure of formation may be manifest as an almost transverse arrest of the entire hand with only rudimentary radial and ulnar digits present," yet showed a case of symbrachydactyly as an example. The Japanese Society for Surgery of the Hand considers symbrachydactyly to be synonymous with transverse failure of formation and therefore believes that symbrachydactyly be moved to category I of the IFSSH classification. Symbrachydactyly is now being seen as a distal manifestation of transverse deficiency, whereas transverse arrest is seen as a more proximal manifestation of transverse deficiency. However, this understanding combines symbrachydactyly in which the initial deficiency is hypoplasia of the middle phalanges with preservation of the distal elements, with transverse deficiency in which the distal elements are missing completely.

Jones and Kaplan [13] suggested a new documentation system for congenital absent digits based on their review of photographs and PA radiographs of 235 hands in 204 children born with absent digits. This documentation system does not attempt to imply any underlying embryological causation, but unlike most other classifications, it provides a simple description of either the morphological or radiographic appearance of a child's hand to facilitate communication between physicians. Three letters can describe each hand: R (radial), C (central), and U (ulnar) as well as five numbers. The first letter and number describe which rays are missing, and the second and third letters and numbers describe the rays that are present. A normal hand is therefore described as R0. An absent thumb would be described as R1U4. The spectrum of radial deficiencies includes R2U3, R3U2, and R4U1 (Fig. 12.4). The spectrum of ulnar deficiencies

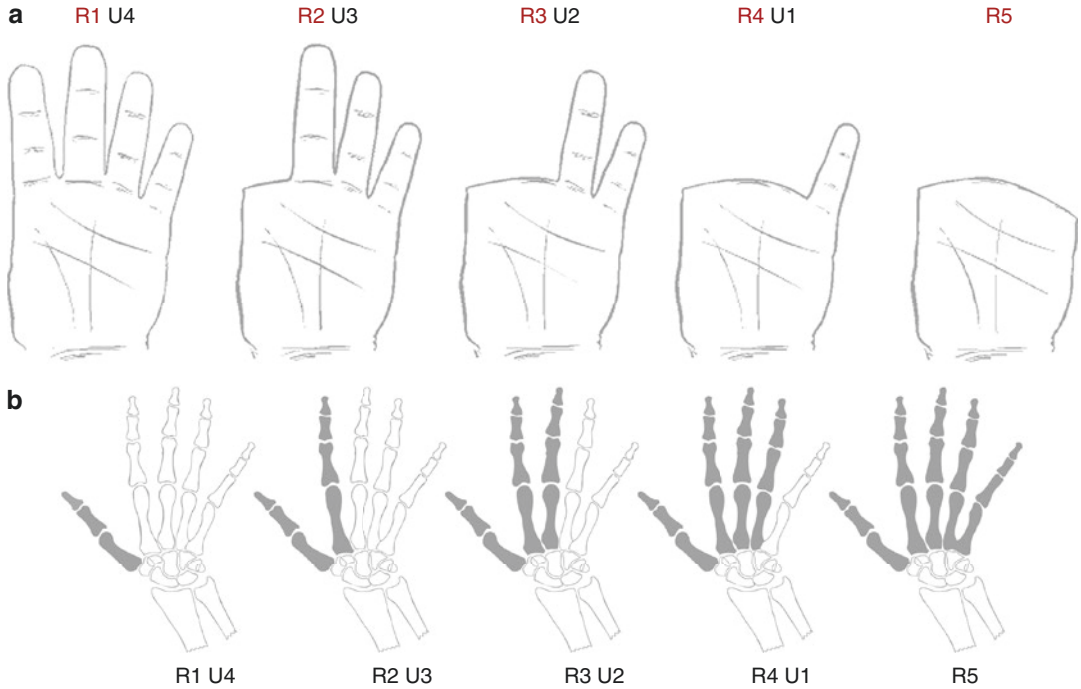

Fig. 12.4 (**a**, **b**) Schematic representation of congenital absent digits affecting the radial side of the hand. (Published with kind permission of Neil F. Jones ©2014. All rights reserved)

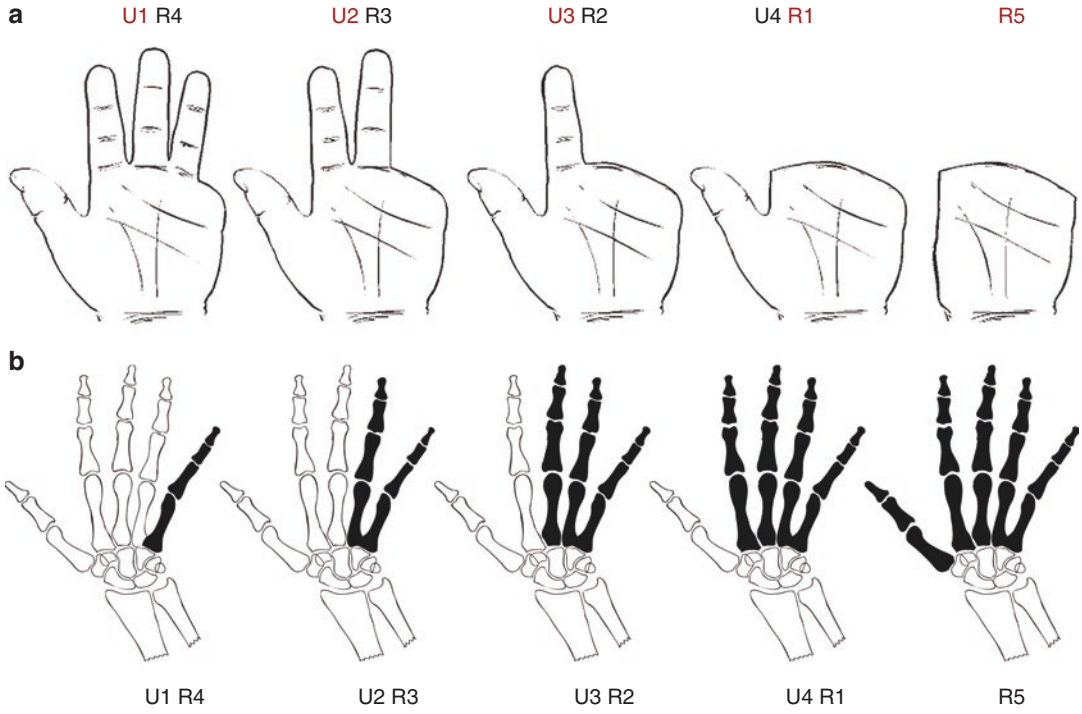

Fig. 12.5 (**a**, **b**) Schematic representation of congenital absent digits affecting the ulnar side of the hand. (Published with kind permission of Neil F. Jones ©2014. All rights reserved)

includes U1R4, U2R3, U3R2, and U4R1 (Fig. 12.5). A hand with a thumb but absent fingers would be designated as U4R1. This is the most common phenotype and corresponds to the Blauth and Gekeler monodactylic type III form of symbrachydactyly (see Fig. 12.2).

Typical cleft hand or central longitudinal deficiency as it is now known would be designated as C1R2U2. Other central deficiencies (Fig. 12.6) include C1R1U3, C1R3U1, C2R1U2, C2R2U1, and C3R1U1 (the old "atypical" cleft hand (see Fig. 12.1), which corresponds to the Blauth and Gekeler oligodactylic type II form of symbrachydactyly). Complete absence of all five digits would be designated as R5, which corresponds to the Blauth and Gekeler peromelic type IV form of symbrachydactyly (see Fig. 12.3). The documentation system can be further refined by describing the level at which the rays are absent: w, radiocarpal joint to carpometacarpal joint; m, distal to the carpometacarpal joint to just distal to the metacarpophalangeal joint; p, distal to the metacarpophalangeal joint out to the proximal third of the middle phalanx or the tip of the thumb; and d, distal to the proximal third of the middle phalanx to the tip of the finger.

The Jones and Kaplan system incorporates all the previous subclassification systems that have attempted to describe congenital absent digits in transverse deficiencies, central deficiencies, and symbrachydactyly and simplifies the documentation of these children's hands. Blauth and Gekeler [9] and Buck-Gramcko [14] postulated a "reduction theory" in symbrachydactyly which starts at the level of the middle phalanges producing hypoplasia of the middle phalanges ("brachymesophalangia") and then proceeds proximally, so that the distal phalanges or parts of the distal phalanges are always present as digital nubbins with rudimentary nails. With progression, there is absence of the proximal and middle phalanges of the central three fingers, the index, middle, and ring fingers, resulting in the oligodactylic type II "atypical cleft hand" form of symbrachydactyly, which corresponds to the C3R1U1 phenotype (see Fig. 12.1). Reduction progresses to involve

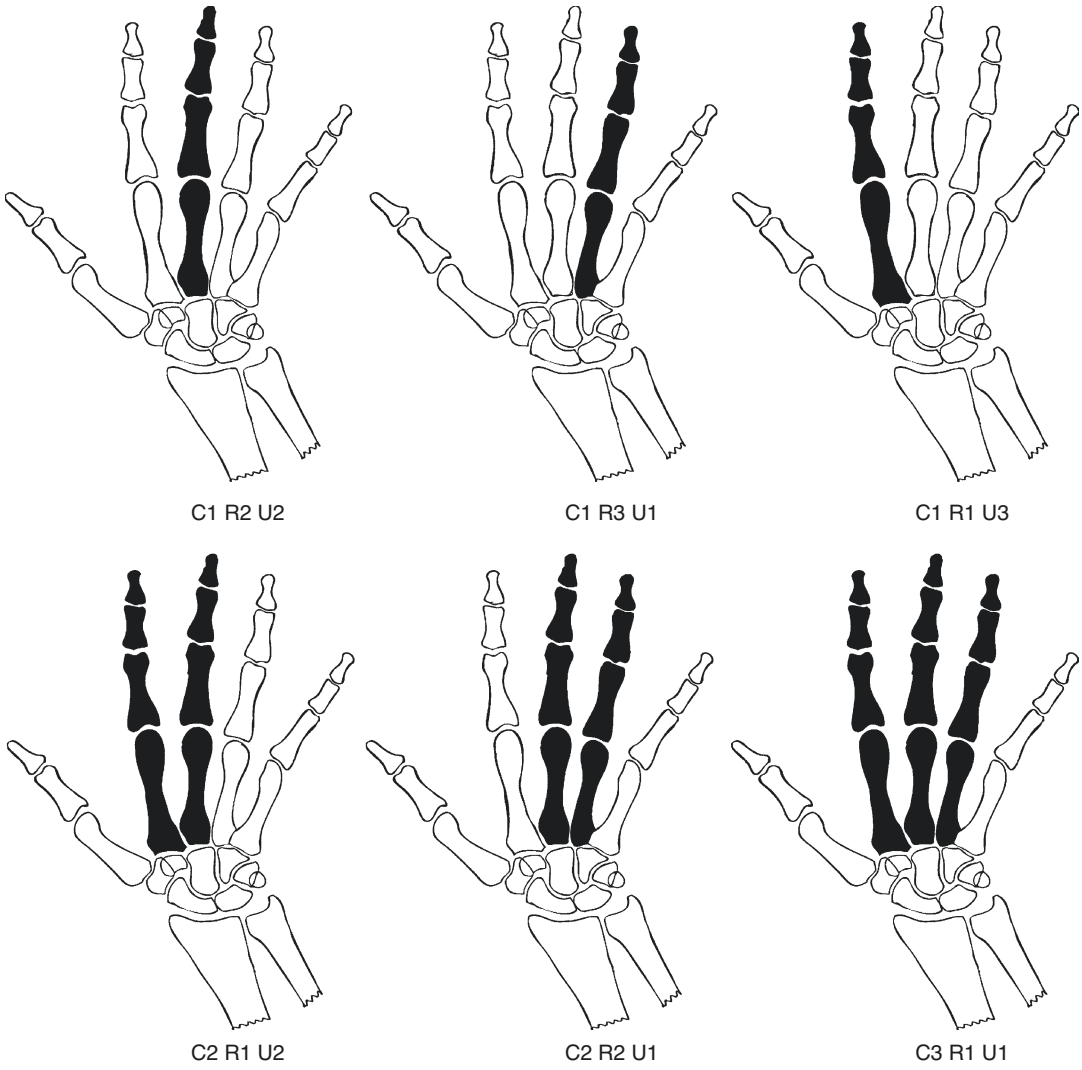

Fig. 12.6 Schematic representation of congenital absent digits affecting the central part of the hand. (Published with kind permission of Neil F. Jones ©2014. All rights reserved)

the small finger resulting in the type III monodactylic form of symbrachydactyly, which corresponds to the U4R1 phenotype (see Fig. 12.2) and finally extends to the thumb resulting in the type IV peromelic or adactylic form of symbrachydactyly with absence of all digits, corresponding to the R5 phenotype (see Fig. 12.3). Therefore, symbrachydactyly is represented by the C3R1U1, U4R1, and R5 phenotypes.

Another issue is the reclassification of cleft hand within symbrachydactyly. The description "typical cleft hand" has now been replaced with the term "central longitudinal deficiency." But the old term "atypical" cleft hand (see Fig. 12.1) has now been reclassified as "symbrachydactyly central absence type" within category I transverse deficiency [15, 16]. However, reduction of rays proceeds ulnarly from the central three digits in the oligodactylic type II form of symbrachydactyly, leaving only a thumb and no fingers, resulting in the monodactylic type III form of symbrachydactyly and corresponding to a U4R1 phenotype (see Fig. 12.2), whereas in an "atypical" cleft hand, reduction proceeds radially leav-

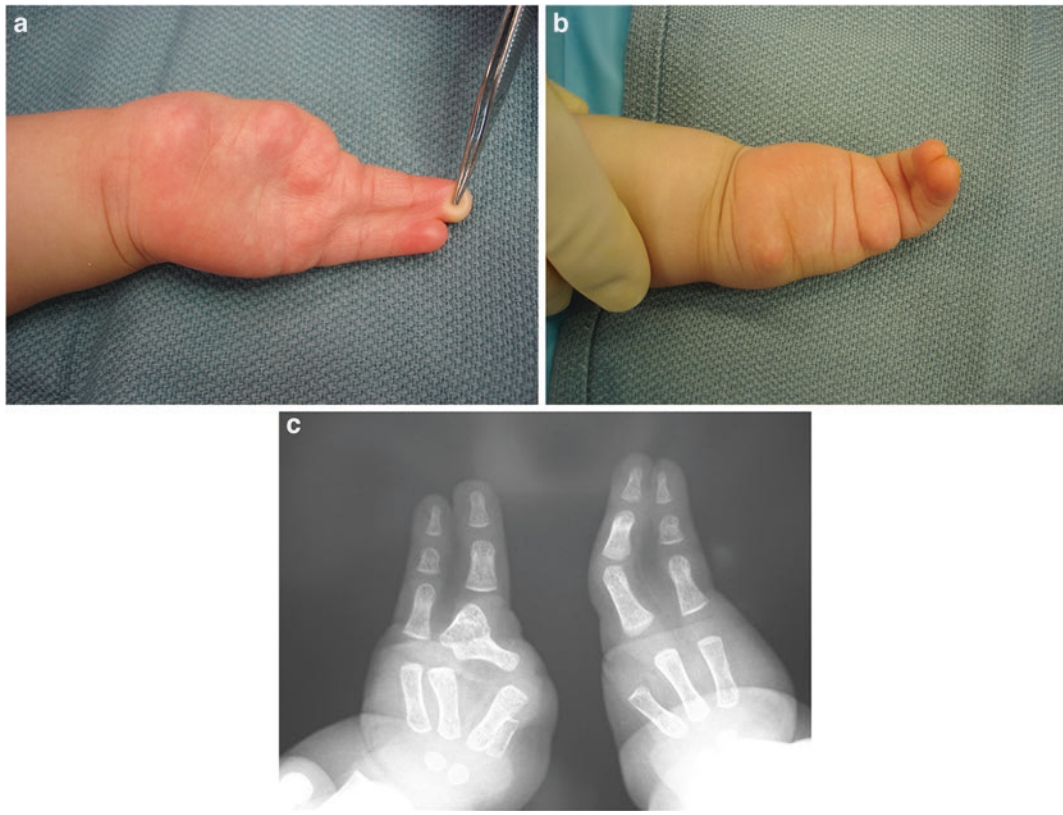

Fig. 12.7 (**a**–**c**) A 2-year-old boy with bilateral"atypical" cleft hands, missing the thumb, index, and middle fingers. The ring and small fingers are involved in a complete simple syndactyly. This would be classified as a R3U2 hand. (Published with kind permission of Neil F. Jones ©2014. All rights reserved)

ing the ring and small fingers or only a single small finger on the ulnar side of the hand, resulting in a R3U2 or R4U1 phenotype (Fig. 12.7). In the authors' opinion, these are two completely different phenotypes that are being placed together in the same category!

Clinical Features

The hand affected by symbrachydactyly can present with a variety of findings. A common feature is short digits frequently involved in varying degrees of simple incomplete to complex complete syndactyly or instead of fingers just "nubbins" [17]. Another feature associated with symbrachydactyly is skin invagination in the palm, thought to represent the attachments of forearm extrinsic muscle-tendon units [18]. The extensor tendons in symbrachydactyly are more normal and extend out over the hypoplastic metacarpals, but the flexor tendons often form a single amorphous tendon mass within the carpal tunnel [19].

Distinguishing symbrachydactyly from other conditions caused by other transverse failures of formation can be difficult. Kallemeier et al. [20] examined the relationship between transverse deficiency and symbrachydactyly in 271 children with a diagnosis of transverse deficiency at the level of the forearm; two hundred seven of these children (93%) had manifestations of symbrachydactyly—soft tissue "nubbins" or skin invagination at the distal aspect of their limbs. They concluded that symbrachydactyly and congenital transverse deficiency of the forearm represent two points on a single continuum, in that transverse deficiency

at the level of the forearm represents a more proximal form of symbrachydactyly.

Miura and Suzuki [21] also highlighted these difficulties when they attempted to differentiate between typical cleft hand and the "atypical" cleft hand (central absence type) seen in symbrachydactyly. They examined the length of the metacarpals in normal hands, syndactyly, cleft hands, symbrachydactyly, and constriction band syndrome and found that hands with symbrachydactyly and failure of formation of parts had shortened metacarpals, whereas hands with syndactyly, constriction band syndrome, and typical cleft hand had normal length metacarpals. Koehler et al. [22] also highlighted the varied presentation of symbrachydactyly in patients with Moebius syndrome. They found 93% of their patients with Moebius syndrome to have bilateral symbrachydactyly as opposed to the more normal unilateral involvement seen in isolated symbrachydactyly. They also found more common radial involvement (85%) as opposed to the more typically affected central rays.

Pediatricians and even some surgeons have difficulty differentiating transverse failure of formation, symbrachydactyly, and congenital constriction ring syndrome. A child's hand affected by a transverse failure of formation usually has shortened digits with smooth "amputation" stumps, without "nubbins" or evidence of constriction rings (Fig. 12.8). Radiographs may show tapering of the phalanges or shortened metacarpals. A child's hand affected by symbrachydactyly usually shows either a thumb and a small finger separated by "nubbins" or a wide cleft (see Fig. 12.1) or a thumb but missing all four fingers just represented by "nubbins" (see Fig. 12.2) or absence of all five digits represented just by "nubbins" (see Fig. 12.3). Radiographs will reveal shortened or absent metacarpals in the affected digits. Finally, a child's hand affected by congenital constriction ring syndrome will show a relatively smooth amputation of one or several fingers with evidence of constriction rings affecting other digits or more proximally the wrist or forearm (Fig. 12.9a) or amputation of several fingers with adhesion of the amputation stumps together distally (acrosyndactyly) with sinuses representing the web spaces more proximally (Fig. 12.9b). Radiographs typically show normal bony architecture proximal to the constriction rings.

Etiology

The exact cause of symbrachydactyly is not known. Mesenchymal stem cell defects in the hand plate are presumed to be the cause due to the hypoplastic nature of the hand in symbrachydactyly [23]. The likely mesodermal nature of the defect explains the persistence of ectodermal structures such as the finger pulp, nail fold, and nail even in severe presentations [24]. Bavnick and Weaver proposed that subclavian artery disruption at different points in embryological development could explain a variety of mesodermal anomalies seen in Poland's syndrome, Moebius syndrome, and Klippel-Feil syndrome [25]. There is no known hereditary pattern of inheritance described for symbrachydactyly.

There is no known animal model for symbrachydactyly. There are, however, mice with functional null mutations in growth and differentiation factor 5 (Gdf5) that display shortened limb bones with a phenotype very similar to symbrachydactyly in humans. They are referred to as brachypodism mice [26]. The metacarpals, metatarsals, and proximal phalanges are significantly shortened, and the middle phalanges are often absent. Kanauchi et al. [26] examined the bony histology of the hypoplastic bones in these brachypodism mice. The hypoplastic bones showed an endochondral ossification pattern but lacked a growth plate and epiphysis. The authors speculated that a similar mechanism explains the hypoplastic bones seen in symbrachydactyly.

Surgical Treatment

Surgical options for reconstruction of children with transverse failure or symbrachydactyly include nonvascularized toe phalangeal bone grafting, distraction osteogenesis, and microsurgical toe-to-hand transfers.

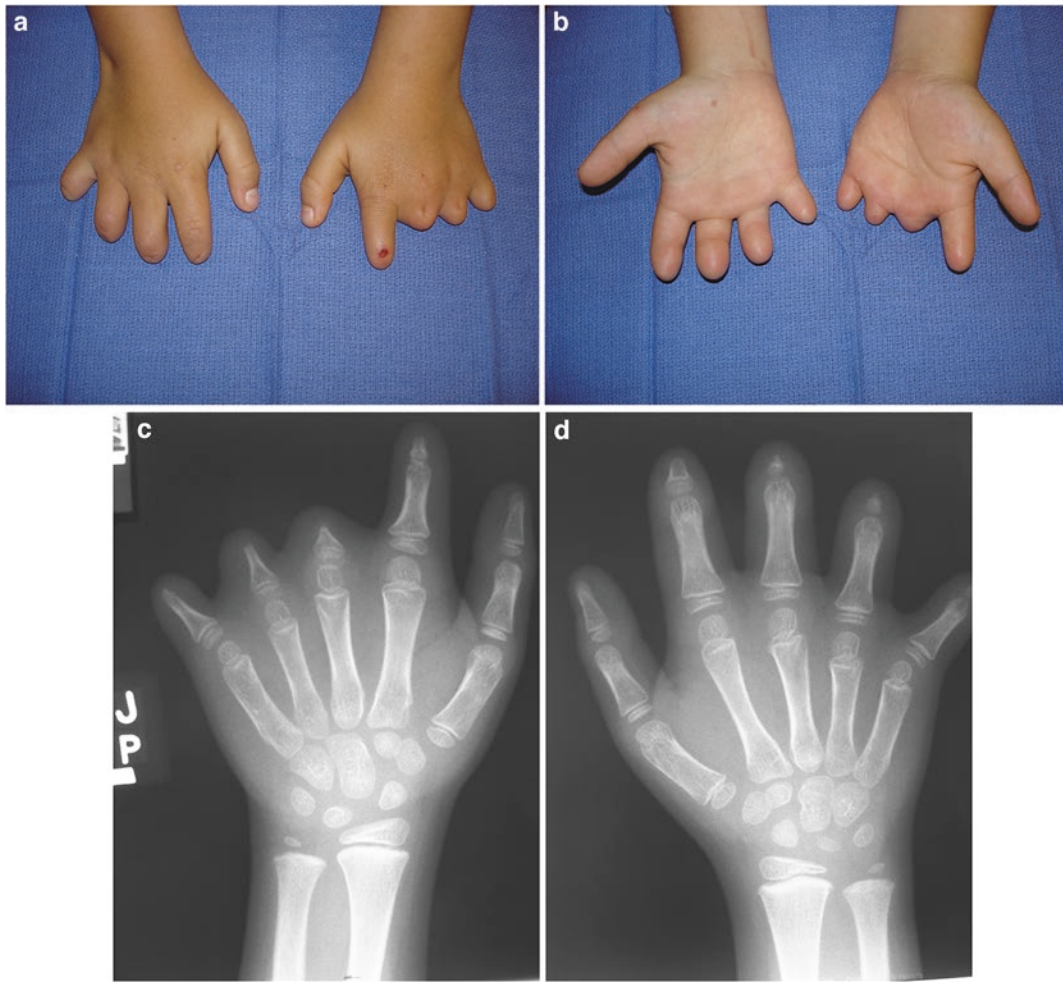

Fig. 12.8 Dorsal and palmar photographs (**a**, **b**) and radiographs (**c**, **d**) of a 6-year-old boy with a transverse failure of formation affecting both hands. In the right hand the failure of formation is at the level of the base of the middle phalanges. In the left hand, the level of failure of formation is at the level of the proximal phalanges in the middle, ring, and small fingers and at the base of the middle phalanx in the index finger. (Published with kind permission of Neil F. Jones ©2014. All rights reserved)

Nonvascularized Toe Phalangeal Bone Grafts

The first treatment option advocated for the treatment of short digits in symbrachydactyly was the nonvascularized transfer of toe phalanges.

The first report of nonvascularized toe phalangeal transfer was by the German surgeon Wolff in 1910 [27] and 1911 [28]. He reported the transfer of the second toe proximal phalanx to the proximal phalanx of a finger that had been destroyed by a tuberculosis infection. Entin [29] first used this technique in 1959 in the treatment of severe transverse deficiency. The technique was reintroduced by Carroll and Green in 1975 [30]. They reported on 159 toe phalanges transferred in 79 patients. They found that no open physes continued to grow, but did not see evidence of resorption. Complications of this technique in their series included skin necrosis at the tip of the lengthened digit in four patients and a pin tract infection in one patient.

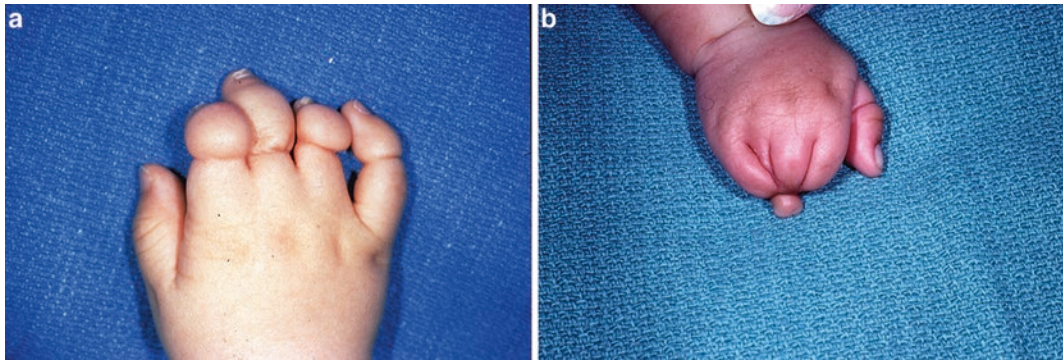

Fig. 12.9 Congenital constriction ring syndrome affecting the index, middle, ring, and small fingers of the right hand (**a**). Acrosyndactyly of the right hand with amputation of the distal phalanges and coalescence of the terminal portions of the fingers as well as more proximal sinuses which represent the webspaces (**b**). (Published with kind permission of Neil F. Jones ©2014. All rights reserved)

Goldberg and Watson [31] examined their experience with 20 patients and 36 digits treated with nonvascularized toe phalangeal transfer. In contrast to the findings of Carroll and Green [30], 90% of the growth plates in children under the age of 18 months remained open at an average follow-up of almost 4 years. This rate dropped to 67% in patients 18 months to 5 years old and to 50% in patients over the age of 5 years. They reported growth rates 90% of the contralateral non-transferred phalanges when growth plates remained open.

Buck-Gramcko [32] reported on his experience with 40 patients with symbrachydactyly and constriction band syndrome who underwent transfer of 63 nonvascularized phalangeal bone grafts. He reported 100% "take" of the bone graft provided that the periosteum over the phalanx was not disrupted and the graft was not split. He found that the best timing for transfer of the phalanges was between 19 and 48 months. Attempts to recreate a functional joint led to variable results with a range of motion ranging from 0° to 90°. Complications in his series included skin necrosis in five patients and joint subluxation requiring reduction in two patients.

Radocha et al. [33] described their experience in the transfer of 73 phalanges with a minimum follow-up of 1 year. They found a 94% rate of open physes in patients operated on before 1 year of age. The rate dropped to 71% for those operated on between 1 and 2 years of age and dropped further to 48% for those older than 2 years of age. Growth rates per age group were found to be 1 mm/year in the two younger age groups and 0.5 mm/year in the group over the age of 2. The authors stressed the importance of extraperiosteal dissection during harvesting of the phalanx, ligament and tendon repairs in the recipient digit and a young age (under 12 months) as important factors in maintaining an open physis and therefore the potential for further growth.

Cavallo et al. [34] reported on the transfer of 64 phalanges in 22 children with aphalangia from symbrachydactyly and constriction band syndrome. They found a total digital elongation of 6 mm at an average of 5 years of follow-up. The average range of motion at the newly created joint was found to be 60°. The most common complication in their series was graft instability or malposition, seen in 17% of the cases, more commonly in cases of atypical cleft hand.

Gohla et al. [35] reported on the transfer of 113 nonvascularized toe phalanges in 48 patients with diagnoses of symbrachydactyly and constriction band syndrome. The operative technique used was similar, and the patients were grouped as previously described by Buck-Gramcko [32]. Epiphyseal plate survival was highest in those patients treated before 18 months of age with an 87% rate of open physes at follow-up examination. The rate of open physes dropped only to 86% in patients aged 19 months to 4 years and to 64% in patients over the age of 4 years. They also looked at rates of bone resorption and found a 45% rate of resorption in patients over the age of

4 years compared to a rate of only 4% in patients under 18 months old. Eighteen of the 48 patients developed a complication, including four cases with necrosis of the skin resulting in the loss of the phalangeal bone grafts. Six children had scarring significant enough to require secondary procedures such as Z-plasties or local flaps. Six other transfers were complicated by digital instability or graft displacement.

Kawabata et al. reported 5- and 10-year follow-up on 54 nonvascularized toe transfers in 29 patients with symbrachydactyly. At 5-year follow-up, 23% of physes were closed and growth rate averaged 0.83 mm/year. At 10-year follow-up, 78% of physes were closed and growth rate averaged 0.22 mm/year. Five transfers were complicated by partial necrosis of the skin pocket which required revision surgery [36].

Donor Site Morbidity and Patient/Parental Satisfaction

The transfer of nonvascularized bone into a soft tissue envelope has been complicated by bone resorption, lack of bone growth, and donor site morbidity. Unglaub in 2006 [37] looked at outcomes of toe phalangeal transfers including growth, resorption, donor site morbidity, patient satisfaction, and parental satisfaction. He divided patients into similar groups as did Buck-Gramcko [32]: under 1.5 years old, 1.5–4 years old, and older than 4 years. Patients under 1.5 years showed good growth of the transferred phalanges with very few cases of resorption. Patients in the middle age group showed no growth in the transferred bone. Patients over 4 years of age had a 54% rate of graft resorption. He found little morbidity attributable to the donor site. He felt that the functional gains of the procedure were mostly from increased length as little active motion was achieved in the transferred joints in his series. Seventy-five percent of the parents in this series were highly satisfied with the functional gains and "manual skillfulness" provided by the nonvascularized toe phalangeal bone graft procedure.

The issue of donor site morbidity was also addressed by Bourke and Kay [38] who noted that all the toes with phalanges harvested by the technique described by Buck-Gramcko [32] were shortened and floppy and had a tendency to cross over other toes. They introduced a technique of placing a nonvascularized iliac crest bone graft in the donor toe with epiphysis present. This tubular bone graft was placed between the epiphysis at the base of the resected phalanx and a small cap of bone left from the harvested phalanx and pinned in place with a longitudinal Kirschner wire (K wire). They reported that their series of 11 patients had better preservation of toe length and stability.

Garagnani et al. [39] studied donor site morbidity clinically and radiographically in a series of 40 patients with hypoplastic digits. A total of 136 phalanges were harvested using supraperiosteal dissection as previously described, with repair of the extensor tendon after removal of the phalanx. The mean follow-up for the series was 122 months with a minimum follow-up of 36 months. The Oxford Ankle-Foot Questionnaire (OAFQ) is a validated questionnaire for children aged 5–16 years old that assesses subjective patient and parental satisfaction. Over 80% of patients and families reported some degree of emotional problems related to their feet. Footwear-related problems were noted by over 60% of both patients and families. All of the patients interviewed reported a tendency to hide their feet. From a clinical perspective, shortening of the harvested toes was universal, and malrotation was seen in 76–100% of the toes. Not surprisingly, clinical deformity increased when multiple phalanges were harvested from a single foot. Radiographic examination revealed hypoplasia of surrounding bony structures including the distal phalanx, middle phalanx, and metatarsal. One patient in their series even underwent amputation of bilateral overriding and unstable fourth toes with significant postoperative improvement in the appearance of the feet.

Indications and Patient Selection

Jones [40] described three specific indications for the transfer of nonvascularized toe phalanges. The first is stabilization of a floppy hypoplastic digit consisting of only a soft tissue envelope. The second is lengthening and stabilization of a digit that contains a remnant of the proximal phalanx. The third indication is stabilization of an intercalated defect between the distal phalanx and the metacarpal of a thumb. Based on the out-

comes described earlier, the ideal patient for nonvascularized toe phalangeal transfers is a child under the age of 18 months with multiple short digits and a bony skeleton out to at least the level of the distal metacarpals with a sufficient soft tissue envelope [41].

Surgical Technique

Under tourniquet control, the hypoplastic digit is explored through a dorsal longitudinal incision. If a significant palmar soft tissue contracture is present, a volar approach could be chosen. Blunt dissection within the soft tissue is used to create a cavity for the donor bone. It is crucial to maintain a sufficient pad of soft tissue at the distal aspect of the digit to prevent necrosis caused by pressure from the donor bone. Typically, the flexor and extensor tendons are confluent over the hypoplastic metacarpal head. They are sharply divided to create independent flexor and extensor tendons and radial and ulnar collateral ligaments.

Typically, the proximal phalanx from the third or fourth toe is used as a donor phalanx. The second toe can be used if a microsurgical second toe transfer is not planned for the future. A gently curved incision is used over the dorsum of the toe because a straight incision over the dorsum of the toe can result in an extension contracture of the toe. The extensor tendon is split longitudinally to expose the proximal phalanx. Previous experience [31–33] has shown that an extraperiosteal dissection of the proximal phalanx in a child under the age of 18 months provides the best chance for preventing resorption of the transferred bone. The collateral ligaments of the PIP joint are divided off the proximal phalanx, while the collateral ligaments and volar plate of the metatarsophalangeal joint are harvested with the proximal phalanx.

The tourniquet on the leg is then released and hemostasis achieved. A variety of methods have been described to prevent shortening of the donor toe [32, 33, 38]. The simplest of these is suturing the extensor tendon to the flexor tendon. Iliac crest bone graft with its associated apophysis as described by Bourke and Kay [38] can be inserted to help maintain the length and stability of the toe. A 0.035-in K wire is then introduced retrograde through the toe into the metatarsal head and left in place for 4–5 weeks to hold the toe out to length.

The toe phalanx is transferred to the hand and the bone graft can be positioned in one of three basic constructs. In digits with a partial proximal phalanx, the graft can be placed distally in the "on top" position. In digits with an intercalary defect between a hypoplastic distal phalanx and metacarpal, the graft can be interposed between the two bones. Finally, the graft can potentially be used to simultaneously reconstruct the metacarpophalangeal joint and provide length to the floppy digit in children lacking all skeletal elements distal to the metacarpal head.

A 0.035-in or 0.028-in K wire is inserted through the phalanx. Nonabsorbable sutures are placed but not tied between the flexor tendon and the volar plate of the transferred phalanx as well as between the radial and ulnar capsule of the MCP joint and the radial and ulnar collateral ligaments of the transferred phalanx. The K wire is then advanced distally out through the distal soft tissues of the digit. The phalangeal bone graft is reduced into the soft tissue envelope of the digit and held in appropriate position relative to the metacarpal. The previously placed sutures are tied. The K wire is then advanced retrograde into the metacarpal. The extensor tendon and dorsal capsule of the MCP joint are repaired to the dorsal capsule of the donor phalanx. The hand is immobilized in a plaster splint, and the K wire is left in place for 4–6 weeks postoperatively. In patients with a phalanx too small to permit distraction lengthening or typical bone grafting, Iba et al. describe using a 4th metacarpal head graft in an "on top plasty" fashion to lengthen the proximal phalanx in a patient with symbrachydactyly [42].

Because of only modest growth of nonvascularized toe phalangeal bone grafts; the problems of subluxation, instability, and resorption of the bone graft; and problems of the donor toe, we now rarely use this technique. Currently, we only use nonvascularized toe phalangeal transfer for elongating and stabilizing soft tissue finger stumps with the bone out to the level of the metacarpal heads or just distal to the PIP joints and for intercalated bone grafting in a thumb missing the proximal phalanx (Figs. 12.10 and 12.11).

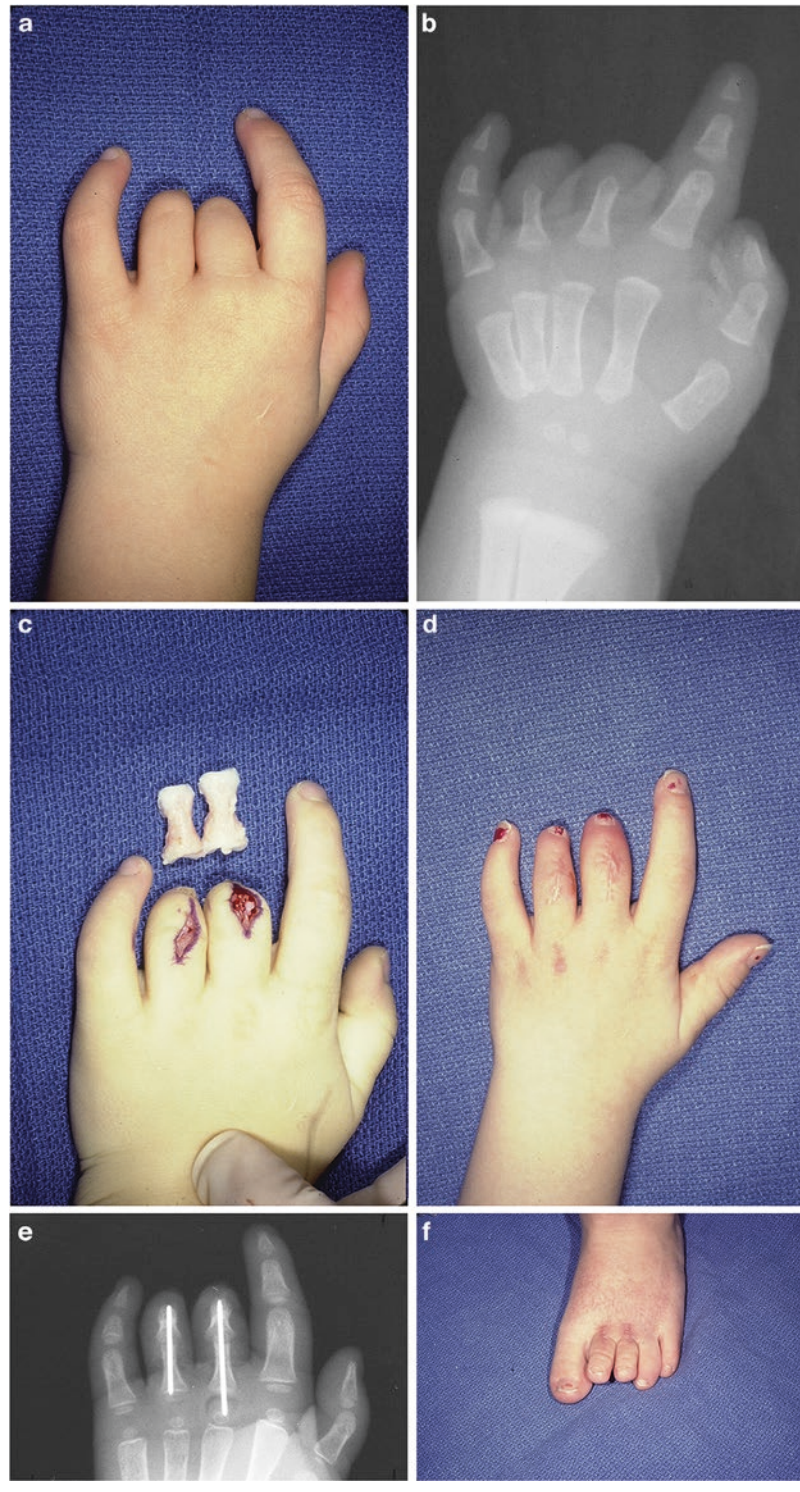

Fig. 12.10 Dorsal and palmar photographs and radiograph of a 4-year-old girl with a transverse failure of formation of her left middle and ring fingers at the level of the proximal phalanges (**a**, **b**). The soft tissue envelopes of these two fingers were stabilized and elongated using nonvascularized bone grafts from the proximal phalanges of the left second and third toes (**c**). Resultant lengthening of the left middle and ring fingers with the nonvascularized toe phalangeal bone grafts (**d**, **e**). The donor site in the left foot (**f**). (Published with kind permission of Neil F. Jones ©2014. All rights reserved)

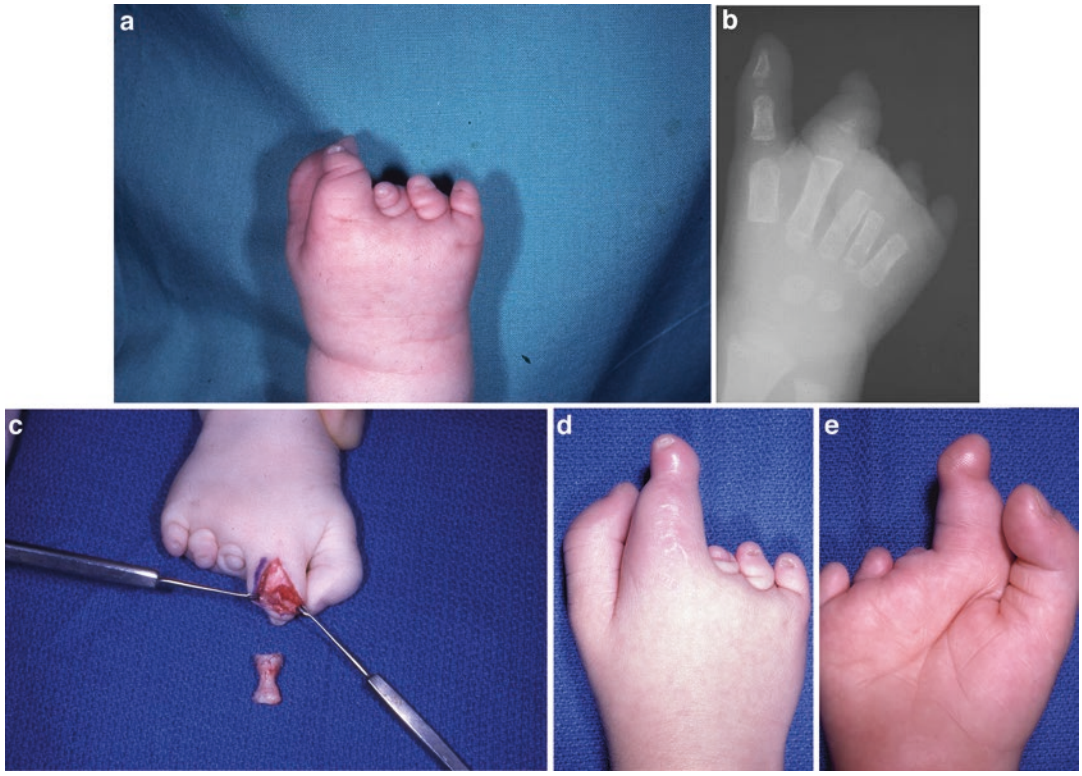

Fig. 12.11 A 1-year-old boy with monodactylic type III symbrachydactyly affecting his right hand, classified as a U4R1 hand (**a**, **b**). His parents initially refused a microsurgical toe-to-hand transfer. Therefore, he underwent a nonvascularized toe phalangeal bone graft from the right third toe to elongate and stabilize the right index finger (**c**). The postoperative result after nonvascularized toe phalangeal bone grafting of the right index finger (**d**, **e**). (Published with kind permission of Neil F. Jones ©2014. All rights reserved)

Limitations

The main limitations of the toe phalangeal transfer technique are the pre-existing soft tissue envelope of the hand and the limited growth potential of the transferred bone. The pre-existing soft tissue envelope of the hand dictates the amount of bone length that can be achieved with a single-stage operation. Attempting to overlengthen the soft tissue envelope acutely can result in the complications noted by Carroll and Green [30]. The growth potential of the transferred phalanx is quite limited. Even in the best-case scenario, a toe proximal phalanx lengthens the digit at an average of 5.8 mm [34] with the maximum lengthening seen with growth to be 18 mm [35].

Bone Distraction Osteogenesis

Bone distraction osteogenesis has also been used in the treatment of symbrachydactyly in an attempt to overcome the limitations of nonvascularized toe phalangeal transfers and to potentially avoid the need for additional bone grafting in some cases (Figs. 12.12 and 12.13).

Codivilla reported the first use of distraction osteogenesis in 1905 [43] with lengthening of the lower extremities in cases of congenital deficiencies. Matev reported the first use of distraction osteogenesis in the hand in 1970 [44] with lengthening of three patient's thumb amputations through a metacarpal osteotomy. Kessler [45] reported the use of bone distraction to treat 11

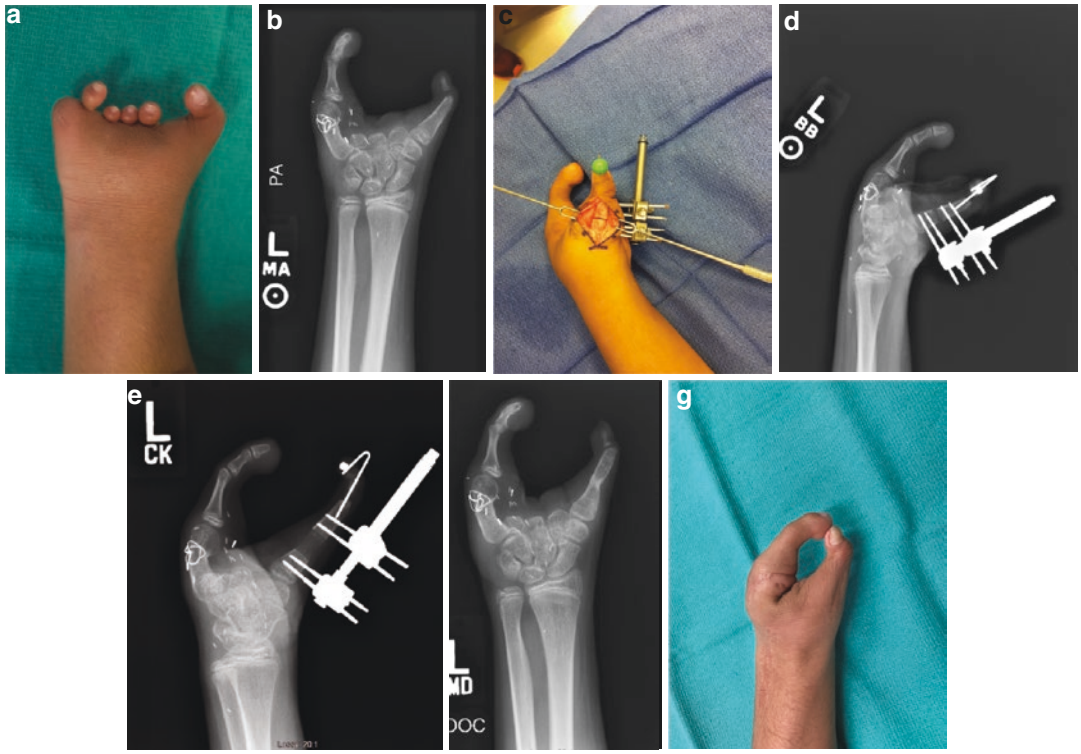

Fig. 12.12 A 2-year-old boy with monodactylic type III symbrachydactyly of his left hand (**a**). He underwent successful microsurgical transfer of the left second toe into the left small finger position, but the thumb remained hypoplastic with respect to the toe transfer. Radiographs demonstrate the absent proximal phalanx and a hypoplastic distal phalanx of the thumb (**b**). At age 8, he underwent an osteotomy of the thumb metacarpal and distraction osteogenesis (**c**, **d**). Over the next 3 months, the thumb was lengthened 0.25 mm per day for a total of 18 mm, followed by spontaneous bone regeneration (**e**). Postoperative radiographs revealed consolidation of the bony regenerate without the need for secondary bone grafting (**f**). Two years postoperatively, the child has excellent pinch between the lengthened thumb and the toe transfer in the small finger position (**g**). (Published with kind permission of Neil F. Jones ©2020. All rights reserved)

children with congenital aplasia or hypoplasia of the digits. Iliac crest bone grafting and internal fixation were required to achieve final stability. Wenner in 1986 [46] recommended the use of intramedullary K wires to prevent unwanted angulation during distraction osteogenesis.

Seitz and Froimson [47] described distraction of 12 digits for a variety of diagnoses including congenital differences. Nine of the 12 patients achieved complete consolidation of their regenerate without requiring secondary bone grafting. Complications included one pin tract infection and one premature cessation of growth. They advocated using a uniplanar fixator for lengthening the non-weight-bearing upper extremity. In a further series published in 1995 [48], Seitz and Froimson reported 14 single-stage lengthenings using a half frame construct. Digital lengthening of 2–3.5 cm was achieved without the use of bone graft in 13 cases. They recommended a slow rate of lengthening (0.25 mm four times per day) to minimize the discomfort associated with the procedure.

Ogino et al. [49] reported their experience of lengthening 15 digits in patients with symbrachydactyly, brachydactyly, and congenital constriction band syndrome. They only lengthened in one symbrachydactyly patient in a total of six patients using distraction osteogenesis. Other methods used were single-stage lengthening with iliac crest or local bone graft and "on-the-top-plasty." They used a fixator as described

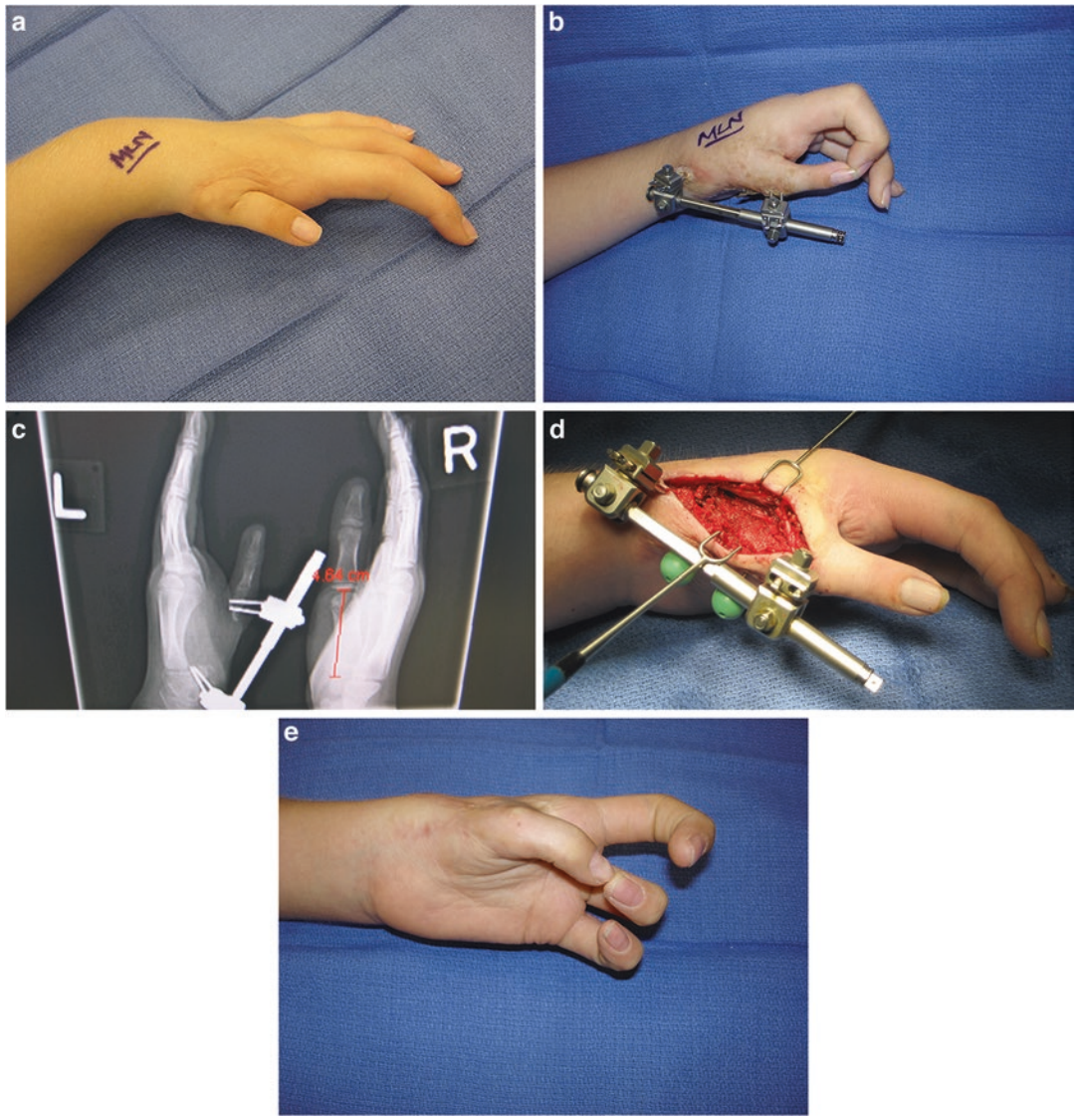

Fig. 12.13 An 8-year-old boy with an unsatisfactory result following pollicization of his left index finger with inadequate length to the new thumb (**a**). He underwent distraction lengthening of 27 mm of the "thumb metacarpal" (index finger proximal phalanx) (**b**, **c**). He subsequently underwent secondary cortico-cancellous bone grafting of the resultant defect, (**d**) and after bony consolidation, he was able to oppose the tip of the thumb to the tips of the little and ring fingers (Kapandji stage 4) (**e**). (Published with kind permission of Neil F. Jones ©2014. All rights reserved)

by Matev and distracted the bone at a rate of 0.5–1 mm per day. After the fixator was in place for 13–34 days, they removed the fixator and used internal fixation and iliac crest bone graft to maintain the length gained with the fixator. The digits treated with distraction osteogenesis showed the greatest average increase in length of 17 mm with no cases of delayed union, whereas two cases of nonunion occurred with single-stage lengthening.

Pensler et al. [50] reported using distraction osteogenesis to treat 12 digits in children with Apert's syndrome. The average age at the time of operation was 4.7 years, and the average duration

of distraction was 31.1 days. The fixator was generally left in place for 2 days for every 1 mm of lengthening that was performed. The average lengthening was 23.6 mm. Seventeen percent of the digits (two of 12) required intraoperative manipulation to correct angular deformities that had developed during the course of lengthening.

The first use of distraction osteogenesis specifically for the treatment of symbrachydactyly was reported by Hulsbergen-Kruger et al. [51] who treated three patients with symbrachydactyly with the goal of obtaining pinch grip in the affected hands. They first attempted to lengthen previously transferred proximal toe phalanges, but met with complications due to the tight soft tissue envelope and pin exposure. In their second case, an infection developed during lengthening of the thumb ray. Despite this complication, they were able to achieve 2.2 cm of lengthening. In their third case, a more stable fixator construct was designed and 2.6 cm of lengthening was achieved.

Dhalla et al. [52] compared two different techniques of distraction osteogenesis in a mixed patient population including ten digits in children with some form of transverse arrest. They compared the use of two half pins on either side of the osteotomy site in seven digits with a second group of 20 digits in which a single half pin was used on either side of the osteotomy (because the bone was too small to accommodate four half pins) and lengthened over a centrally placed K wire. The mean preoperative bone length in the dual half pin group was 30 mm compared to 18 mm in the single half pin group. The mean gain in length for the dual half pin group was 14 mm compared to 12 mm in the single half pin group. The rate of complications in the single half pin group was 75% (15) compared to 43% (3) in the dual half pin group. Only seven of the complications required reoperation. All of the infections were seen in the single half pin group. This study highlights the feasibility of successfully lengthening even very short bones, albeit with a high rate of complications. The authors recommended the use of prophylactic antibiotics in the single half pin fixator cases.

Miyawaki et al. [53] reported their experience with bone distraction osteogenesis of seven metacarpals in four hands with symbrachydactyly. They used a mini-fixator with a distraction rate of 1 mm per day. Lengthening occurred over a mean of 37.3 days and the fixator remained in place for a mean duration of 84 days. An intramedullary 1.0-mm K wire was used to help maintain alignment. In three hands, a single fixator was used to lengthen the fourth and fifth metacarpals simultaneously. The mean increase in bone length was 22.3 mm. The only major complication was a fracture of a fifth metacarpal that occurred during distraction. No growth disturbances were observed in the lengthened bones at an average of 3.9 years of follow-up. A functional benefit of the procedure was that pinch strength improved in all of the treated hands.

Matsuno et al. [54] examined the bone growth that occurred after distraction osteogenesis in a variety of congenital hand diagnoses including symbrachydactyly. They found that earlier bone lengthening tended to result in greater bone growth after distraction and consolidation. Growth plates closed soon after lengthening in patients older than 10 years of age. In their series, seven metacarpals in three symbrachydactyly patients were lengthened at an average of 8 mm with a total time in the fixator of 104 days. These metacarpals grew at an average of 7.6 mm during the average follow-up period of 59 months. Complications in the symbrachydactyly group included bony prominence at the distal aspect of the lengthened ray. The symbrachydactyly patients tended to be operated on at an earlier age, which they speculated to be the reason that bone growth was seen after lengthening.

Seitz et al. reported on the long-term outcomes of distraction lengthening of over 400 individual bones in 141 patients [55]. Patients were evaluated postoperatively by their therapist regarding multiple outcome measures. Eighty-eight percent of patients reported no difficulty in performing functional activities of daily living, and only 5% reported inability to carry out activities of daily living. Ninety-seven percent of patients reported never having significant pain. Ninety-two percent

of patients were satisfied with their outcome from surgery. Static two-point discrimination was unchanged when compared to the contralateral limb in all cases. When asked if the surgery and aftercare were worth it, 98.5% of patients reported that they would undergo the procedure again. Major complications including the need for supplemental bone grafting (6%), premature consolidation (0.7%), soft tissue compromise (0.7%), digital tip necrosis, angular deformity, pin loosening, joint stiffness, joint subluxation, regenerate fracture, or infection occurred in 9%. Five percent of the major complications required reoperation. Minor complications occurred in 45% and consisted entirely of pin tract infections, treated with oral antibiotics.

Indications and Patient Selection

In the symbrachydactyly hand, distraction lengthening is indicated for digits lacking sufficient length to generate pinch and prehension. Adequate bone stock (bone length of at least 10 mm [52]) must be present to allow for lengthening to occur. If adequate bone stock is not present, lengthening of transferred toe phalanges can be performed 6 months post-transfer [55]. Patient and family selection is of utmost importance with these procedures. Patients and their families must be educated about the procedure and be able to understand and comply with the extensive aftercare program, including frame adjustments, pin site care, frequent appointments with the surgeon, long duration of treatment, and the high likelihood of complications.

Surgical Technique

Seitz et al. published their technique for lengthening nonvascularized toe phalangeal transfers in symbrachydactyly in 2010 [5]. The goal of lengthening was to provide prehension and improved mechanical advantage. The toe phalanges were harvested using a similar technique as previously discussed. Early reconstruction of a first web space is advantageous. In hands with significantly hypoplastic index finger rays, resections of the index metacarpal and Z-plasty web space deepening were performed at the same time as toe phalangeal transfers. The resected metacarpal can be used as bone graft for lengthening other rays. Six months after the phalangeal transfer, lengthening can be started. Two 2-mm self-tapping half pins are placed on each side of the osteotomy, which is made using an osteotome in older children and a Beaver blade in younger children after circumferential periosteal elevation. The periosteum and skin are closed with absorbable suture. The lengthening program begins 5 days after surgery and consists of four lengthenings of 0.25 mm each per day. Showers are permitted at 2 weeks postoperatively. The consolidation phase lasts for two to three times the lengthening period. Seitz highlights the complicated nature of the treatment for children as well as their families.

Limitations

The main limitation of distraction osteogenesis is that it only provides function through increased digital length and is complicated by frequent pin tract infections.

Microsurgical Toe-to-Hand Transfer

The next step in the evolution of treatment for transverse deficiency and symbrachydactyly, particularly for its more severe types III and IV, is microsurgical toe-to-hand transfers.

The first report of a microsurgical toe-to-hand transfer for a congenital hand difference was by O'Brien et al. who in 1978 [56] performed two toe-to-thumb transfers for congenital absence of the thumb. Gilbert [57] reported a series of 21 second toe-to-hand transfers for congenital hand anomalies, four of which were transferred to the thumb. Active motion of the toe was mainly determined by the motion of the native metacarpal. Toe transfers in children with amniotic band syndrome were technically easier due to more normal anatomy compared with children with aplasia. He felt that the best timing for a toe transfer was 16 months of age. Gilbert reported on a more extensive series of 49 toe transfers to 38 hands [58]. Eleven of these children had two toes transferred, one from each foot. One toe transfer failed in a 16-month-old child with apla-

sia and ten of 85 epiphyseal plates closed prematurely.

Lister described 12 second toe transfers to reconstruct thumbs in cases of transverse arrest, constriction ring syndrome, and symbrachydactyly [59]. The average age at transfer was 3 years old, with the youngest child only 10 months old. Similar to Gilbert, he found that anatomical variations were always seen in cases of transverse arrest and symbrachydactyly. Only three transfers demonstrated interphalangeal motion at final follow-up, but 11 of the children regained good sensation.

Shvedovchenko [60] reported on the transfer of 103 toes in 66 children for diagnoses including brachydactyly, ectrodactyly, adactyly, hypoplasia, and after trauma. Forty-nine children had congenital hand differences. Distraction osteogenesis was performed to lengthen three of the transferred toes. Vilkki [61] performed toe-to-hand transfers in 30 children with congenital hand differences, 14 of whom had aplasia of all the fingers and four had reconstruction of a thumb.

Kay [62] reported a series of 66 toe transfers in 40 children, 85% of whom had congenital differences. Fourteen children had two toes transferred at the same operation. There were no failures, but 75% required secondary surgeries to improve function or appearance. Kay emphasized the benefit of the simultaneous transfer of two toes. Growth of the transferred toes was found to be at an average of 91% of the contralateral toe. All children recovered protective sensation and the majority demonstrated adequate light touch perception.

Van Holder et al. [63] described 14 children with congenital hand differences including transverse failure of formation, constriction ring syndrome, and symbrachydactyly who underwent staged double second toe transfers. Foucher et al. [64] reported 65 toe transfers in 58 children, 51 of whom had a diagnosis of symbrachydactyly. Two toe transfers failed when only one artery was anastomosed and other complications included lateral instability of the transferred metatarsophalangeal joint. The average range of motion was reported to be 38° and the average two-point discrimination was 5 mm.

Richardson et al. [65] reported 18 toe transfers in 13 children with symbrachydactyly, and Jones et al. [66] reported 82 toe transfers in 68 children with diagnoses including symbrachydactyly, transverse deficiencies, and constriction ring syndrome.

Indications

Despite success rates of over 95% in most reported series of microsurgical toe-to-hand transfers, the procedure remains rarely performed in children. Hand surgeons may be unwilling to risk the loss of a toe transfer in children who already have a congenital hand difference. Secondly, some hand surgeons feel that children with unilateral digital absence adapt well to their impairment over time. Finally, it can be very difficult for parents to make a decision to proceed with a complicated surgery that may potentially result in the loss of a toe with no benefit despite the surgery on the hand.

It can be helpful to show parents photographs and videos of other children who have undergone toe transfers to help them appreciate the benefits that can be achieved through such surgery. The senior author's practice is to introduce the parents of a candidate child for a toe transfer to the parents of a child who has previously undergone a toe transfer for a congenital hand difference. This allows the parents to discuss their concerns with other parents who have had to make a similar decision. It also affords them the opportunity to see a child with a toe transfer in person and obtain a better understanding of the appearance and function of a toe transfer. Goodell et al. highlighted the importance of two or more digits in adolescents with symbrachydactyly. In this study, patients with two or more digits available for opposition incorporated their affected hand significantly more in bimanual activities ($p \leq 0.0009$) and used normal strategies for in-hand manipulation. This emphasizes the important functional gains that can potentially be achieved through microsurgical toe-to-hand transfers [67].

Jones and Kaplan [68] suggest that the morphologic and radiographic appearance of a congenital hand difference, rather than its embryological etiology, should dictate the indications for a toe transfer, based on analysis of 100 toe transfers performed for reconstruction of children born with congenital absent digits. For a child with a hand missing a thumb, it seems intuitive to reconstruct a thumb to restore opposition. Similarly, for a child born with a thumb but no fingers, it makes sense to reconstruct a finger or even two fingers to restore opposition and pinch.

In children with an absent thumb, Jones and Kaplan [68] believe that there are three indications for microsurgical reconstruction. The first indication is an isolated absence of the thumb distal to the carpometacarpal joint with a remnant of a thumb metacarpal and thenar musculature as well as four normal or nearly normal fingers, the R1U4 hand, usually due to a transverse deficiency. Microsurgical toe transfers provide superior outcomes when compared to nonvascularized toe phalangeal bone grafting, index finger pollicization, and distraction osteogenesis, because they provide greater length and preserve the potential for growth as well as the full complement of fingers. The second indication is an absent thumb together with absence of the index, middle, and ring fingers but with one or two fingers remaining on the ulnar side of the hand, R3U2 and R4U1 hands, usually seen in the old "atypical" cleft hand. The absent thumb can be reconstructed with a second toe transfer with minimal donor site morbidity. In older children, a "trimmed" great toe can be considered since it provides a functional digit that is very similar in appearance and size to the contralateral normal thumb [69]. On rare occasions when there is an associated cleft foot, an abnormal great toe may be transferred to reconstruct the absent thumb [70]. The third indication is absence of all five digits, classified as a R5 hand.

There is a distinct difference between children only missing a thumb and children missing a thumb as well as missing the index, middle, and ring fingers. The former group of children has three reconstructive options available to them: pollicization of the index finger, distraction lengthening, or microsurgical reconstruction with a toe-to-thumb transfer. The only reconstructive option for children in the latter group is a toe-to-thumb transfer.

Jones and Kaplan [68] suggest that there are two indications for toe transfers to reconstruct absent fingers. The first indication is the absence of all four fingers but with a normal thumb, the U4R1 hand, usually due to monodactylic type III symbrachydactyly. A single second toe transfer can restore pinch and grip when placed in the ring or small finger position. Alternatively, two second toes can be transferred into the middle and small finger positions to restore chuck grip, performed either simultaneously or as sequential staged transfers. The second indication is to reconstruct a child's hand with complete absence of all five digits, the R5 hand, usually due to adactylic type IV symbrachydactyly . Usually, one second toe can be transferred into the thumb position first. Then a subsequent second toe transfer can be placed in the ring or small finger position. Performing these two transfers sequentially, rather than simultaneously, allows the second toe transfer to be placed in the optimum position relative to the new "thumb."

Consequently, there are four specific indications for considering microsurgical toe-to-hand transfers for reconstruction of children born with transverse failure of formation or symbrachydactyly:

1. Transverse failure of formation of the thumb, distal to the CMC joint: R1U4 phenotype (Fig. 12.14)
2. Central absence type of symbrachydactyly, the old "atypical" cleft hand, with absence of the thumb, index, middle, and (possibly) the ring fingers: R3U2 or R4U1 phenotypes
3. Transverse failure of formation or monodactylic type III symbrachydactyly, with absence of all four fingers distal to the base of the proximal phalanges: U4R1 phenotype (Figs. 12.15, 12.16, and 12.17)
4. Peromelic or adactylic type IV symbrachydactyly, with absence of all five digits: R5 phenotype (Figs. 12.18 and 12.19)

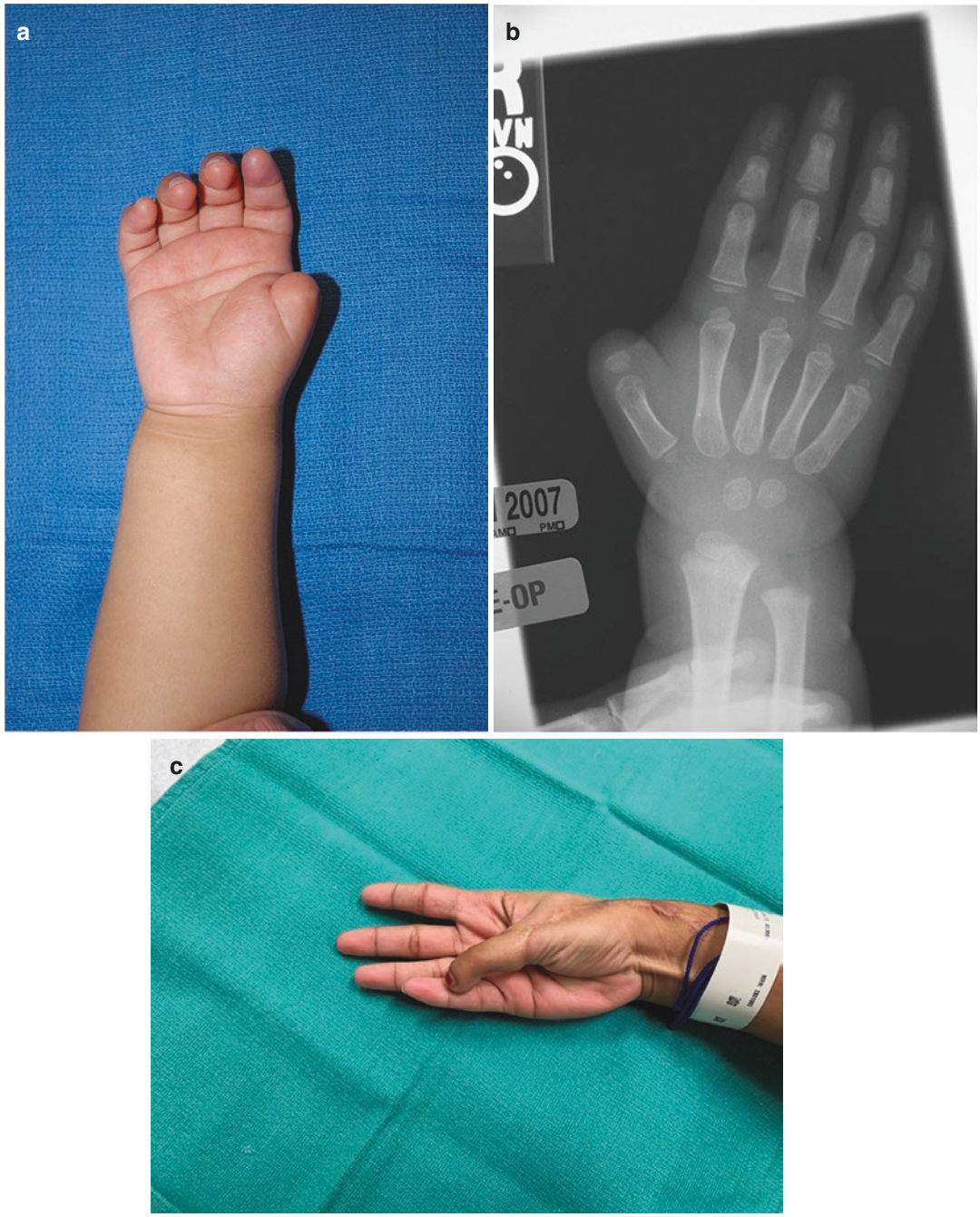

Fig. 12.14 A 3-year-old girl with transverse failure of formation of her right thumb at the level of the base of the proximal phalanx (**a**, **b**). She underwent a left second toe-to-thumb transfer. Thirteen years postoperatively, she is able to oppose to the tips of all four fingers (Kapandji stage 5). (**c**). (Published with kind permission of Neil F. Jones ©2020. All rights reserved)

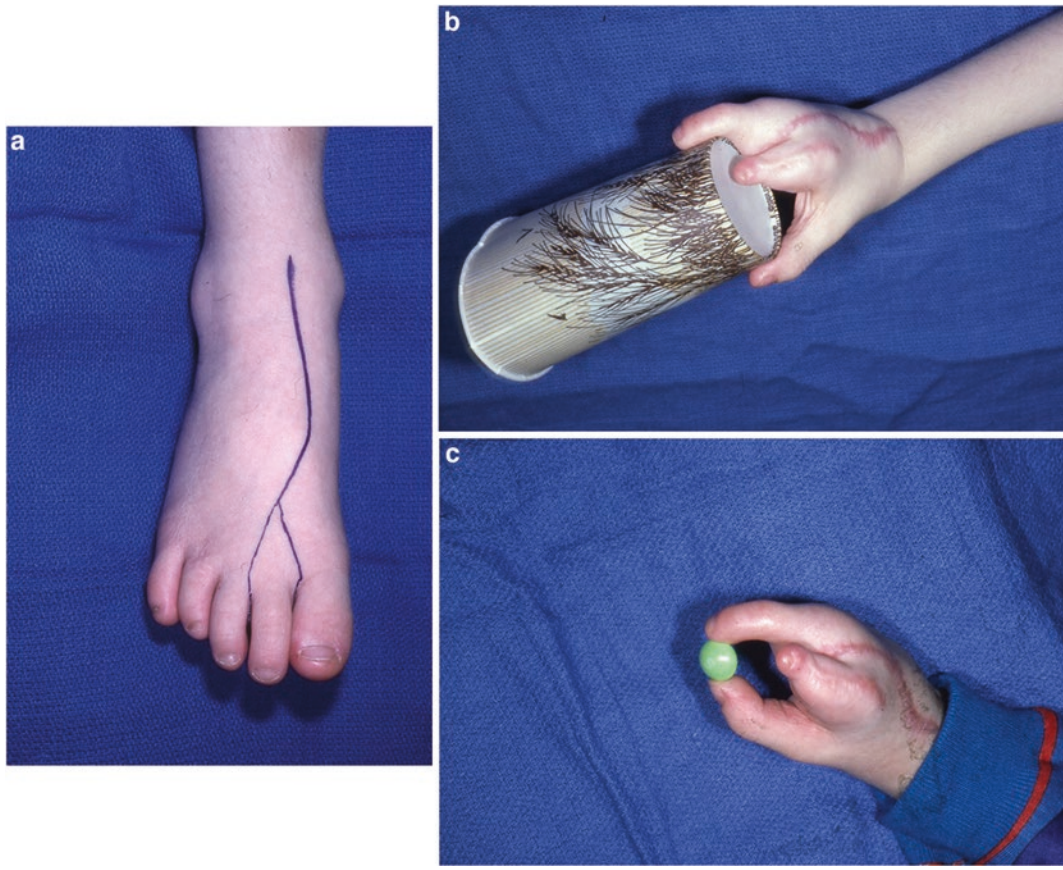

Fig. 12.15 The parents of the 1-year-old boy shown in Fig. 12.11a with monodactylic type III symbrachydactyly of his right hand, who had previously undergone a nonvascularized toe phalangeal bone graft to his right index finger, subsequently agreed to a microsurgical toe transfer (**a**). One year postoperatively, he had excellent grasp and pinch between the thumb and the second toe transfer into the middle finger position (**b**, **c**). The index finger reconstructed with the nonvascularized toe phalangeal bone graft was then completely excluded from functional activities. (Published with kind permission of Neil F. Jones ©2014. All rights reserved)

Timing of Surgery

The optimal age for toe transfers is debatable. Generally, the earlier a transfer can be performed, the faster that the child will adapt to the new digit. The true limiting factor in toe transfers is the size of the donor and recipient vessels, which must be of adequate diameter to allow for anastomoses. The senior author typically performs his transfers at approximately 24 months of age. Both Gilbert [57, 58] and Lister [71] have performed toe transfers as early as 6–12 months of age. In general, toe transfers for congenital constriction ring syndrome can be performed at an earlier age, because the proximal recipient structures in the hand are more likely to be normal. Children with unilateral congenital hand differences should be reconstructed at an earlier age before use of the contralateral hand dominates.

Preoperative Evaluation

In order to evaluate the skeletal foundation for a toe transfer, plain radiographs are obtained of the hands and feet. Some hand surgeons routinely obtain preoperative angiograms of the donor foot and the recipient hand, but the senior author does not obtain preoperative angiograms. Immediately preoperatively, a pencil 8-mHz ultrasound Doppler probe is used to map the dorsal and plantar arterial anatomy in the foot.

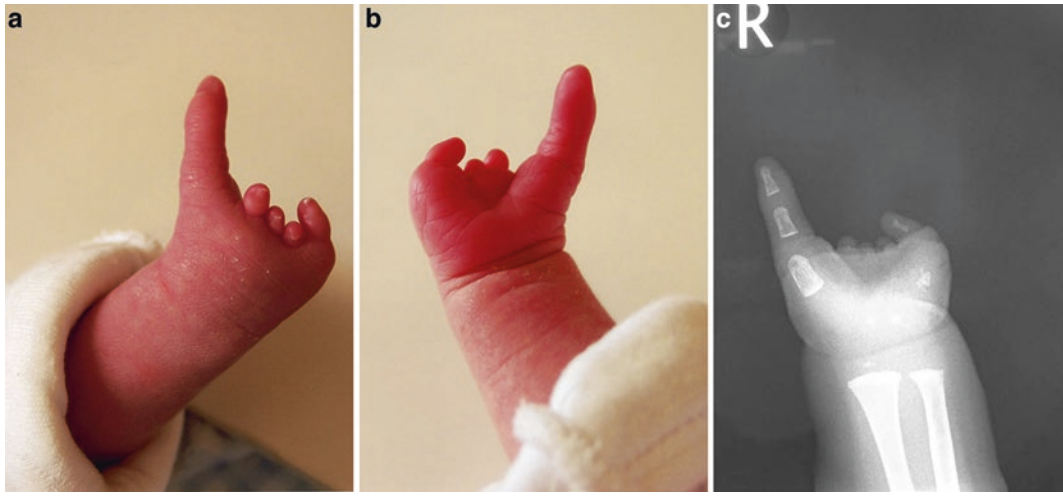

Fig. 12.16 (**a**–**c**) Dorsal and palmar photographs and radiograph of a 6-month-old girl with oligodactylic type III symbrachydactyly of her right hand. This would be classified as a U4R1 hand. (Published with kind permission of Neil F. Jones ©2014. All rights reserved)

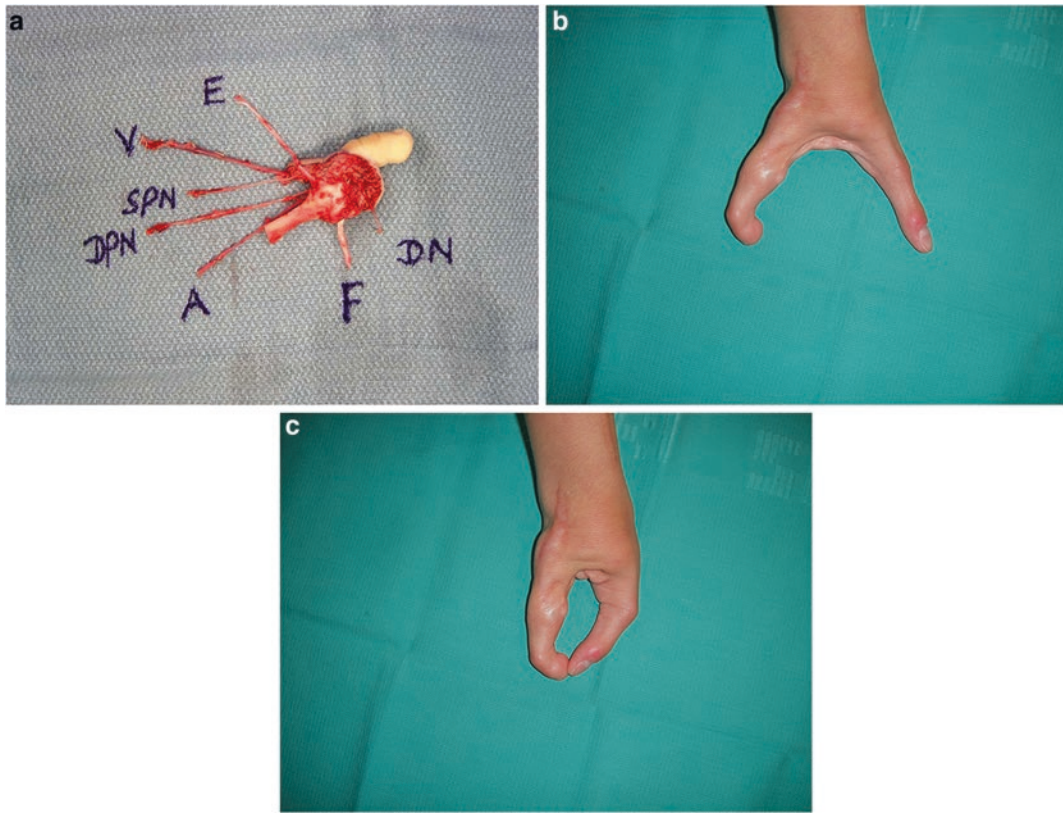

Fig. 12.17 At age 2, she underwent a second toe-to-small finger transfer (**a**). Seven years postoperatively, she has excellent grasp of large objects and precise pinch between the thumb and toe transfer (**b**, **c**). (Published with kind permission of Neil F. Jones ©2014. All rights reserved)

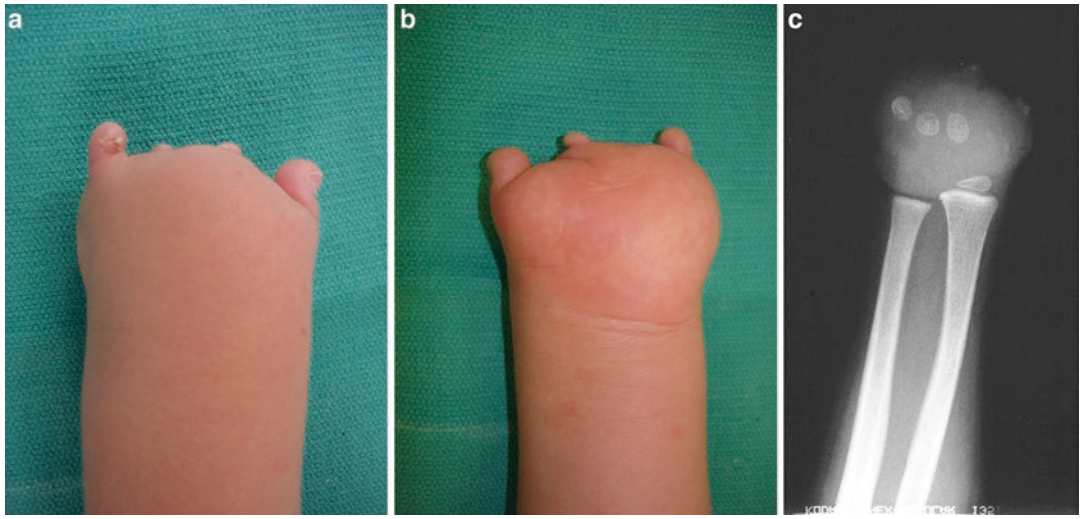

Fig. 12.18 (**a**–**c**) Dorsal and palmar photographs and radiograph of a 2-year-old boy with adactylic type IV symbrachydactyly affecting all five digits of his left hand. The digits are missing from the level of the metacarpal bases and would be classified as an R5 hand. (Published with kind permission of Neil F. Jones ©2014. All rights reserved)

Surgical Technique

Ideally, toe transfer surgery is carried out using two surgical teams who work simultaneously on the hand and foot, both under tourniquet control. Dissection of the hand should precede dissection of the foot to ensure that adequate recipient structures are present in the hand. If vessels in the hand are insufficient for microsurgical anastomoses, vein grafts can be used to reach suitable vessels in the forearm.

Triangular skin flaps on the dorsal and plantar surface of the foot are used to harvest the toe. On the dorsum of the foot, the venous drainage of the great toe or second toe is traced proximally to a large branch of the greater saphenous vein at the level of the ankle. The arterial supply of the great toe or second toe can be dissected either in a proximal-to-distal or a distal-to-proximal direction. The first dorsal metatarsal artery (FDMA) can be dissected proximal to distal from its origin from the dorsalis pedis artery. An alternative approach is to identify the FDMA in the dorsum of the great toe-second toe webspace and trace it proximally. The arterial anatomy of the toes is highly variable [72]. In an ideal situation, the FDMA lies superficially, but it can also lie within or deep to the interosseous muscle. The first plantar metatarsal artery (FPMA) can be used if the FDMA is absent. The FDMA is present in 66% of patients, and the FPMA is present in 34% of cases [72].

The extensor tendons to the toe to be transferred are identified and dissected in a distal-to-proximal direction. The digital nerves are then identified in the subcutaneous fat on the plantar aspect of the webspace. Because they are shorter than the digital nerves in the hand, intraneural dissection of the common digital nerve must be carried out to gain length. In some cases, a branch of the deep peroneal nerve can be identified and included in the harvest of the toe. Division of the transverse intermetacarpal ligament allows for further dissection of the flexor aspect of the toe. The flexor digitorum longus and brevis tendons are isolated proximal to the tendon sheath. It is important to determine the length of flexor tendon needed prior to transection of the tendons. An osteotomy is then performed usually at the metaphyseal flare for a second toe harvest.

Once dissection of the foot has been completed, the tourniquet is released allowing reperfusion of the toe. After satisfactory perfusion of the toe on a single artery and vein is confirmed, the artery and vein are then ligated. The foot

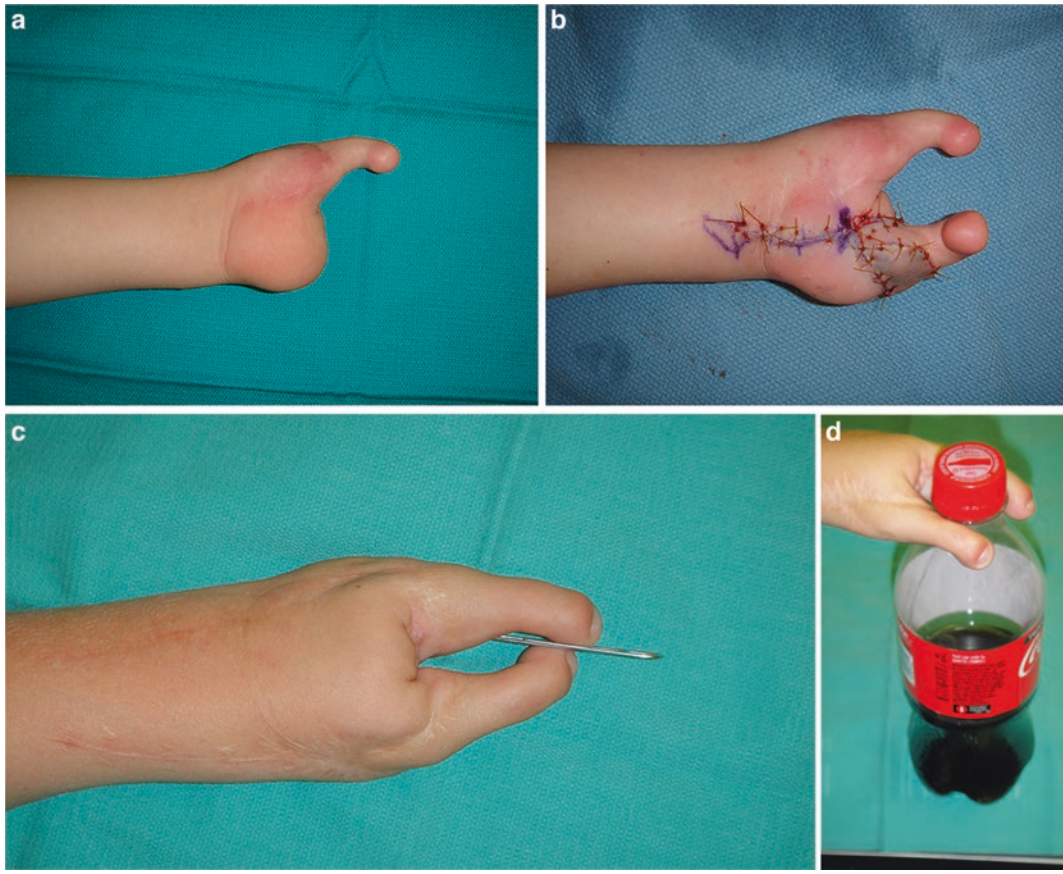

Fig. 12.19 The child underwent staged second toe transfers, firstly into the thumb position (**a**) and 6 months later into the small finger position (**b**). Six years postoperatively, the child demonstrates excellent ability to pick up small objects by side-to-side pinch between the two second toe transfers (**c**) and strong grasp to lift up a heavy bottle (**d**). (Published with kind permission of Neil F. Jones ©2014. All rights reserved)

wound is closed primarily after repair of the intermetatarsal ligament. Skin grafting may be required to close the donor site if a great toe is harvested. A posterior splint is applied to the foot and leg.

The toe is then transferred to the previously dissected incision in the hand. Resection of the metatarsal is performed to achieve the correct length of the toe in either the thumb or finger position. If the toe is being used to reconstruct the thumb, the toe is rotated 120°. Bony fixation can be performed with 90–90 interosseous wires, K wires, or plates and screws, but special care should be taken to avoid injury to the epiphyseal plate. The flexor and extensor tendons are repaired. Tendon grafts may be required, especially in reconstruction of aplastic hands. The digital nerves of the toe transfer are coapted to appropriate digital nerves in the hand. Nerve grafts or even nerve transfers may be necessary. A branch of the deep peroneal nerve may be coapted to a branch of the superficial radial nerve. Finally, the arterial and venous anastomoses are performed under the operating microscope using standard microsurgical techniques using 10-0 microsutures. Vascular anastomoses are typically end-to-end, but end-to-side anastomoses can also be used.

The hand is then dressed in a large bulky dressing with a portion of the transferred toe left visible for clinical observation. Vascular checks including color and capillary refill are performed every hour by the nursing staff. A variety of objective monitoring techniques of digital perfu-

sion including surface temperature, tissue pH, transcutaneous PO2, and laser Doppler flowmetry have been proposed, but the senior author uses a continuous oxygen saturation probe (pediatric pulse oximetry). Continuous differential pulse oximetry seems to be superior to laser Doppler flowmetry and surface temperature measurement [73] and allows almost immediate detection of thrombosis of either the arterial or venous anastomoses. Intravenous dextran-40 is used for 5 days postoperatively, and the child is maintained on aspirin for 1 month postoperatively. The child is typically discharged on postoperative day 7.

Outcomes

Jones and Kaplan [74] compared 15 children who underwent microsurgical toe-to-hand transfers, 12 of whom had congenital hand differences, to age-matched children using the Pediatric Outcomes Data Collection Instrument (PODCI). The PODCI is an 86-question survey that evaluates six dimensions including upper extremity function, basic mobility and transfers, sports and physical function, pain and comfort, happiness, and global function. In this study, survey results from 15 parents, ten adolescents, and normative data for age-matched children were compared. There was no statistically significant difference between the toe transfer patients and the normal pediatric population in 13 of the 18 groups. The adolescents' scores were significantly lower in upper extremity function and transfer/mobility, but adolescents self-reported higher scores than their parents in sports/physical function and happiness. The toe transfer adolescents also reported a significantly higher level of happiness than the general pediatric population.

Summary

It is difficult to prove definitively the superiority of microsurgical toe-to-hand transfers over other more conventional reconstructive techniques, but it is impossible to deny the satisfaction of seeing a child make normal use of a hand reconstructed with toe-to-hand transfers.

References

1. Flatt AE. The care of congenital hand anomalies. St. Louis: Mosby; 1977.
2. Swanson AB. A classification for congenital limb malformations. J Hand Surg Am. 1976;1(1):8–22.
3. Kay HW, Day HJ, Henkel HL, Kruger LM, Lamb DW, Marquardt E, et al. The proposed international terminology for the classification of congenital limb deficiencies. Dev Med Child Neurol Suppl. 1975;34:1–12.
4. Manske PR, Oberg KC. Classification and developmental biology of congenital anomalies of the hand and upper extremity. J Bone Joint Surg Am. 2009;91(Suppl 4):3–18.
5. Oberg KC, Feenstra JM, Manske PR, Tonkin MA. Developmental biology and classification of congenital anomalies of the hand and upper extremity. J Hand Surg Am. 2010;35(12):2066–76.
6. Tonkin MA, Tolerton SK, Quick TJ, Harvey I, Lawson RD, Smith NC, et al. Classification of congenital anomalies of the hand and upper limb: development and assessment of a new system. J Hand Surg Am. 2013;38(9):1845–53.
7. Goldfarb CA, Wall LB, Bohn DC, Moen P, Van Heest AE. Epidemiology of congenital upper limb anomalies in a Midwest United States population: an assessment using the Oberg, Manske, and Tonkin classification. J Hand Surg Am. 2015;40(1):127–32.
8. Pol R. 'Brachydaktylie'—'Klinodaktylie'—Hyperphalangie und ihre Grundlagen: Form und Entstehung der meist unter dem Bild der Brachydaktylie auftretenden Variet¨aten, Anomalien und Mißbildungen der Hand und des Fußes. Virchows Arch Pathol Anat. 1921;229:388–530.
9. Blauth W, Gekeler J. Morphology and classification of symbrachydactylia. Handchirurgie. 1971;3(4):123–8.
10. Sugiura Y, Kaneko M, Kataoka O, Nagira F, Ueke T, Tajima T, et al. Bone changes of unknown etiology affecting phalanges of fingers in children: report of eight cases. Pediatr Radiol. 1976;4(4):243–50.
11. Ogino T, Minami A, Kato H. Clinical features and roentgenograms of symbrachydactyly. J Hand Surg Br. 1989;14:303–6.
12. Yamauchi Y. Symbrachydactyly. In: Buck-Gramcko D, editor. Congenital malformations of the hand and forearm. London: Churchill Livingstone; 1998. p. 149–57.
13. Jones NF, Kaplan J. A new documentation system for congenital absent digits. Hand. 2012;7(4):391–9.
14. Buck-Gramcko D. Symbrachydactyly: a clinical entity. Tech Hand Up Extrem Surg. 1999;3:242–58.
15. Buck-Gramcko D. Cleft hands: classification and treatment. Hand Clin. 1985;1:467–73.
16. Manske PR. Symbrachydactyly instead of atypical cleft hand. Plast Reconstr Surg. 1993;91:196.
17. Kay SP, McCombe DB, Kozin SH. Deformities of the hand and fingers. In: Wolfe SW, Pederson WC,

Hotchkiss RN, Kozin SH, editors. Green's operative hand surgery. 6th ed. Philadelphia: Churchill Livingstone; 2010. p. 1303–69.
18. Swanson AB, Swanson GD, Tada K. A classification for congenital limb malformation. J Hand Surg Am. 1983;8(5 Pt 2):693–702.
19. Patterson RW, Seitz WH Jr. Nonvascularized toe phalangeal transfer and distraction lengthening for symbrachydactyly. J Hand Surg Am. 2010;35(4):652–8.
20. Kallemeier PM, Manske PR, Davis B, Goldfarb CA. An assessment of the relationship between congenital transverse deficiency of the forearm and symbrachydactyly. J Hand Surg Am. 2007;32(9):1408–12.
21. Miura T, Suzuki M. Clinical differences between typical and atypical cleft hand. J Hand Surg Br. 1984;9(3):311–5.
22. Koehler DM, Goldfarb CA, Snyder-Warwick A, Roberts S, Wall LB. Characterization of hand anomalies associated with Möbius syndrome. J Hand Surg Am. 2019;44(7):548–55.
23. Ogino T. Clinical features and teratogenic mechanisms of congenital absence of digits. Dev Growth Differ. 2007;49(6):523–31.
24. Knight JB, Pritsch T, Ezaki M, Oishi SN. Unilateral congenital terminal finger absences: a condition that differs from symbrachydactyly. J Hand Surg Am. 2012;37(1):124–9.
25. Bavinck JN, Weaver DD. Subclavian artery supply disruption sequence: hypothesis of a vascular etiology for Poland, Klippel-Feil, and Möbius anomalies. Am J Med Genet. 1986;23(4):903–18.
26. Kanauchi Y, Takahara M, Harada M, Ogino T. Growth of severely hypoplastic phalanges and metacarpals in symbrachydactyly: an experimental study in mice. J Hand Surg Am. 2008;33(9):1589–96.
27. Wolff H. Diskussion zu Lexer: Gelenktransplantation. Verhandlungender Deutschen Gesellschaft für Chirurgie, 39. Kongress. Ther Ber. 1910:105.
28. Wolff H. Auswechselung von Finger und Zehenknochen: Beitrag zur Autoplastik. Münchener Medizinische Wochenschrift. 1911;58:578.
29. Entin MA. Reconstruction of congenital abnormalities of the upper extremities. J Bone Joint Surg Am. 1959;41-A(4):681–701.
30. Carroll RE, Green DP. Proceedings of the American Society for Surgery of the Hand. J Bone Joint Surg Am. 1975;57-A(5):727.
31. Goldberg NH, Watson HK. Composite toe (phalanx and epiphysis) transfers in the reconstruction of the aphalangic hand. J Hand Surg Am. 1982;7(5):454–9.
32. Buck-Gramcko D, Pereira JA. Proximal toe phalanx transplantation for bony stabilization and lengthening of partially aplastic digits. Ann Chir Main Memb Super. 1990;9(2):107–18.
33. Radocha RF, Netscher D, Kleinert HE. Toe phalangeal grafts in congenital hand anomalies. J Hand Surg Am. 1993;18(5):833–41.
34. Cavallo AV, Smith PJ, Morley S, Morsi AW. Non-vascularized free toe phalanx transfers in congenital hand deformities—the Great Ormond Street experience. J Hand Surg Br. 2003;28(6):520–7.
35. Gohla T, Metz C, Lanz U. Non-vascularized free toe phalanx transplantation in the treatment of symbrachydactyly and constriction ring syndrome. J Hand Surg Br. 2005;30(5):446–51.
36. Kawabata H, Tamura D. Five- and 10-year follow-up of nonvascularized toe phalanx transfers. J Hand Surg Am. 2018;43(5):485.
37. Unglaub F, Lanz U, Hahn P. Outcome analysis, including patient and parental satisfaction, regarding non-vascularized free toe phalanx transfer in congenital hand deformities. Ann Plast Surg. 2006;56(1):87–92.
38. Bourke G, Kay SP. Free phalangeal transfer: donor-site outcome. Br J Plast Surg. 2002;55(4):307–11.
39. Garagnani L, Gibson M, Smith PJ, Smith GD. Long-term donor site morbidity after free nonvascularized toe phalangeal transfer. J Hand Surg Am. 2012;37(4):764–74.
40. Jones NF. Nonvascularized toe phalangeal bone grafts for congenital anomalies of the hand. J Am Soc Surg Hand. 2004;4(1):27–34.
41. Netscher DT, Richards WT. Rational treatment for multiple digit congenital absence: case report of non-vascularized toe phalangeal transfers and distraction lengthening for symbrachydactyly. Ann Plast Surg. 2006;56(2):211–5.
42. Iba K, Wada T, Yamashita T. On-top plasty using a free metacarpal head graft for lengthening of proximal phalanx in symbrachydactyly – a case report. Hand Surg. 2013;18(2):273.
43. Codivilla A. On the means of lengthening, in the lower limbs, the muscles and tissues which are shortened through deformity. J Bone Joint Surg Am. 1905;s2-2:353–69.
44. Matev IB. Thumb reconstruction after amputation at the metacarpophalangeal joint by bone lengthening. J Bone Joint Surg. 1970;52A:957–65.
45. Kessler I, Baruch A, Hecht O. Experience with distraction lengthening of digital rays in congenital anomalies. J Hand Surg Am. 1977;2(5):394–401.
46. Wenner SM. Angulation occurring during the distraction lengthening of digits. Orthop Rev. 1986;15(3):177–9.
47. Seitz WH Jr, Froimson AI. Callotasis lengthening in the upper extremity: indications, techniques, and pitfalls. J Hand Surg Am. 1991;16(5):932–9.
48. Seitz WH Jr, Froimson AI. Digital lengthening using the callotasis technique. Orthopedics. 1995;18(2):129–38.
49. Ogino T, Kato H, Ishii S, Usui M. Digital lengthening in congenital hand deformities. J Hand Surg Br. 1994;19(1):120–9.
50. Pensler JM, Carroll NC, Cheng LF. Distraction osteogenesis in the hand. Plast Reconstr Surg. 1998;102(1):92–5.
51. Hülsbergen-Krüger S, Preisser P, Partecke BD. Ilizarov distraction-lengthening in congenital anomalies of the upper limb. J Hand Surg Br. 1998;23(2):192–5.

52. Dhalla R, Strecker W, Manske PR. A comparison of two techniques for digital distraction lengthening in skeletally immature patients. J Hand Surg Am. 2001;26(4):603–10.
53. Miyawaki T, Masuzawa G, Hirakawa M, Kurihara K. Bone-lengthening for symbrachydactyly of the hand with the technique of callus distraction. J Bone Joint Surg Am. 2002;84-A(6):986–91.
54. Matsuno T, Ishida O, Sunagawa T, Ichikawa M, Ikuta Y, Ochi M. Bone lengthening for congenital differences of the hands and digits in children. J Hand Surg Am. 2004;29(4):712–9.
55. Seitz WH Jr, Shimko P, Patterson RW. Long-term results of callus distraction-lengthening in the hand and upper extremity for traumatic and congenital skeletal deficiencies. J Bone Joint Surg Am. 2010;92(Suppl 2):47–58.
56. O'Brien BM, Black MJ, Morrison WA, MacLeod AM. Microvascular great toe transfer for congenital absence of the thumb. Hand. 1978;10(2):113–24.
57. Gilbert A. Toe transfers for congenital hand defects. J Hand Surg Am. 1982;7(2):118–24.
58. Gilbert A. Reconstruction of congenital hand defects with microvascular toe transfers. Hand Clin. 1985;1(2):351–60.
59. Lister G. Microsurgical transfer of the second toe for congenital deficiency of the thumb. Plast Reconstr Surg. 1988;82(4):658–65.
60. Shvedovchenko IV. Toe-to-hand transfers in children. Ann Plast Surg. 1993;31(3):251–4.
61. Vilkki SK. Advances in microsurgical reconstruction of the congenitally adactylous hand. Clin Orthop Relat Res. 1995;(314):45–58.
62. Kay SP, Wiberg M. Toe to hand transfer in children. Part 1: technical aspects. J Hand Surg Br. 1996;21(6):723–34.
63. Van Holder C, Giele H, Gilbert A. Double second toe transfer in congenital hand anomalies. J Hand Surg Br. 1999;24(4):471–5.
64. Foucher G, Medina J, Navarro R, Nagel D. Toe transfer in congenital hand malformations. J Reconstr Microsurg. 2001;17(1):1–7.
65. Richardson PW, Johnstone BR, Coombs CJ. Toe-to-hand transfer in symbrachydactyly. Hand Surg. 2004;9(1):11–8.
66. Jones NF, Hansen SL, Bates SJ. Toe-to-hand transfers for congenital anomalies of the hand. Hand Clin. 2007;23(1):129–36.
67. Goodell PB, Bauer AS, Oishi S, Arner M, Laurell T, Taylor SL, et al. Functional assessment of children and adolescents with symbrachydactyly: a unilateral hand malformation. J Bone Joint Surg Am. 2017;99(13):1119–28.
68. Jones NF, Kaplan J. Indications for microsurgical reconstruction of congenital hand anomalies by toe-to-hand transfers. Hand. 2013;8:367–74.
69. Wei FC, Chen HC, Chuang CC, Noordhoff MS. Reconstruction of the thumb with a trimmed-toe transfer technique. Plast Reconstr Surg. 1988;82(3):506–15.
70. Chang J, Jones NF. Simultaneous toe-to-hand transfer and lower extremity amputations for severe upper and lower limb defects: the use of spare parts. J Hand Surg Br. 2002;27(3):219–23.
71. Lister G. Reconstruction of the hypoplastic thumb. Clin Orthop Relat Res. 1985;195:52–65.
72. Villen GM, Julve GG. The arterial system of the first intermetatarsal space and its influence in toe-to-hand transfer: a report of 53 long-pedicle transfers. J Hand Surg. 2002;27B:73–7.
73. Jones NF, Gupta R. Postoperative monitoring of pediatric toe-to-hand transfers with differential pulse oximetry. J Hand Surg Am. 2001;26(3):525–9.
74. Kaplan JD, Jones NF. Outcome measures of microsurgical toe transfers for reconstruction of congenital and traumatic hand anomalies. J Pediatr Orthop. 2014;34(3):362–8.

Dorsal–Ventral Deficiency

13

Mohammad M. Al-Qattan

Introduction

The limb bud develops into an upper limb by complex interactions between the ectoderm and mesoderm. There are three axes of limb development: the proximal–distal axis mediates the outgrowth of the limb, the anterior–posterior axis mediates the differentiation of radial and ulnar elements of the forearm/hand, and the dorsal–ventral axis mediates the differentiation of dorsal and ventral structures in the hand only [1]. Differentiation of dorsal–ventral structures in the arm and forearm also occurs, but the mediators for such a differentiation are yet to be identified. This chapter deals with dorsal–ventral abnormalities within the hand only.

Embryology of the Dorsal–Ventral Axis of Development

Figure 13.1 shows a cross section of the limb bud. The ventral ectoderm expresses the transcription factor "ENGRAILED 1" (EN-1). EN-1 is essential for the normal development of ventral structures in the hand such as the thick hairless palmar skin, the pulp of the fingers, the palmar creases, and the flexor tendons. EN-1 will also restrict the "wingless" protein WNT7A to the dorsal ectoderm. Ectodermal WNT7A will induce the expression of a "LIM" transcription factor called LMX1B in the dorsal mesoderm. The normal expression of WNT7A and LMX1B in the dorsal ectoderm and mesoderm, respectively, leads to the normal development of dorsal structures of the hand such as the nails, the thin hairy dorsal skin, and the extensor tendons. WNT7A also acts as a "maintainer" of sonic hedgehog (SHH) activity within the zone of polarizing activity in the posterior mesoderm [2]. SHH is the key modulator of the anterior–posterior axis including the development of the ulnar ray and the induction of fibroblast growth factor 4 (FGF4) in the nearby posterior part of the apical ectodermal ridge (AER). FGF4 helps the ectodermal FGF8 to maintain the outgrowth of the limb along the proximal–distal axis; and FGF4 also helps to maintain SHH activity. This reciprocal relationship between SHH and FGF4 is known as the SHH-FGF4 loop [3, 4]. In other words, the two key proteins of the dorsal–ventral axis (EN-1 and WNT7A) interact with each other as well as with the mesoderm (via LMX1B induction). The dorsal–ventral axis also interacts with the anterior–posterior axis (via SHH maintenance) and the proximal–distal axis (via the SHH-FGF4 loop). EN-1 also contributes to the induction of the AER.

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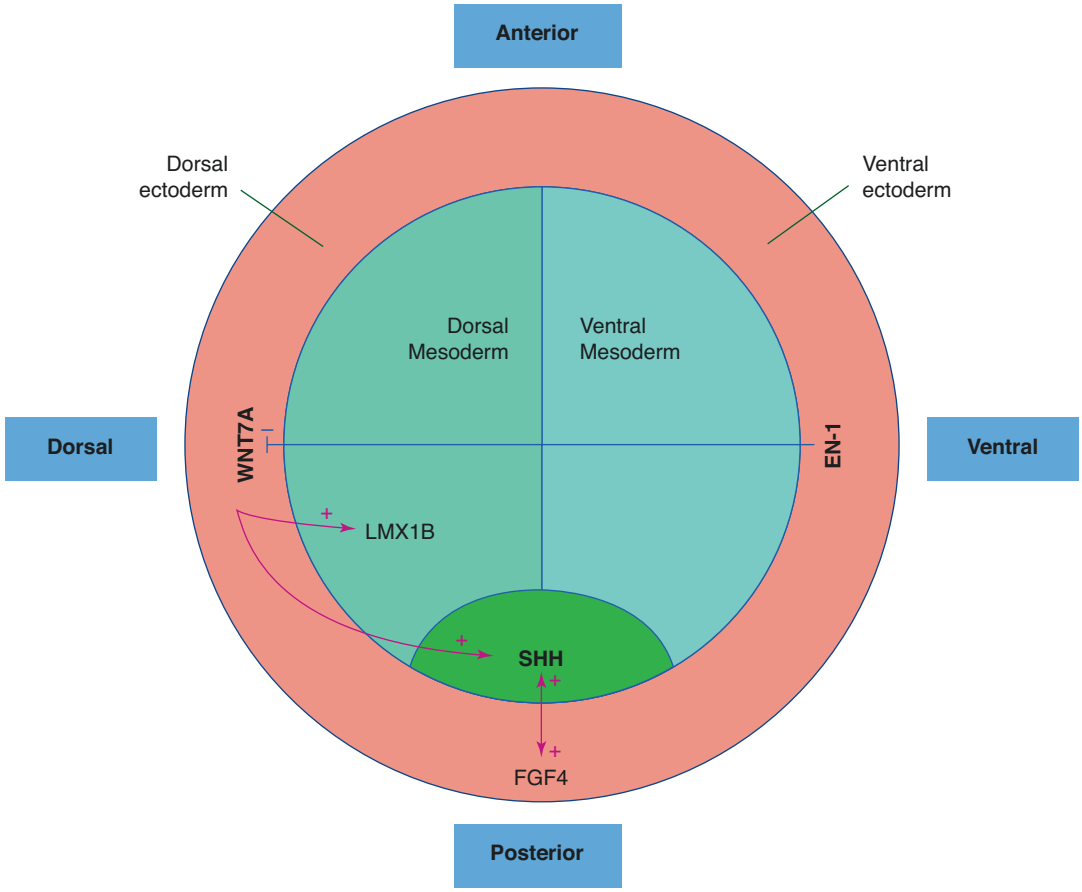

Fig. 13.1 A cross section of limb a bud showing the interactions of the two key players of the dorsal–ventral axis: EN-1 (ENGRAILED-1) and WNT7A

The ENGRAILED-1 Pathway and Dorsal Dimelia

Al-Qattan [2] defined the ENGRAILED-1 pathway (Fig. 13.2). In this pathway, EN-1 is a "transcription factor." In other words, it is expressed following the action of a "ligand" on a "receptor." The "ligands" are bone morphogenetic proteins 4 and 7 (BMP4, 7) that act on the receptor BMPR1A. This results in the expression of EN-1 in the ventral ectoderm. EN-1 will have three main functions: induction of the AER, development of ventral structures of the hand, and restriction of WNT7A to the dorsal ectoderm. Disruption of this pathway will result in the lack of EN-1 functional expression in the ventral ectoderm. Ventral structures will not develop; and the unrestricted WNT7A will be expressed in the dorsal as well as the ventral ectoderm. Ectopic ventral WNT7A will induce the ectopic expression of LMX1B in the ventral mesoderm. The end result is "dorsal dimelia," which is a hand with dorsal structures on the ventral aspect.

Dorsal Dimelia in Experimental Animals

Experimental dorsal dimelia is induced by disruption of the EN-1 pathway. It is important to note that these animals will show dorsal dimelia of all digits in the fore- and hindfeet. In other words, each digit will show a double nail: one

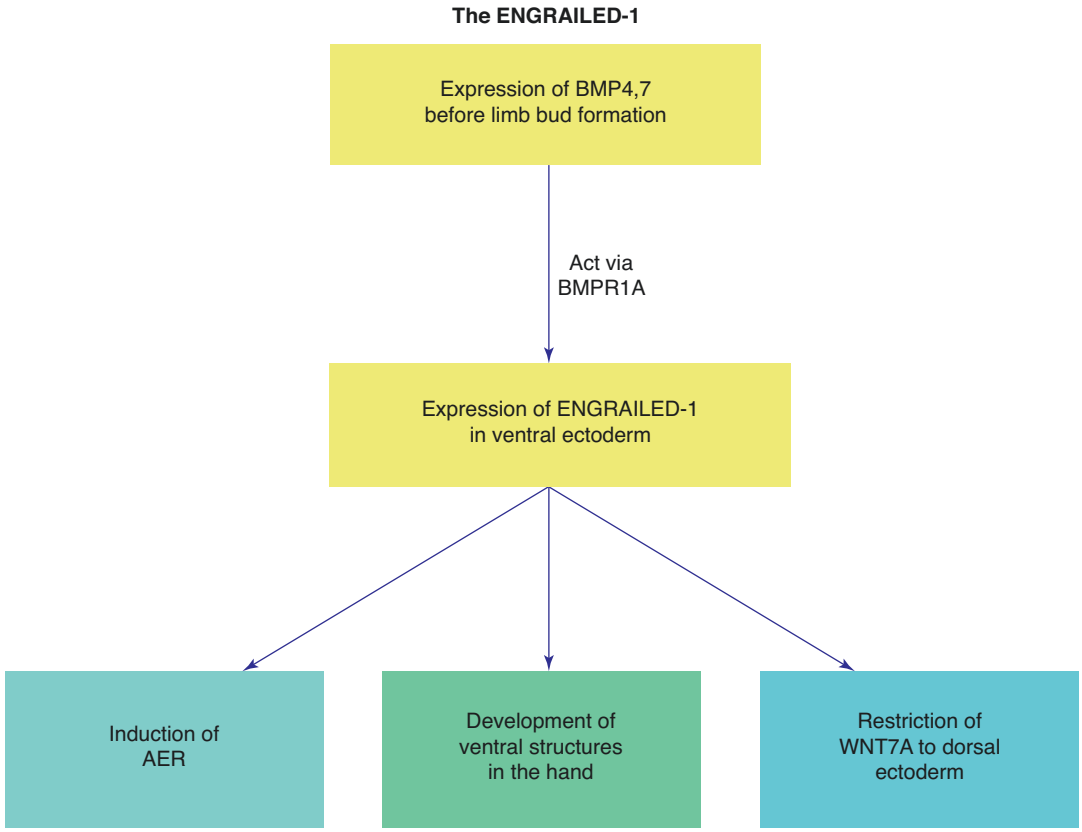

Fig. 13.2 The EN-1 pathway

normal dorsal nail and another ectopic ventral nail. Experimental dorsal dimelia was induced in *Bmpr1a* conditional knockout animals [5], null mutations of *En-1* [6], mis-expression of *Wnt7a* in the ventral ectoderm [7], and mis-expression of *Lmx1b* in the ventral mesoderm [8].

Dorsal Dimelia in Humans

Dorsal dimelia in humans may be classified into two main groups: distal dorsal dimelia and proximal dorsal dimelia [9].

Proximal Dorsal Dimelia in Humans

Al-Qattan et al. [10] described one Egyptian family with isolated dorsalization of the skin of the proximal palm and the instep of the sole of the foot. Inheritance was autosomal dominant. Fingers and toes were completely normal. Hand function and gait were also normal. The proximal palm had a subcutaneous hamartoma with hyperpigmented hairy skin. Linkage analysis/exome sequencing showed an R584w variant in the *GLE1* gene. *GLE1* is involved in mRNA export; and RNA in situ hybridization showed a high *Gle-1* expression in mouse embryo ventral cells and somites.

Distal Dorsal Dimelia in Humans

Distal dorsal dimelia is characterized by dorsalization of the distal palm and digits [11]. When fully expressed, the digit will have an ectopic palmar nail (the palmar and dorsal nails meet at the tip) (Fig. 13.3), the palmar skin of the digit and distal palm will show thin hyperpigmented skin,

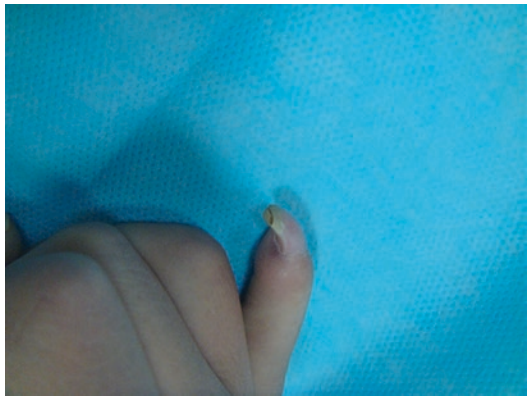

Fig. 13.3 Dorsal dimelia. Note the dorsal and ventral nails meeting at the tip of the little finger

digital flexion is lacking, and the X-ray will show a tapering distal phalanx. The fully expressed phenotype is also known in the literature as "congenital palmar nail syndrome" [12, 13]. This fully expressed phenotype has amazing resemblance to the conjoined nail of Siamese "tripus" twins [14]. The twins have three lower limbs (hence the term tripus). Each twin has one normal lower limb on one side of the body. On the other side, the two adjacent lower limbs are fused into one. The conjoined feet will have eight separate toes, whereas the two big toes are fused into one digit. This digit will have all the features of "palmar nail syndrome."

Al-Qattan et al. [15] stressed that the clinical picture of distal dorsal dimelia in humans may not always be fully expressed. Hence, some cases may have isolated palmar nail, while others may have isolated dorsalization of the palmar skin.

Al-Qattan and Kfoury [11] reviewed all cases of distal dorsal dimelia in humans and categorized them into three groups: syndromic, familial, and sporadic. Bilateral little finger dimelia has been described in syndromic patients with partial deletion of the long arm of chromosome 6 [16] and Patau syndrome (trisomy 13) [17]. One case with *DLX5* mutation and split-hand–split-foot malformation (also known as lobster-claw deformity) had dorsal dimelia of all digits [18]. The latter is the only human case with involvement of all digits. In all other human cases, dorsal dimelia involves either the ulnar or radial digits. Familial cases may have a family history of dorsal dimelia [19, 20] or ulnar ray deficiency [12, 21]. This is interesting because it links dorsal dimelia to SHH activity. In fact, several sporadic cases occurred in patients with ulnar ray deficiency [22, 23] or ulnar-sided cleft hand [9, 15, 24]. As expected, all these patients with ulnar defects showed dorsal dimelia in the ulnar digits.

However, several sporadic cases involving the ulnar digits occurred in patients with negative family history and no other concurrent anomalies [25–28]. Al-Qattan et al. [15] screened several sporadic cases with dorsal dimelia involving the ulnar digits for candidate genes such as loss-of-function mutations of BMP4, *BMP7, BMPR1A,* and *EN-1*, as well as gain-of-function mutations of *WNT7A* and *LMX1B*. However, the genetic analysis did not show any mutations. It was concluded that sporadic dorsal dimelia is probably a stochastic developmental error that is commonly seen with other concurrent hand malformations. In support of the latter statement, the author reported three cases of dorsal dimelia involving the radial digits; and in all cases there was radial-sided malformations such as thumb polydactyly [11] or radial ray deficiency [29, 30].

Management of Dorsal Dimelia

Proximal dorsal dimelia requires no treatment. In contrast, patients with distal dorsal dimelia may have cosmetic (the palmar nail) and functional (the lack of flexion) concerns. Options of management include conservative treatment (observation only) or surgery in the form of excision of the palmar nail along with pulp reconstruction or amputation of the distal phalanx [28]. Affected digits are usually held in extension with no active or passive flexion because of symphalangism. Osteotomy and fixation of the proximal interphalangeal joint in a more functional position is an option, but no such procedure has been reported in the literature in patients with dorsal dimelia.

Dorsal dimelia of the index finger may occur in patients with absent thumb [29]. This poses a problem when there is a need to pollicize the

affected index finger. Anatomically, the affected finger has cartilaginous symphalangism of the interphalangeal joints. There is also a mirror-image flat extensor tendon on the palmar and dorsal aspects of the finger with no intrinsic muscle attachments. More important, there are two neurovascular bundles: one dorsal and one palmar. Al-Qattan and Kfoury reported these anatomical findings in a patient who had amputation of a duplicated digit with dorsal dimelia [11]; and these findings have obvious implications in the pollicization procedure.

The WNT7A Pathway and Ventral Dimelia

Figure 13.4 shows the WNT7A pathway. WNT7A (which is normally expressed in the dorsal ectoderm) acts at the cellular level by stimulation of specific receptors and the activation of two different pathways [2]: the calcium-mediated pathway and the beta-catenin (canonical) pathway. The former pathway leads to the expression of LMX1B in the dorsal mesoderm that will result in the normal development of dorsal structures in

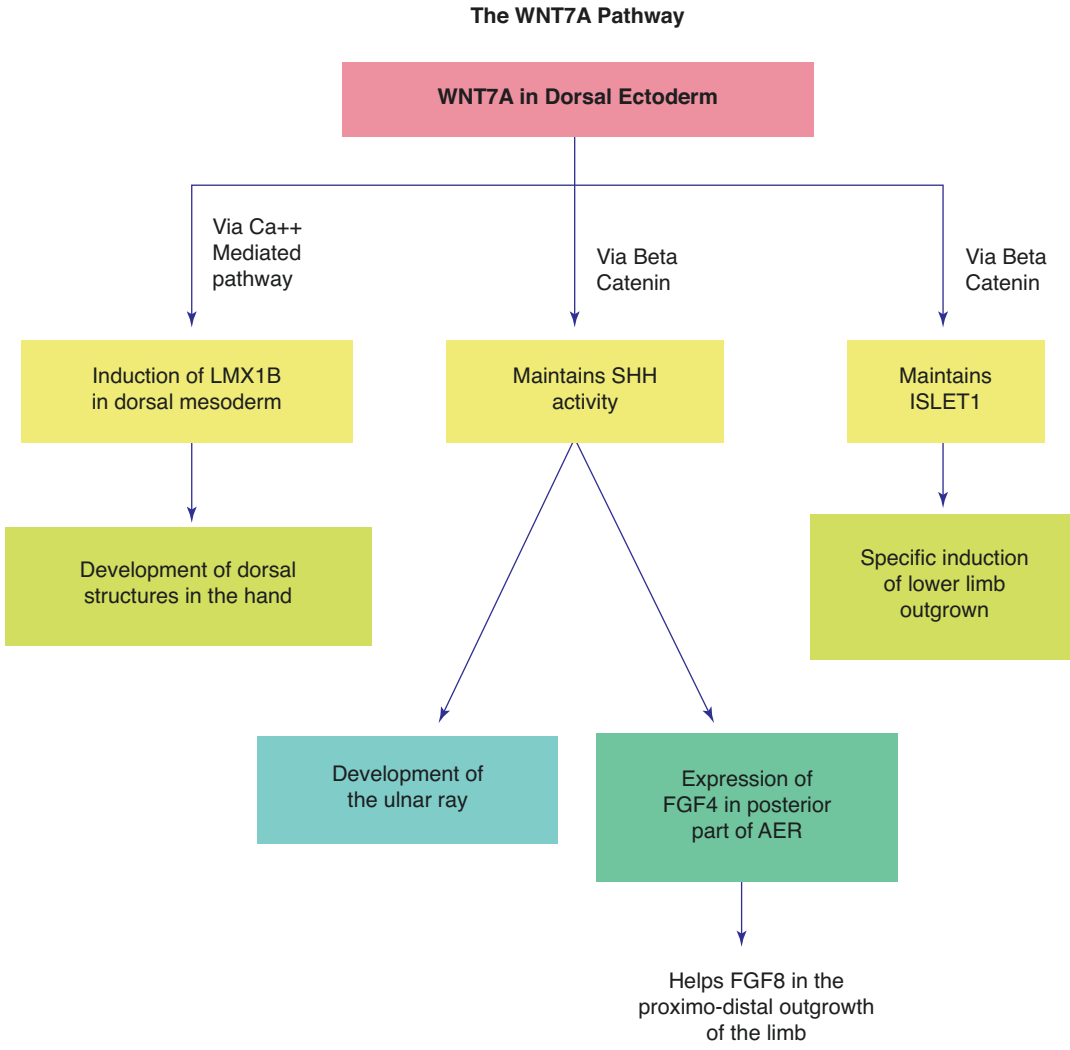

Fig. 13.4 The WNT7A pathway

the hand. The latter pathway is responsible for maintaining SHH activity. As mentioned before, SHH is responsible for the development of the ulnar ray and the induction of FGF4 in the posterior part of the AER. The beta-catenin pathway also maintains the expression of another protein called ISLET 1. ISLET 1 is a major contributor to the initiation/outgrowth of the vertebrate hind limb and pelvis [31].

Looking at the WNT7A pathway, one can speculate the phenotypes of syndromes associated with loss-of-function mutations of *WNT7A*: (1) the loss of LMX1B will result in ventralization of the dorsum of the hand; (2) the loss of SHH activity will result in a variable degree of ulnar ray deficiency as well as short upper limbs; and (3) the loss of ISLET1 maintenance will result in truncated lower limbs and pelvic dysplasia. The end result is a triad of ventral dimelia, ulnar ray deficiency, and truncated lower limbs.

Ventral Dimelia in Experimental Animals

Parr and McMahon [32] studied the effects of loss of function of *Wnt7a* in mice. The knockout mouse models showed ventral dimelia and ulnar ray deficiency but without truncation of the hind limbs. This may indicate that Wnt7A (beta-catenin)–ISLET 1 interactions are more functional in humans than mice.

Ventral Dimelia in Humans

Al-Qattan [9] classified ventral dimelia into three groups according to the severity of the phenotype. The classification was supported by the genetic basis of each group. The mildest phenotype is the nail–patella syndrome that is caused by *LMX1B* mutations. Features of nail–patella syndrome include hypoplastic/aplastic nails, absent patella, and renal defects. The second group has partial loss-of-function mutations of *WNT7A* leading the triad of ventral dimelia, mild ulnar ray deficiency, and truncated lower limbs. In the genetics literature, this is known as

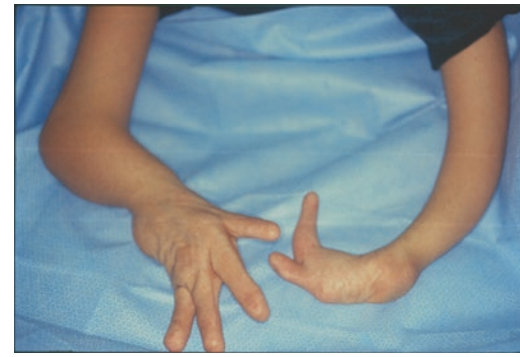

Fig. 13.5 Ventral dimelia. Note the absent nails and the variable degrees of ulnar ray deficiency. The lower limbs are truncated at the knees

Fuhrmann syndrome. Two *WNT7A* mutations are known to be associated with the Fuhrmann phenotype: the R222W [33] and the A109T [34] mutations. The third group has complete loss of function of *WNT7A*; and as expected, this group has the most severe phenotype: severe ventral dimelia, severe ulnar ray deficiency, and frequently absent lower limbs. In the genetics literature, this severe phenotype is known as Al-Awadi syndrome. Three *WNT7A* mutations are known to be associated with Al-Awadi syndrome: the E72K [35], the R292C [34], and the G204S [36, 37] mutations (Fig. 13.5).

Management of Ventral Dimelia

The hand function in nail–patella syndrome is excellent and requires no specific treatment. In Fuhrmann syndrome, the ulnar ray deficiency is mild and hence poses no functional problems. The main problem is the lack of interphalangeal joint flexion. However, patients manage very well in daily activities. In Al-Awadi syndrome, the ulnar ray deficiency is severe and should be treated accordingly with special attention to thumb/first web space reconstruction. These patients also frequently have radiohumeral synostosis and may have hand-in-flank deformity and hence osteotomies are indicated [38, 39]. The severe lower limb deficits in both Fuhrmann and Al-Awadi syndromes make rehabilitation of the limb/limbs an essential part of the management.

Update on Dorsal Dimelia

I have previously classified human cases of dorsal dimelia into syndromic, familial, and sporadic types [11]. Dorsal dimelia has been considered as a rare defect, since only a single case of chromosome 6 deletion and another case of trisomy 13 were associated with bilateral little finger dorsal dimelia [16, 17]. More recently, we have stressed on the fact that dorsal dimelia is not as rare as previously thought [40]. Ulnar–mammary syndrome (OMIM 181450) is caused by heterozygous mutations in *TBX3* and is characterized by mammary gland defects and ulnar-sided upper limb defects. I have reviewed the literature [40] and found that these ulnar-sided upper limb defects may present as ulnar ray deficiency in about one third of patients, ulnar polydactyly in another one third of patients, and as dorsal dimelia of the little finger in the remaining one third of patients. More interestingly, we have described a Saudi girl with ulnar–mammary syndrome and a novel de novo frameshift variant of the *TBX3* gene (Pro 641 Argfs* 229) with isolated bilateral little finger dimelia and without mammary defects or other systemic anomalies [40]. We named this the *forme fruste* phenotype of ulnar–mammary syndrome [40]. In our report [40], we also brought the attention that dorsal dimelia of the little finger is also a constant feature of the distal 4q deletion syndrome [41]. Patients show the dorsal dimelia as well as minor heart defects. It is interesting to note that the area of deletion maps to 4q33 and it encompasses the *HAND2* gene. This is interesting because HAND2–TBX3 interactions are known to exist [42]. From the clinical point of view, patients with dorsal dimelia of the little finger should be screened for both *TBX3* mutations and *HAND2* deletions.

Update of Ventral Dimelia

The Saudi families that we reported with the novel homozygous missense mutation Gly204 Ser in the *WNT7A* gene included patients with tetra-amelia or absence of ulna/fibula along with severe limb deficiency [37]. This is now given a specific OMIM number (27682) in the genetics literature. In contrast to tetra-amelia or severe truncation of the lower limbs, Santos syndrome (OMIM # 613005) represents the mildest form of WNT7A deficiency [43]. It is characterized by nail aplasia/hypoplasia of the hands with no lower limb truncation. Instead, patients show fibular hypoplasia/agenesis, clubfeet, and oligodactyly. Recently, the novel variant in *WNT7A* (Gly312 Ser) in the homozygous state has been identified as the cause of Santos syndrome [44]. Hand surgeons interested in the pathogenesis of the clinical features of syndromes related to *WNT7A* gene mutations may refer to my review articles on the topic [45, 46]. The articles also explain the variability in the severity of the phenotypic expression. The lesson to be learned is that any patient with multi-digit nail hypoplasia/aplasia should be screened for *WNT7A* mutations even in the absence of other classic features of known *WNT7A*-related syndromes.

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References

1. Al-Qattan MM, Yang Y, Kozin SH. Embryology of the upper limb. J Hand Surg Am. 2009;34:1340–50.
2. Al-Qattan MM. WNT pathways and upper limb anomalies. J Hand Surg Eur. 2011;36:9–22.
3. Laufer E, Nelson CE, Johnson RL, Morgan BA, Tabin C. Sonic hedgehog and Fgf-4 act through a signaling cascade and feedback to integrate growth and patterning of the development of limb bud. Cell. 1994;79:993–1003.
4. Niswander L, Jeffrey S, Martin GR, Tickle C. A positive feedback loop coordinates growth and patterning in the vertebrate limb. Nature. 1994;37:609–12.
5. Ahn K, Mishina Y, Hanks MC, Behringer RR, Crenshaw EB. BMPR-1A signaling is required for the formation of the apical ectodermal ridge dorsal-ventral patterning of the limb. Development. 2001;128:4449–61.
6. Loomis CA, Harris E, Michand J, Wurst W, Hanks M, Jayver A. The mouse engrailed-1 gene and ventral limb patterning. Nature. 1996;382:360–3.
7. Riddle R, Ensini M, Nelson C, Tsuchida T, Jessel TM, Tabin C. Induction of the LIM homeobox gene Lmx1

by wnt7a establishes dorsal ventral pattern in the vertebrate limb. Cell. 1995;83:631–40.
8. Vogel A, Rodriguez C, Warnken W, Izpisna-Belmonte JC. Dorsal cell fate specified by chick Lmx1 during vertebrate limb development. Nature. 1995;387:716–20.
9. Al-Qattan MM. Classification of dorsal and ventral dimelia in humans. J Hand Surg Eur. 2013;38(9):928–33. https://doi.org/10.1177/1753193413484671. [Epub ahead of print]
10. Al-Qattan MM, Shamseldin HE, Al-Kuraya FS. Familial dorsalization of the skin of the proximal palm and the instep of the sole of the foot. Gene. 2012;500:216–9.
11. Al-Qattan MM, Kfoury H. Dorsal dimelia of a thumb. J Plast Reconstr Aesthet Surg. 2011;64:e177–80.
12. Rider MA. Congenital palmar nail syndrome. J Hand Surg Br. 1992;17:371–2.
13. Al-Qattan MM, Hassanain J, Hawary MB. Congenital palmar nail syndrome. J Hand Surg Br. 1997;22:674–5.
14. Al-Qattan MM, Al-Rabeeah A. Similarities between a conjoined nail and the palmar nail syndrome. J Hand Surg Br. 2000;25:8–10.
15. Al-Qattan MM, Al-Mazyed M, Shamseldin H, Al-Kuraya FS. Dorsal dimelia: report of two cases with an emphasis on the variation of phenotype expression and a search for candidate genes. J Hand Surg Eur. 2010;35:715–20.
16. Kalisman M, Goldferg R, Ship AG. Dorsal skin and fingernail on the volar aspect of the hand: an unusual anatomic deformity. Plast Reconstr Surg. 1982;69:694–6.
17. Fattah A, Pickford MA. Dorsal dimelia in patau syndrome: a case report. J Hand Surg Eur. 2007;32:534–6.
18. Shamseldin HE, Faden MA, Al-Ashram W, Al-Kuraya FS. Identification of a novel DLXS mutation in a family with autosomal recessive split hand and foot malformation. J Med Genet. 2012;49:16–20.
19. Egawa T. Congenital claw-like fingers and toes. Case report of two siblings. Plast Reconstr Surg. 1977;59:569–72.
20. Miura T. Two families with congenital nail anomalies: nail formation in ectopic areas. J Hand Surg Am. 1978;3:348–51.
21. Corona-Rivera JR, Corona-Rivera E, Fragoso-Herrera R, Nuno-Arana I, Loera-Castaneda V. Probable new syndrome in a Mexican family with congenital palmar polyonychia and post-axial limb defects. Am J Med Genet A. 2004;125:205–9.
22. Alves GF, Poon E, Joh J, Salamao PR, Griffiths WA. Circumferential finger nail. Br J Dermatol. 1999;140:960–2.
23. Kiryu M, Huzita S, Saitou O. Congenital hypoplasia of the little finger associated with nail anomaly. Jpn J Plast Reconstr Surg. 1978;21:216–21.
24. Miura T. Cleft hand involving only the ring and small fingers. J Hand Surg Am. 1988;13:530–5.
25. Keret D, Ger E. Double fingernails on the small fingers. J Hand Surg Am. 1987;12:608–10.
26. Kikuchi I, Ono T, Ogata K. Ectopic nail: case reports. Plast Reconstr Surg. 1978;61:781–3.
27. Kinoshita Y, Kojima T, Uchida M, Kurimoto S. Calm nail deformity of the little finger. Plast Reconstr Surg. 1993;91:158–61.
28. Thoma A, Alexopoulou I. Circumferential little finger nail plate. Can J Plast Surg. 1995;3:161–2.
29. Al-Qattan MM. Dorsal dimelia of the index finger in a patient with absent thumb and radial club hand. Ann Plast Surg. 2011;67:90–1.
30. Al-Qattan MM. Fanconi anemia with concurrent thumb polydactyly and dorsal dimelia. A case report with discussion of embryology. Ann Plast Surg. 2013;70:116–8.
31. Kawakami Y, Marti M, Kawakami H, Itou J, Quach T, Johnson A, et al. Islet 1 mediated activation of the ß-catenin pathway is necessary for hind limb initiation in mice. Development. 2011;138:4465–73.
32. Parr BA, McMahon AP. Dorsalizing signal WNT7A required for normal polarity of D-V and A-P axes of mouse limb. Nature. 1995;374:350–3.
33. Kantaputra PN, Mundle S, Spirathomsawat W. A novel homozygous Arg 222 TRP missense mutation in WNT7A in two sisters with severe Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome. Am J Med Genet A. 2010;152:2832–7.
34. Woods CG, Sticker S, Seeman P, Stern R, Cox J, Sherridan E, et al. Mutations in WNT7A cause a range of limb malformations, including Fuhrmann syndrome and Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome. Am J Hum Genet. 2006;79:402–8.
35. Garavelli L, Wischeiyer A, Rosato S, Gelmini C, Reverberi S, Sassi S, et al. Al-Awadi-Raas-Rothschild (Limb/pelvis/uterus-hypoplasia/aplasia) syndrome and WNT7A mutations: genetic homogenecity and nasological delineation. Am J Med Genet A. 2011;155:332–6.
36. Al-Qattan MM, Al-Balwi M, Eyaid W, Al-Abdulkarim I, Al-Turki S. Congenital duplication of the palm syndrome: gene analysis and the molecular basis of its clinical features. J Hand Surg Eur. 2009;34:247–51.
37. Eyaid W, Al-Qattan MM, Fetaini N, Al BM. A novel homozygous missense mutation (CGLOG>A, P.Gly 204 Ser) in the WNT7A gene causes tetra-amelia in two Saudi families. Am J Med Genet A. 2011;155:599–604.
38. Al-Qattan MM. Congenital duplication of the palm in a patient with multiple anomalies. J Hand Surg Br. 2003;28:276–9.
39. Al-Qattan MM, Eyaid W, Al-Balwi M. Congenital duplication of the palm syndrome. Ann Plast Surg. 2007;59:341–3.
40. Al-Qattan MM, Maddirevula S, Alkuraya FS. A de novo TBX3 mutation presenting as dorsalization of the little fingers: a forme fruste phenotype of ulnar-mammary syndrome. Eur J Med Genet. 2019; https://doi.org/10.1016/j.ejmg.2019.01.005.
41. Vogt J, Ryan E, Tischkowitz MD, Reardon W, Brueton LA. The tale of a nail sign in chromosome 4q34 deletion syndrome. Clin Dysmorphol. 2006;15(3):127–32.

42. Osterwalder M, Speziale D, Shoukry M, Mohan R, Ivanek R, Kohler M, et al. HAND2 targets define a network of transcriptional regulators that compartmentalize the early limb bud mesenchyme. Develop Cell. 2014;31(3):345–57.
43. Santos SC, Pardono E, da Costa MIF, de Melo AN, Graciani Z, de Albuquerque E, et al. A previously undescribed syndrome combining fibular agenesis/hypoplasia, oligodactylous clubfeet, anonychia/ungual hypoplasia, and other defects. Am J Med Genet. 2008;146A:3126–31.
44. Alves LU, Santos S, Musso CM, Ezquina SA, Opitz JM, Kok F, Otto PA, et al. Santos syndrome is caused by mutation in the WNT7A gene. J Hum Genet. 2017;62(12):1073–8.
45. Al-Qattan MM. Molecular basis of the clinical features of Al-Awadi-Raas-Rothschild (limb/pelvis/uterus-hypoplasia/aplasia) syndrome (AARRS) and Fuhrmann syndrome. Am J Med Genet A. 2013;161A(9):2274–80.
46. Al-Qattan MM. WNT pathways and upper limb anomalies. J Hand Surg Eur Vol. 2011;36(1):9–22.

Part III

Failure of Hand Plate Formation/Differentiation

Syndactyly

14

Daniel J. Jordan, Kavish Maheshwari,
Rakhee Nayar, and Sandip Hindocha

Epidemiology

Syndactyly is defined as the fusion of adjacent digits. The commonest of congenital hand deformities, it has an incidence of approximately 1 in 2000 live births, is twice as common in males, as well as in the Caucasian population [1–4].

Syndactyly can involve union of the soft tissues only, but is also seen with varying amounts of bone involvement. It predominantly occurs due to the failure of differentiation between adjacent digits caused by the absence of programmed cell apoptosis in the interdigital mesenchyme, which normally occurs during the seventh and eighth weeks of gestation [1, 5]. In decreasing frequency the third, fourth, second, and first web spaces are affected, with around 57% of cases occurring in the third web space [2, 3, 6]. The condition presents bilaterally in up to half of cases [2, 6].

Commonly presenting in a sporadic fashion, syndactyly involves a family history in 10–40% of cases [2, 7]. Inheritance is thought to be through an autosomal dominant pattern with variable penetrance and expressivity, and this possibly explains the male predominance [1, 2].

Syndactyly can be found as an isolated finding or seen with other anomalies such as acrosyndactyly, clinodactyly, synostosis, cleft hand, and polydactyly. It is also seen as part of congenital defect syndromes including Poland, Pfeiffer, Holt–Oram, and Apert. The latter is discussed in detail in specific chapters elsewhere in this volume.

Development of the Human Limb

Before discussing the specifics related to each syndactyly, it is useful to understand how the malformation is believed to develop. The authors do not aim to explore the molecular biology of the human limb formation in detail, but aim to summarize the current findings in a systematic approach, discussing the multiple genes and vast number of encoding proteins which are so far believed to be key to vertebrate limb growth.

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Control of Limb Growth

Arising from the main trunk, or body, the limb buds and consequent upper and lower limbs are formed between the fourth and eighth weeks of gestation. The limb bud is initially directed along three axes, along which the mesodermal cells grow and later become fixed. These axes include running along the shoulder to finger direction, the proximal-distal axis; the dorsal ventral axis, from the dorsum to the palm of the hand; and the anterior–posterior axis from thumb to little finger. The latter axis appears to be the most important in digit formation. The final and specific limb architecture resulting in the aesthetic limb normally involves cell proliferation, cell fate determination, cell differentiation, and apoptosis [8, 9].

The control of the human limb structure and positional identity appears to originate from two distinct signal centers: the apical ectodermal ridge (AER), which is key for limb growth, and the zone of polarizing activity (ZPA) [10–12]. The ZPA appears to identify the position and overall patterning in relation to the anterior–posterior axis. Each center is dependent on the other [13]. Both AER and ZPA produce FGF8 (fibroblast growth factor 8), which is required for limb development [14].

By the 44th day the ZPA begins to regress, at which time the formation of the metacarpophalangeal joints and proximal phalanges begins. Chondrification of the middle phalanges occurs toward day 48, followed by the distal bones by day 51 and on day 54 digit separation has normally occurred.

Genetic and Molecular Pathways

Encoding proteins influence the processes described above. In particular, the hedgehog pathways, fibroblast growth factors (FGF), bone morphogenetic proteins (Bmp), cartilage-derived morphogenetic protein, and Homeobox (HOX) gene family have been found to be instrumental in relation to limb formation [15].

Syndactyly and polydactyly appear to both have a relationship with the Hedgehog (Hh) family of intercellular signaling proteins. These have a predominant function related to cell fate, with most research directed toward the Sonic hedgehog (Shh) pathway [16]. Shh has particular relevance as it is expressed in the ZPA overseeing anterior–posterior limb patterning [17]. In mice, Shh appears to be a secreted molecule, related to the Drosophila Hh, which regulates the balance of Gli3 repressor and activator and through these its target genes.

Indian hedgehog (Ihh) is biologically akin to Shh and has been seen to play a key role in a pathway which is involved in regulating the rate of chondrocyte differentiation [18]. Ihh appears to be repressed by FGF receptor (FGFR) 3 [19, 20] and has been seen to play a role in bone ossification [21]. Multiple papers have suggested a role for the Ihh pathway, particularly in the later development of syndactyly as well as in other congenital abnormalities [22, 23].

The ZPA positioning and its involvement with Shh are determined in the main by transcription factors including dHand, Gli3, Alx4, and several Bmp antagonists, namely Formin and Gremlin. Changes involving any of these molecular components or pathways have been found to lead to -dactyly malformations (brachy-, syn-, and poly-) [24–28].

The FGF family (in particular, FGF8) have been seen to influence the latter stages of mesenchymal ossification [29] and are discussed again later in the chapter. These growth factors are expressed at a similar time as members of the wingless-type MMTV integration site (WNT) family, which have a relationship with the region 2q35. This is a locus hypothesized as the source of syndactyly type 1 [30].

WNT6 and WNT10B have both been described as possible avenues of further research due to their expression in the developing mouse limb bud, as well as their role in cell apoptosis [31, 32]. Cell death along anterior, posterior, and finally interdigital necrotic zones leads to the familiar profile of the hand as the last stage of digit formation [33, 34]. This apoptotic period

appears to coincide with restriction of FGF8 expression and downregulation of Gremlin in these regions [33, 35–38].

The number of phalanges has been shown to be influenced by several signaling molecules, including the Bmp's and their antagonist Noggin (Nog), all having a role in apoptosis [39–45]. Blockade of their signaling pathway has been shown to result in syndactyly [46–48].

The final digit distinctiveness appears dependent on the interdigital mesenchyme. Dahn and Fallon [49] found removal of this in chickens resulted in loss of digit identity, and it appears this is related to both the Shh and Gli3 pathways [24, 25]. Metalloproteases are similarly under scrutiny for their involvement in the formation of normal hand architecture, and appear to have a role independent of the Bmp for interdigital web regression [50].

Other areas requiring further research as they appear to induce soft tissue syndactyly in mice include N-Myc and several zinc finger transcription factors [51–53]. A recent study states a wide range of phenotypes can occur with only a Gli3 mutation, ranging from non-syndromic to syndromic syndactyly [54]. Also linked to digital anomalies are the Xq25 loci, with associated developmental delay [55] and defects in cholesterol metabolism [56]. ROR2 [57], nidogen [58], GAS [59], and MBOAT [60] genes have been shown to be related to limb and digit formation in animal and patient groups; likewise, mutations in Jagged [61], Serrate [62], and MSX [63] genes appear to cause syndactyly among other congenital abnormalities.

Governing the end point in body patterning are a whole host of transcription factors, all encoded by the Homeobox (HOX) gene family. Within the human genome, 39 HOX genes have so far been discovered which, as in most vertebrates, organize themselves into four clusters. These play an essential role in the development of the axial skeleton, central nervous system as well as the gastrointestinal and urogenital tracts, and our main interest, the limbs. Limb abnormalities have been seen with deletions of some of these HOX clusters (−A and -D) and in mutations affecting one or more HOX genes [64]. The specific HOX genes involved in syndactyly will be discussed in the non-syndromic section of this chapter.

The pattern of inheritance for these varies. Most of the syndactyly types follow an autosomal dominant inheritance, which makes these phenotypes less severe, but SD7 and SD9 are generally autosomal recessive, and SD5 is X-linked recessive. Autosomal dominant types have a variable expression with an incomplete penetrance [14].

Anatomical Classification

The classification of syndactyly is often described in respect to the anatomical findings. In this way, the syndactyly can be either simple or complex, and complete or incomplete. Simple syndactyly involves only the soft tissues, whereas complex includes side-to-side bony fusion with an origin both dorsal to and palmar to the neurovascular structures lying along the digits border.

When the adjacent digits are fused to the fingertip it is described as complete syndactyly, while incomplete refers to only partial union, with fusion ceasing at some point along the length of the digits involved. Distal growth of the digits can cause a lateral angulation to the normally longer digit, causing joint abnormalities as well as gross deformity up to the point of the distal separation of the fusion.

The most severe presentation, complex-complicated syndactyly, involves skeletal deformity accompanied by tendon and neurovascular abnormalities, the incidence of which rises as the complexity of the syndactyly increases [2].

Phenotypical Classification

Since its first description in the literature, syndactyly has also been classified by its phenotype. The simple and complex, and complete and incomplete descriptions are an easier reference for discussion among colleagues, whereas the phenotypical classification is more specific in terms of the digits involved, as well as the major-

ity having a genetic source. This has led to syndromic and non-syndromic syndactylies being described. The genetic links related to syndactyly have allowed them to be incorporated into the Mendelian Inheritance in Man (MIM) database [65].

In 1978, Temtamy and McKusick [66] concluded, from information gathered from both the literature and their own experience, that there were at least five phenotypically different types of syndactyly involving the hands, with or without foot involvement. The majority of these appeared to be inherited as autosomal dominant traits. Within each pedigree there is uniformity of the type of syndactyly, allowing for the variation characteristic seen in dominant traits. These genetic forms of syndactyly are required to be analyzed separate to syndactyly related to congenital amniotic bands for which currently, there is little or no evidence of a genetic basis. This chapter focuses on the current understanding of the genetic and molecular causes of syndactyly. It will also discuss the varying clinical presentations as well as highlight its management.

The non-syndromic syndactylies appear to only involve digit and appendage malformation, and have since been expanded to nine phenotypes, named syndactyly I to IX, although some are more commonly known by their synonyms [67–69] (Table 14.1, and Figs. 14.1, 14.2, 14.3, 14.4, 14.5, 14.6, 14.7, 14.8, and 14.9) [69].

Syndromic syndactyly describes syndactyly discovered alongside additional malformations of the body. This list is extensive and continues to

Table 14.1 The nine non-syndromic syndactyly phenotypes

Syndactyly (MIM) [14, 65]	Sub-groups	Gene	Loci	Phenotype
SD1/Zygodactyly		–	2q34-q36	Syndactyly of the third + fourth finger web space and/or the web between the second and third toes Accounts for 70% of nonsyndromic syndactyly cases
(MIM 185900)	Zygodactyly 1(Weidenreich type)	–	3p21.31	Foot zygodactyly without hand or bony involvement
	Zygodactyly 2 (Lueken type)	–	2q34-q36	Bilateral cutaneous and/or bony hand and foot involvement
	Zygodactyly 3 (Montagu type)	–	2q31-q32	Specific bilateral webbing, cutaneous or bony, of the third + fourth finger
	Zygodactyly 4 (Castilla type)	–	–	Bilateral cutaneous webbing of the fourth + fifth toe
SD2/ synpolydactyly (MIM 185900)	SPD1 (Vordingborg type)	Homeobox A and Homeobox D 13	2q31.1	Syndactyly of the third + fourth fingers associated with polydactyly of all components or of part of the fourth finger in the web. Foot polydactyly of the fifth toe included in a web of syndactyly of the fourth + fifth toes
	SPD 2 (Debeer type)	Fibulin 1	22q13.31	Syndactyly of the third/fourth finger web space and synostosis of the metacarpal and metatarsal bones
	SPD 3 (Malik type)		14q11.2-q12	Third and fourth finger syndactyly with varying degrees of polydactyly of the fourth finger web space. There is also polydactyly of the fifth toe commonly
SD3 (of the ODDD spectrum) (MIM 186100) (Johnston-Kirby type)		Gap Junction Protein Alpha 1 (Connexin 43)	6q21-q23.2 6q22-24	Complete/bilateral, generally soft tissue syndactyly between the fourth and fifth fingers. The fifth finger is short with absent or rudimentary middle phalanx

Table 14.1 (continued)

Syndactyly (MIM) [14, 65]	Sub-groups	Gene	Loci	Phenotype
SD4 (2 types) Haas type (MIM 186200) Anderson-Hansen type		LMBR1	7q36	Complete syndactyly, bilateral with polydactyly, generally six metacarpals and six digits
SD5 (MIM 186300) (Dowd type)		Homeobox D 13	2q31-q32	Soft tissue syndactyly usually affects the third and fourth fingers and second and third toes with associated metatarsal and metacarpal fusion (fourth and fifth or the third and fourth)
SD6/Mitten Hand (MIM n/a)		–	–	Unilateral syndactyly of digits 2–5
SD7/Cenani–Lenz (MIM 212780)		LRP4 FMN1 GREM1	11p11.2 15q13.3	Severe shortening of the ulna and radius with fusion, fusion of the metacarpals and "disorganization" of phalangeal development including syndactyly
SD8 (MIM n/a) Two subtypes: Orel-Holmes type and Lerch type		MF4	Xq26	Fusion of the fourth and fifth metacarpals
SD9/Mesoaxial Synostotic (MIM 609432) (Malik-Percin type)		–	17p13.3	Complete syndactyly and synostosis of the third and fourth fingers with severe bone reduction in the proximal phalanges, hypoplasia of the thumbs and halluces, aplasia/hypoplasia of the middle phalanges of the second and fifth fingers, and complete or partial soft tissue syndactyly of the toes

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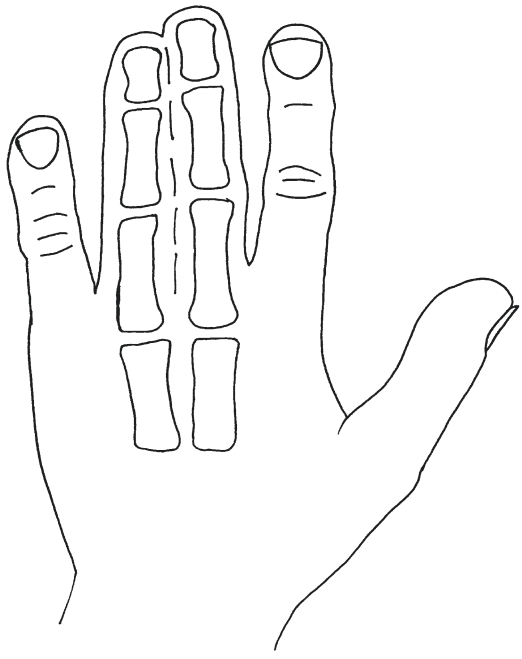
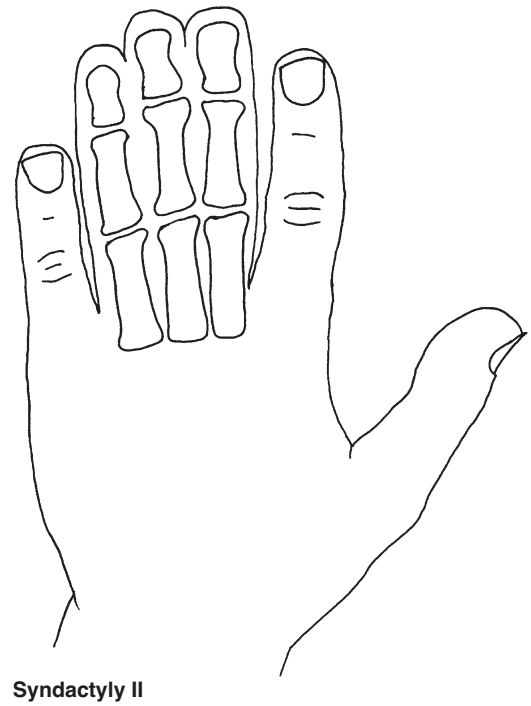


Syndactyly I
Zygodactyly

Fig. 14.1 Syndactyly 1. (Reprinted from Jordan et al. [69]. Copyright © Jordan et al.; Licensee Bentham Open)



Syndactyly II
Synpolydactyly

Fig. 14.2 Syndactyly 2. (Reprinted from Jordan et al. [69]. Copyright © Jordan et al.; Licensee Bentham Open)

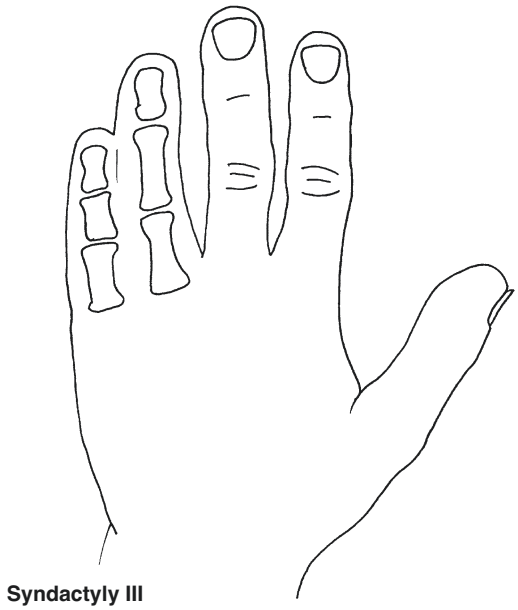


Fig. 14.3 Syndactyly 3. (Reprinted from Jordan et al. [69]. Copyright © Jordan et al.; Licensee Bentham Open)

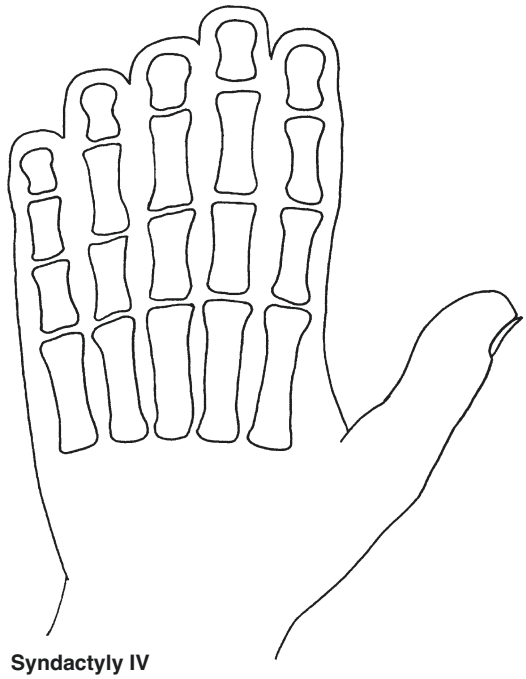


Fig. 14.4 Syndactyly 4. (Reprinted from Jordan et al. [69]. Copyright © Jordan et al.; Licensee Bentham Open)

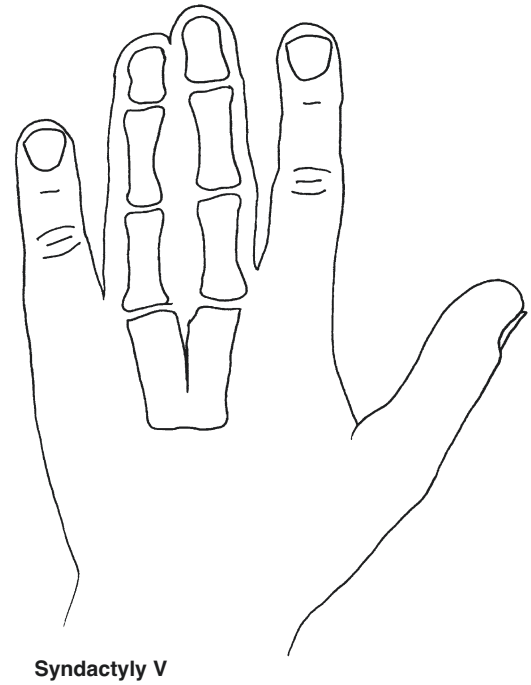


Fig. 14.5 Syndactyly 5. (Reprinted from Jordan et al. [69]. Copyright © Jordan et al.; Licensee Bentham Open)

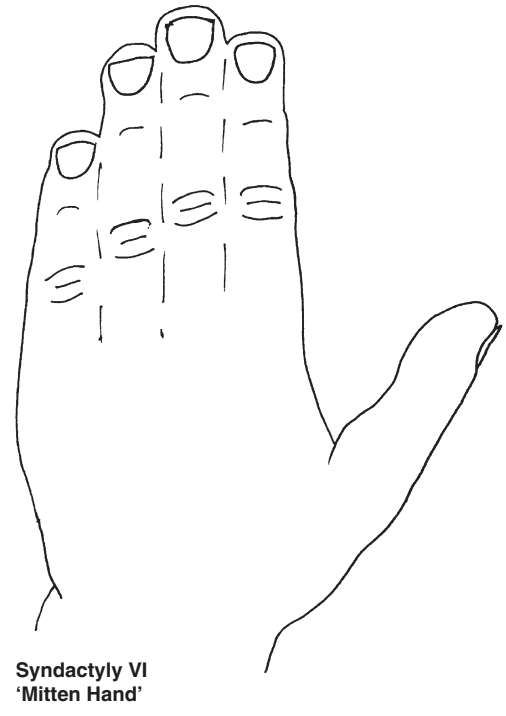


Fig. 14.6 Syndactyly 6. (Reprinted from Jordan et al. [69]. Copyright © Jordan et al.; Licensee Bentham Open)

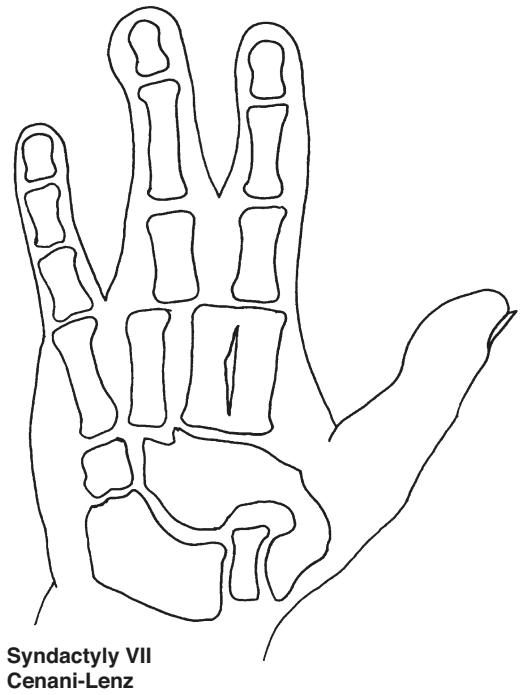


Fig. 14.7 Syndactyly 7. (Reprinted from Jordan et al. [69]. Copyright © Jordan et al.; Licensee Bentham Open)

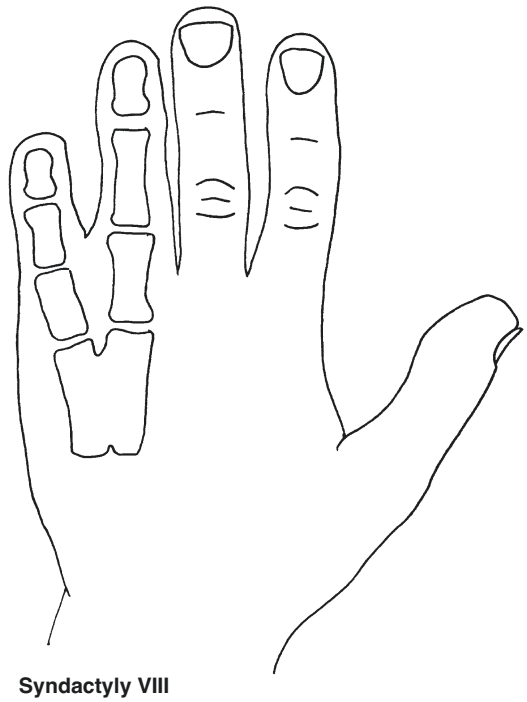


Fig. 14.8 Syndactyly 8. (Reprinted from Jordan et al. [69]. Copyright © Jordan et al.; Licensee Bentham Open)

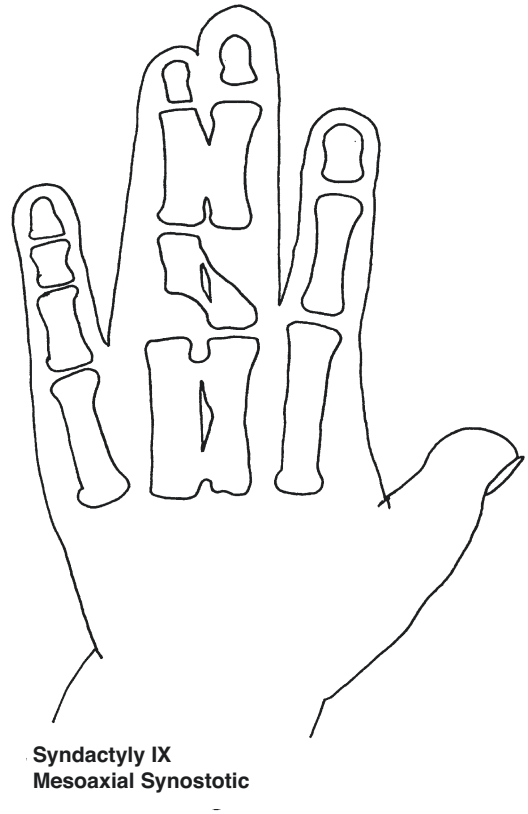


Fig. 14.9 Syndactyly 9. (Reprinted from Jordan et al. [69]. Copyright © Jordan et al.; Licensee Bentham Open)

expand as syndactyly is discovered alongside other abnormalities, the majority of which appear to develop at a time during the fetal development alongside the digit anomaly formation. In this chapter, we will note some of the more well-known syndromes and review their currently known associated traits and the genes suggested as being causative.

Syndactyly: Non-syndromic Forms [69]

Syndactyly, in this and syndromic form, is seen to have an autosomal dominant transmission with variable expression and penetrance [1–4]. This is best represented with the increased prevalence in male offspring, possibly due to reduced penetrance in females. Occasionally skipping generations, it can present in a reduced form indicating variable phenotype.

The non-syndromic forms of syndactyly which are genetically distinct have been expanded from five to nine since the first discussion of syndactyly phenotypes by Temtamy and McKusick [66] and are summarized individually below.

Syndactyly Type I (SD1)

SD1 is characterized by involvement of the third and fourth finger web space and/or the web between the second and third toes. The most common non-syndromic presentation of syndactyly, it has been described with involvement of other digits and the underlying bones [70]. It is also known under the name zygodactyly.

The phenotype of zygodactyly has been seen to vary. It has been seen to affect the upper or lower limb, both simultaneously and independently. SD1 appears to be inherited only as an autosomal dominant trait. Initial genetic studies localized the 2q34-q36 region of the second chromosome, mapped during studies involving both a large German and a non-related Iranian family [71, 72]. This locus has also been linked to a Philadelphia type of craniosynostosis with associated syndactyly [73, 74].

Mouse studies have shown a chemically induced mutation on the chromosome 6 causes syndactyly of digits 2 and 3 of the hind legs (Sndy Jrt/Sndy +). This varies from simple complete to incomplete phenotype, and although sparing the front limbs appears to correlate well with the characteristics of SD1. The homologous region of this chromosomal mutation in humans would be found on 3p25.1 [75].

Malik et al. [76] postulated that SD1 can be further divided into four subtypes:

- Subtype 1: Foot zygodactyly without hand or bony involvement.
- Subtype 2: Bilateral cutaneous and/or bony hand and foot involvement.
- Subtype 3: Specific bilateral webbing, cutaneous or bony, of the third and fourth finger.
- Subtype 4: Bilateral cutaneous webbing of the fourth and fifth toe.

They designated the 3p21.31 locus to be specific for this first subtype and named it zygodactyly 1 (ZD1). This appeared to be a new locus for the same phenotype previously described in the German family by Bosse et al. [71].

Syndactyly Type II (SD2)

Synpolydactyly (SPD) is, in terms of both genetic and clinical terms, one of the most heterogeneous malformations of the non-syndromic syndactyly types. It appears to lack penetrance within SPD-affected families, with its typical signs including third and fourth finger syndactyly associated with varying degrees of polydactyly of the fourth finger web space. Polydactyly of the fifth toe is often seen.

SPD has been categorized several times in the literature. There is agreement that SPD is inherited in an autosomal dominant manner. Subtypes have been constructed as new genetic sources have been found.

The Homeobox family of genes were the first group to be acknowledged in relation to Synpolydactyly. Located on the 5′ region of the A- and D-clusters of human chromosomes 7 and 2, respectively, several distinct genes have been recognized [40]. These genes appear to influence limb patterning and of particular interest is the Homeobox D gene (HOXD), and precisely that related to the loci at 2q31 [77].

Following this theory, research into the HOXD13 gene found in one family a relation to polyalanine expansion [78–82]. Specifically, the N terminal region of the protein, involved in binding to DNA, is disturbed. With this there appears to be a correlation between expansion size and the appearance and severity of the SPD phenotype in affected patients, with a greater number of limb involvement seen with increasing expansion size [83]. It has correspondingly been found that minimal duplication does not seem to cause the phenotypical deformity [84]. Since its finding, HOXD13 has been linked with multiple limb deformities including SD5, brachydactyly, and several syndromic forms of syndactyly [85, 86].

The HOXD13 gene link has been supplemented by the discovery that a translocation between Chromosomes 12 and 22 resulting in a defect in the Fibulin gene, normally located on the latter, was found to cause SPD [87, 88]. Debeer and Schoenmakers team published further papers examining this translocation within the FBLN1 gene and localized specific involvement of an area represented by EST R72964, as well as ruling out several previously characterized genes [89].

This finding initially complicated the SPD phenotype, and resulted in the commonly recognized classification SPD 1–3. With this description, SPD 3 correlates to the more classical presentation of SPD and has been linked to the 14q11.2-q12 loci [90].

Likewise, the grouping of phenotype to gene of SPD 2 to the Fibulin 1 gene on Chromosome 12 (MIM 608180) and SPD 1 with Homeobox D13 (MIM 186000) is now widely accepted. SPD2 is generally thought to include synostosis of the metacarpal and metatarsal bones.

A more recent paper [91] has stated that SPD should be sub-classed more specifically relating to phenotype, stating genotype–phenotype correlation is weak when looking only at the HOXD13 mutation. They propose the phenotypic variant being classed as (1) typical SPD features, (2) minor variants, and (3) unusual phenotypes.

A further SPD subtype is described by one paper [92] where a new distinct clinical form involving a complicated and distinctive hypoplastic synpolydactyly was found. This currently does not appear to have been investigated on a genetic basis, and further research into this will help define this new phenotype as a new or mixed entity.

Continuing research has led to other genes being suggested as causative in SPD, although all of these have been found to involve the Shh pathway on one level or another [93].

Syndactyly Type III (SD3)

In syndactyly type III, the typical and first described phenotype involves complete and bilateral syndactyly between the fourth and fifth fingers. This is a soft tissue syndactyly but has been seen with the distal phalanges fused. An absent or rudimentary middle phalanx results in an often seen shorter fifth digit. The feet are generally not affected. Johnston and Kirby [94] presented a family which was one of the largest fully described pedigrees, involving seven affected males and seven affected females over five generations in a pattern compatible with an autosomal dominant inheritance [66].

Other papers to describe SD3 as a single entity, as opposed to as being part of a syndrome include De Smet et al. [95].

Isolated SD3 appears to be in a disease spectrum that includes oculodentodigital dysplasia (ODDD; MIM 164200), which commonly involves digit as well as craniofacial dysmorphia and neurological degeneration [96]. ODDD has complete penetrance but a varying phenotype. Gene research has led to the locus 6q21-q23 being associated with SD3, with significant crossover of the locus 6q22-q24, linked to ODDD, and in particular the Connexin 43 (Cx43) gene and its involvement with the gap junction protein, alpha 1 (GJA1) [97–99].

With six types, it has been found the Connexin family are key in forming gap junctions allowing small molecule and ion passage, with Cx43 being expressed in the developing limb bud and in particular relating to digit and cartilage condensation [100]. Further studies into both the phenotype and genetic regions above have found localized missense mutations causative for ODDD, of which over eight have been described, as well as tested in animal studies [101–105].

Dobrowolski et al. [106] have described ODDD phenotype in specific mutations (131 M and G138R) while mutations at other points appear to result in no syndactyly (H194P) or solely facial abnormality (G143S). This has led to a belief that increased hemi-channel activity may strengthen ODDD phenotype in Cx43 gap junction deficient patients. Other studies have also confirmed a highly variable phenotype of Cx43 mutations which includes ODDD [107–109].

Syndactyly Type IV (SD4)

With only four reports in the literature, syndactyly type IV is rare [110–113].

Haas [110] was first to describe this phenotype, referred to as Haas type polysyndactyly, with the syndactyly described as complete, affecting the fingers of both hands, with associated polydactyly, generally involving six metacarpals and six digits. Flexion of the fingers results in the hands forming a cup shape. In contradistinction to the type of syndactyly in Apert syndrome, there is no bone fusion. In the reports, there is no mention of SD4 affecting the feet, with descriptions noting there were no associated malformations.

Following an autosomal dominant inheritance trait, 7q36 has been mapped as a locus for SD4 [111]. Shh regulation mutations have been found to be key in SD4 [114, 115], with one paper showing an involvement of an area on the limb region 1 (LMBR1) gene being causative [116].

A second subtype known as Anderson-Hansen type is also present, though not much is known of genetic basis [14].

Syndactyly Type V (SD5)

Another rare form of syndactyly, SD5 is as a rule characterized by the presence of an associated metacarpal and metatarsal fusion. The fourth and fifth, or third and fourth, metacarpals and metatarsals are most commonly fused, with soft tissue syndactyly usually affecting the third and fourth fingers and the second and third toes. In this form, the syndactyly tends to be more extensive and complete. In 1932, Kemp and Ravn [117] described this anomaly in five generations of a family from the island of Seeland. Other descriptions without metatarsal fusion have been documented, but these are usually seen with other foot abnormalities [118].

Syndactyly type V has an autosomal dominant trait but has been described as X-linked recessive. Research has linked SD5 to the locus at 2q31-q32 as well as mutations in the HOXD13 gene, including the pathogenicity of a c.950A → G (p.Q317R) mutation [85]. In this paper, the authors called for a genotype classification of HOXD13 limb morphologies, again confusing the genotype-phenotype boundaries of the syndactylies.

Interestingly, as in SPD, evidence of HOXD13 polyalanine expansion has been found in the Seeland family [119].

Syndactyly Type VI (SD6)

Also known as mitten hand syndactyly, this form consists of unilateral syndactyly of digits 2–5 [66]. One family has been described with this anomaly, where an autosomal dominant inheritance, but with variable expression and incomplete penetrance, is likely. Tentamy and McKusick included this phenotype in their initial classification but, even since their description, due to its rarity it remains the least researched non-syndromic syndactyly.

Syndactyly Type VII (SD7)

In 1967 two brothers with an Apert syndrome-like form of syndactyly were described by Cenani and Lenz [120]. They noted, however, that additional features, including severe shortening of the ulna and radius with fusion, as well as fusion of the metacarpals and "disorganization" of phalangeal development, were present. The feet of both brothers were less severely affected. They identified similar cases reported by Liebenam [121], Borsky [122], and Yelton [123].

Cenani–Lenz syndrome, named after the pair's description, is a very rare phenotype and has been reported to show an autosomal recessive inheritance. There have been accounts of varying phenotypes, including a description of a patient with features consistent with Cenani–Lenz type but also displaying a severe form of SPD1 [70].

The LRP4 gene has been linked to syndactyly in cattle [124, 125], and it is reported with multiple mutations on Chromosome 11p12-p11.2 to be the causative factor in SD7 [126]. In the study group, two families did not exhibit LRP4 mutations, suggesting further gene involvement. Bachelli et al. found that this is unlikely to be

related to the pathways involving Formin or Gremlin expression [127]. A more recent paper suggests a mutation involving the loci of these bmp antagonists can result in a phenotype similar to Cenani–Lenz syndrome [128].

Within the Cenani–Lenz syndactyly group, there appears to be two grossly variant phenotypes: one involving a spoon hand type, and the other an oligodactyly type [129].

Syndactyly Type VIII (SD8)

Fusion of the fourth and fifth metacarpals is an uncommon presentation of syndactyly. First described by Orel in 1928 [130], it was thought to have an X-linked recessive trait, which has been supported by later papers [131, 132].

An autosomal dominant inheritance has been suggested by Lerch [133] after he found a family with male–male transmission as well as female member being affected.

Xq26 has been suggested as a starting point for analysis, a known mapped area for split-hand/foot malformation (SHFM2), with the gene allocated as MF4 (MIM 309630), although there is general consensus that this syndactyly needs further research before its relationship is fully understood [134].

Syndactyly Type IX (SD9)

Type IX, mesoaxial synostotic syndactyly (MSSD) has been described only in two families. The characteristic features consist of complete syndactyly and synostosis of the third and fourth fingers with severe bone reduction in the proximal phalanges, hypoplasia of the thumbs and halluces, aplasia/hypoplasia of the middle phalanges of the second and fifth fingers, and complete or partial soft tissue syndactyly of the toes. Percin initially believed, with family members known to have SD1 trait, this to be a severe form of SD1 having a possible homozygous origin [135].

Malik et al. [136] found similar findings in another family, with an autosomal recessive trait, and ruled out genome candidates at 2q34-q36, 2q31, and 6q22-q23. The previous family had also had HOXD13 and the genome associated with 2q31 disproved as causative by Percin et al. Merging the two families into one study has revealed a likelihood of a causal gene being mapped to chromosome 17p13.3 [68].

Syndactyly: The Syndromic Forms

Syndactyly often presents as part of a syndrome, usually with other congenital abnormalities. Some of the more common syndromes are reviewed as follows.

Acrosyndactyly describes syndactyly associated with congenital constriction bands. It appears to lack a genetic basis, with Tentamy and McKusick [66] being first to find little or no evidence of a clear or simple genetic link. The formation of syndactyly in this syndrome is thought to be as a result of inflammatory changes resulting in scar formation fusing the digits [137–139]. This is reinforced by the appearance of dorsal to palmar epithelium lined sinuses lying proximal to the scar fusion site in these patients.

The ischemic insult after initial digit formation causes digit deformity, although Patterson [138] has also noted the high incidence of deformity in other anatomical regions and raises the possibility of a molecular tissue defect. However, it is noted that any deformity is not usually seen to be symmetrical in the opposite limb pointing away from a genetic source.

Dependent on the degree of bone involvement, acrosyndactyly can be described as mild, moderate, or severe [140–142]. Mild deformity involves normal metacarpal structure with three well-formed digits, meaning three phalanges and two joints, whereas there is loss of a phalangeal bone resulting in one joint in the moderate form. The severe form relates to little or no digit presence with only small phalanges present, and occasionally metacarpal involvement. The variance in acrosyndactyly, as opposed to the other forms of syndactyly tends to involve no extra-skeletal parts and the fusion involving a scar lying either side-to-side or an on-top position.

Poland syndrome (MIM 173800) presents with unilateral hypoplasia or absence of pectoralis muscle with ipsilateral hand and digit anoma-

lies. The syndrome is named after Alfred Poland, who reported on George Elt's absent pectoralis major [143]. Patrick Clarkson later described the syndrome, including its hand anomalies [144]. As of yet no gene or loci has been implicated in its origin. It is believed that there may be a causative source in a disruption sequence related to the brachiocephalic arterial system [145–147].

The radial fingers are more typically involved in Poland syndrome and hypoplasia of the digits is frequent. Breast hypoplasia, in varying degrees, is often a common presentation as well as involvement of the latissimus dorsi, deltoid and/or serratus anterior muscles [148]. Poland syndrome has also been reported with evidence of dextrocardia and sternal deformity. Karnak et al. described a bilateral Poland syndrome [149]; however, most presently agree that Poland syndrome is solely a unilateral disease.

Acrocephalosyndactyly (ACS) is a condition involving syndactyly and craniosynostosis, in which there is a premature fusion of one or more of the fibrous suture lines of the skull. Five types have been described, each having variances on the hand and skull deformity. There is confusion where the distinction between the ACS group and the syndromes involving craniosynostosis, syndactyly, and polydactyly (ACPS), which incorporates a different four syndromes into a further five types, ends. The main ACS/ACPS syndromes are commented on below.

Apert syndrome (MIM 101200) ACS type I is synonymous with the term *acrocephalosyndactyly*. Associated with the FGFR2 gene, and the loci 10q26, includes midface hypoplasia, foot and hand syndactyly with a trend for distal bony fusion [150].

A subgroup of the *Crouzon syndrome* linked to FGFR2 is termed ACS type 2. Although Crouzon syndrome usually involves only a craniofacial dysostosis, Crouzon type 2 also involves mild soft tissue syndactyly.

Saethre–Chotzen syndrome, ACS type III (MIM 101400), involves syndactyly of the second and third fingers, as well as the third and fourth toes, as well as eyelid anomalies and cranial abnormalities. It has been linked to the loci 7p21.2 and 10q26 involving the TWIST 1 and FGFR2 genes, respectively [151, 152].

ACS type V, also known as *Pfeiffer syndrome* (MIM 101600) has been linked to the FGFR 1 and 2 genes [153, 154]. This is likewise classified as ACPS 5, and has since had Noack syndrome, previously ACPS 1, grouped with it.

ACPS 2, *Carpenter syndrome* (MIM 201000), has been linked to RAB23 gene originating from 6p11, with malformations including foot and hand syndactyly/brachydactyly and acrocephaly [155]. ACPS 4 was known as *Goodman syndrome* (MIM 201020) but is thought now to be a variant of type II [156].

Other syndromes and chromosomal location include *acropectorevertebral dysplasia* (MIM 102510) and 2q36 and *Fraser syndrome* (MIM 219000) associated with both the sites 4q21 and 13q13, involving the FRAS1 and FREM2 basement membrane genes, respectively [157, 158], which have also been shown to be linked to fin deformity in zebrafish [159].

Greig cephalopolysyndactyly (MIM 175700) is an autosomal dominant disorder associated with haplo-insufficiency of GLI3. This appears to be caused by deletions, truncations, or point mutations of the associated Gli3 gene. Similarly the zinc finger domain of Gli3 has been found to be causative in *Pallister Hall syndrome* whose phenotype includes central nervous system and craniofacial deformities, as well as anal defects [53].

Various other syndromes of note that have described syndactyly as part of their disease spectrum include Monosomy 2q37; Diploid/triploid mosaicism; Ectrodactyly-Ectodermal dysplasia-Cleft lip/palate syndrome (EEC Syndrome) (MIM 129900, MIM 604292); Filippi syndrome (MIM 272440); Goltz syndrome (MIM 305600); Holt-Oram syndrome (MIM 142900); Jackson-Weiss syndrome (MIM 123150); Microphthalmia with limb anomalies (MIM 20690); Moebius syndrome (MIM 157900); Oral-facial-digital syndrome – types OFD1 (MIM 311200), OFD2 (MIM 252100), OFD4 (MIM 258860), OFD6 (MIM 277170), and OFD9 (MIM 258865); Rubinstein-Taybi syndrome (MIM 180849); Split hand/foot malformations 3 (MIM 246560); Timothy syndrome (MIM 601005); and Bardet-Biedl syndrome (MIM 209900) [160].

Research into the individual phenotypes appears to complicating phenotypical classification as new genes are found both linked, and not linked, to each malformation.

This has been noted by several researchers [161, 162], and attempts have been made to simplify the current classifications, although these are yet to be recognized across all specialties.

Environmental Influence on Limb Formation

It should be noted that sporadic distinct syndactyly with no familial history has been documented. In utero environmental factors that predispose the fetus to syndactyly and other congenital hand abnormalities have been evaluated. Man conducted a study that reports a probable association with these conditions and maternal smoking [163], and there are suggestions that syndactyly occurrence is associated with lower nutritional and economic status, including increased meat and egg intake while pregnant, although more research is required before suggesting that these are causative factors [164].

Anatomy and Management

The normal position of the web commissure lies at the midpoint of the proximal phalanx if looked at from a lateral view. From a distal view the space appears to be shaped like an hourglass with a larger area within the second and fourth web space when compared to the third. The web space appears to normally slope, toward this distal view, from the dorsal aspect of the hand at an angle of 45° (Figs. 14.10 and 14.11).

The mainstay of treatment for syndactyly remains surgical. Indications for operative inter-

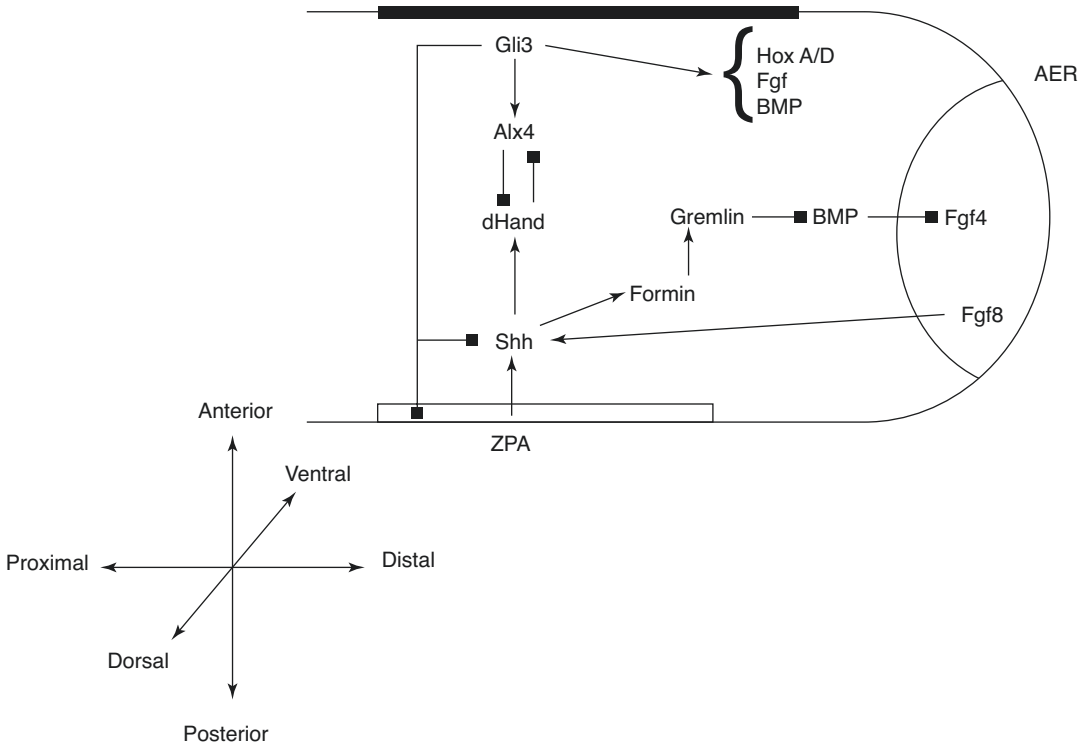


Fig. 14.10 Showing lateral view of interdigital web space. Note 45° dorsal to palmar fall finishing at midpoint of the proximal phalanx

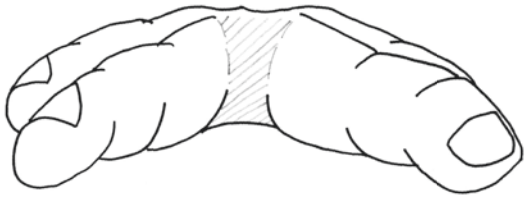


Fig. 14.11 Hourglass shape of interdigital space

vention run along the same principles as that of all hand anomalies:

- Function—to allow hand function and the development of normal grip.
- Cosmesis—to improve the aesthetic appearance of the hand to minimize the psychological and social effects of the deformity.

The timing of the surgical intervention needs to be optimized in order to reduce long-term complications and improve outcome. Many centers begin corrective surgery by 12 to 18 months of age and aim to complete reconstruction by the time the child reaches school, helping social and functional tasks at this time. It is thought that there is less risk of scar contracture in comparison to younger age groups. However, it is imperative that patients be assessed on an individual basis and reconstruction tailored as to the complexity of the syndactyly. Some forms of syndactyly are operated on at 6 months of age [165] or earlier [166].

Involvement of border digits, complex syndactyly, and flexion contractures are all indications for early repair. The aim of early intervention is to reduce the loss of function associated with the deformity and provide normal grip development.

On the contrary, Kettlekamp and Flatt [167] found that surgery performed at less than 18 months of age was associated with a higher complication rate and poorer aesthetic outcome, particularly in relation to the web commissure. Timing of surgery, therefore, is often down to individual surgeon preference.

Multiple-digit syndactyly should be corrected as part of a multistage procedure. Release should be performed on only one side of a digit at a time so as not to risk necrosis, particularly in those supplied by only one artery [168]. As a rule, border digits should be released first followed by a second procedure performed at least 4 months later [169].

Surgical Technique

Surgical correction of syndactyly requires the separation of digits and the creation of a new web space. The main concern with syndactyly is the greater surface area encountered on separation of the digits, with a circumference of approximately 1.4 times the preoperative state. Technique for repair, therefore, must provide a means for adequate resurfacing.

Over the last two centuries, techniques for syndactyly repair have evolved significantly [165]. Many successful methods are described in the literature. Most employ a variant of the procedure described below (Figs. 14.12, 14.13, 14.14, 14.15, 14.16, 14.17, 14.18, 14.19, and 14.20):

1. A zigzag incision for the separation of digits
2. A dorsal flap for the creation of a web commissure
3. A skin graft to resurface raw areas

Skin grafts are associated with various complications: graft loss, hair growth from donor sites, scar contracture, web creep as well as general surgical risks including donor site infection. In general, full thickness grafts are used for resurfacing. Split thickness grafts have been shown to have higher complications from scar contracture [170] and have therefore fallen out of

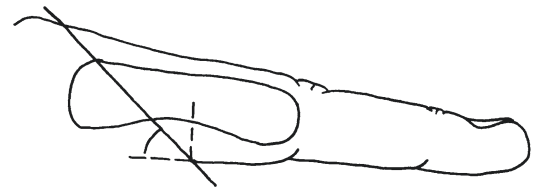


Fig. 14.12 Showing lateral view of interdigital web space. Note 45° dorsal to palmar fall finishing at midpoint of the proximal phalanx

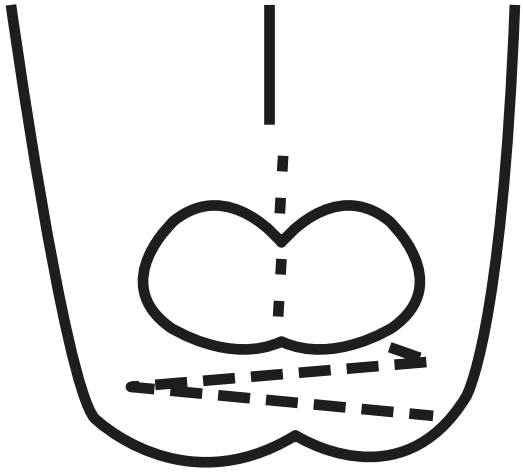


Fig. 14.13 Buck Gramcko nail fold creation

Fig. 14.14 Dorsal Island flap

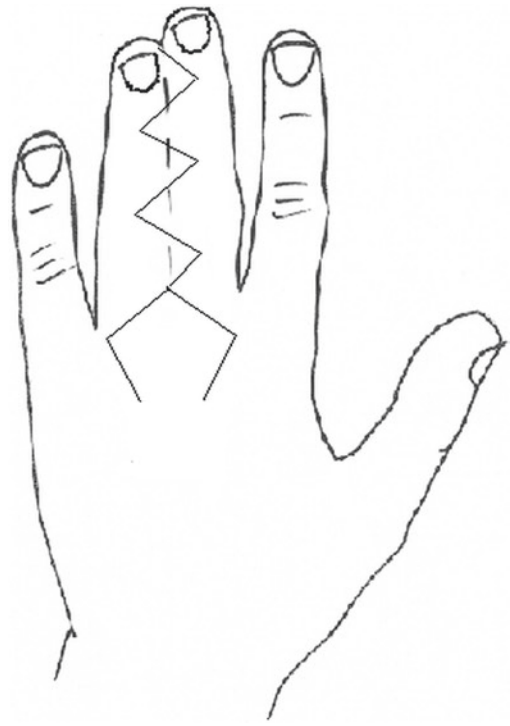


Fig. 14.15 Dorsal pentagonal flap

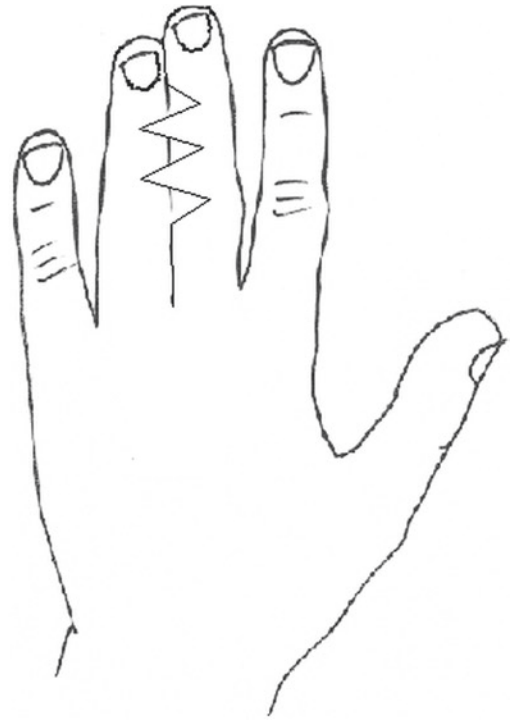


Fig. 14.16 Dorsal view of Jose et al. flap

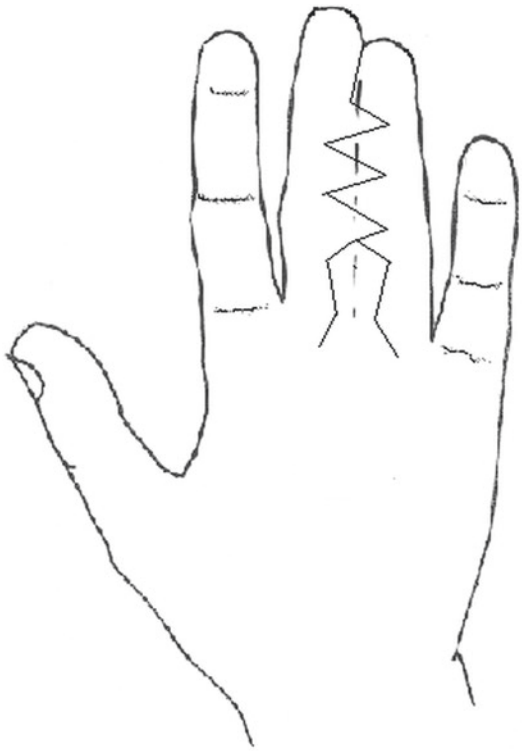


Fig. 14.17 Palmar view of palmar-shaped flap

Fig. 14.18 Volar zigzag approach to release

favor. Full thickness grafts may be taken from the dorsum, hypothenar region, antecubital fossa, and the groin. Although widespread use of the groin as a donor site, it has been recommended that more medial areas are avoided so as to avoid excessive hair growth on the hand [171].

Another consideration with the use of skin grafts is the problems associated with graft management in patients of a young age, mainly due to difficulties with immobilization. Recently, Kamath et al. [172] describe the use of a mini external fixator to facilitate the maintenance of the neo-web space by allowing accurate positioning of the graft and make dressing changes easier and pain free.

Complications associated with graft use have led to the development of flaps that aim to minimize the surface area required for grafting. More recently, there has been a trend toward syndactyly repair without skin grafts. The goals of this technique involve the careful redistribution of available skin to allow direct closure. Various techniques have been described. The procedure is based upon a local flap to recreate the web commissure, while lateral finger defects are closed directly. Modifications of this design include the use of a transposition flap [173], a V-Y advancement flap originating from a distal subcutaneous pedicle [174] and a local dorsal pentagonal flap based on perforators from the dorsal metacarpal artery [175]. More recently, a dorsal hexagonal flap too has been described [176]. Although reliable in terms of resurfacing, these methods are associated with aesthetically displeasing scarring on the dorsum of the hand, which could potentially be avoided using other methods.

Island flaps have been designed to reduce scarring to the socially visible dorsal aspect of the hand. The harvesting of island flaps has been described in the literature by various different means. Yao et al. [177] advocated that the flap be pedicled upon subcutaneous tissue and deep fascia to incorporate known perforators, where other authors have encouraged the direct isolation of

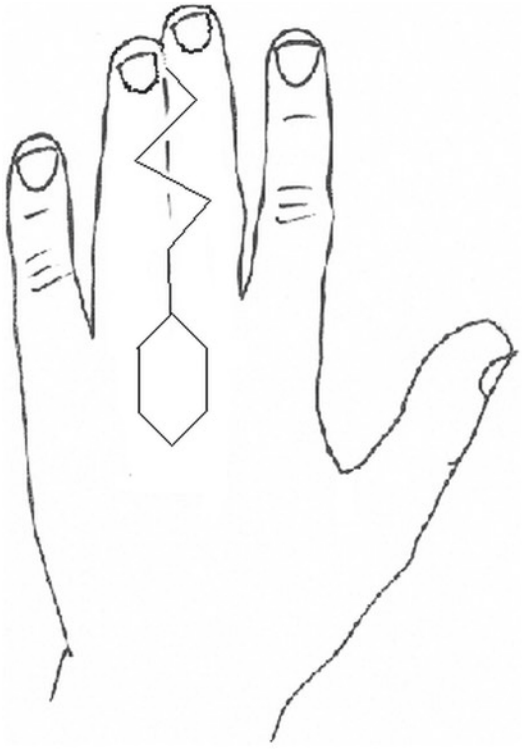


Fig. 14.19 Diagram of V-Y advancement flap for release

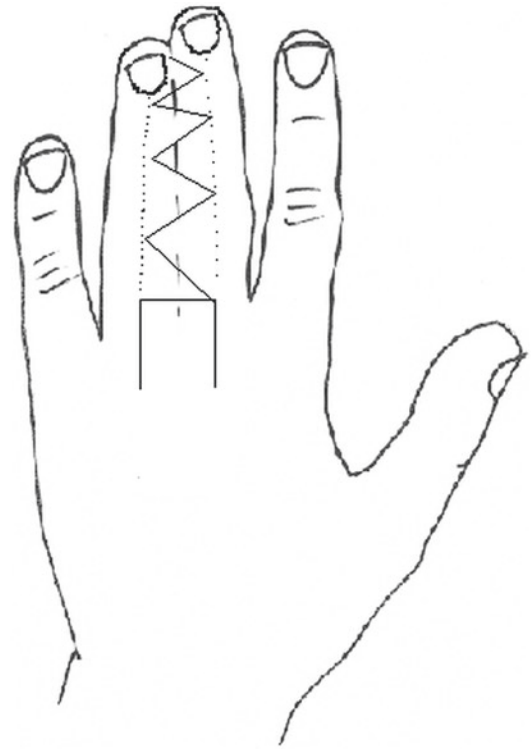


Fig. 14.20 Zigzag dorsal flap

the arterial feeding branch to the web flap [178]. Both methods detail excellent outcome in terms of vascularization.

For closure to be successful in most non-graft techniques, extensive "defatting" of the tissue is performed [179], with any small areas left to heal by secondary intention. There has been concern that the debulking technique employed in these procedures is associated with vascular injury and therefore increased risk of tissue necrosis [180]. It has also been recognized that these techniques can only be used in simple syndactylies, as the available surface on the dorsum of the hand would not be sufficient for extensive resurfacing.

Jose et al. [181] proposed a combination of techniques to reconstruct syndactyly in response to the problems associated with dorsal flaps (scarring) and dorsal metacarpal island flaps (restricted to simple syndactylies only). A palmar flap is used to recreate the web commissure, where lateral digit defects are closed via narrow-based V-flaps and full thickness grafts. Retrospective review of 176 procedures yielded low complication rates (see Figs. 14.13, 14.14, 14.15, 14.16, 14.17, 14.18, 14.19, and 14.20).

In recent times, synthetic dermal substitutes have been used for resurfacing of the raw areas following syndactyly repair [182]. Jung et al. used integra for coverage of exposed bone in complex syndactyly release with good results [183]. Matriderm has also been used with favorable results, though it needed an additional split skin graft on top [184]. A bilayered skin substitute, Hyalomatrix PA, has been used with some good results as well, without the need for a skin graft on top [182, 185]. The advantages of using a dermal substitute are reduction in operative and tourniquet time, absence of donor site scar, and no hair growth at the grafted site in hand [184].

For syndactyly involving the nail, the nail must first be split before creating a new nail fold from triangular flaps based laterally on the distal pulp. Most repairs involving the nail are variations of the Buck-Gramcko technique (see Fig. 14.13) [186].

Complications and Outcome

The most common acute complications of syndactyly correction include infection, necrosis, graft failure, and scar contracture. Long-term complications include web creep, keloid scarring, and joint deformity, which all can result in a reduction of function. All of the listed complications may result in a secondary operative procedure.

Simple syndactyly repairs are often associated with good functional and cosmetic outcome [171, 186]. Many studies, however, have noted poorer outcome with complex syndactyly [161, 187], most likely due to the challenging nature of the reconstruction. Goldfarb et al. [188] found significantly higher rates of joint deformity among complex repairs and a high likelihood of abnormal nail appearance. Overall re-operation rates are quoted as 10% [166] but are up to 50% higher in those with polysyndactyly [188]. It is imperative that follow-up should be continued until skeletal maturity to detect complications, particularly joint deformity, which may require arthrodesis.

There have been concerns that graft-free repairs may be associated with a higher incidence of web creep, thought to be related to increased tension leading to scar contractures. Niranjan et al. [186], however, published long-term outcome data of "graft-free" repairs with a mean follow-up time of 6.6 years, and found superior cosmetic results and good functional outcome.

It is thought that an increased incidence of web creep is seen in dorsal rectangular flaps due to linear scar contracture along the palmar border. Miyamoto et al. [189] performed an analysis of scar stress and web creep using CT reconstructions and found that the dorsal rectangular flap was associated with greater stresses than those seen in palmar rectangular or dorsal V-shaped flaps. The authors advocated that a palmar break should be incorporated into any syndactyly repair to reduce scar contracture in the linear palmar scar and thus reduce the incidence of web creep.

Despite the abundance of techniques available for syndactyly reconstruction, it remains unclear as to which procedure is superior in terms of various outcomes and more data is needed to assess this.

Future Management Options

In view of the development of genetic and perinatal investigation for syndactyly, future management could be aimed at in utero intervention. The role of gestational ultrasound scans has allowed early diagnosis of upper limb anomalies and can now be supplemented with genetic review of those likely to be carriers. An animal study has observed that amniotic constriction bands can be released in utero to allow limb development to continue in a more anatomical manner [190].

Husler et al. [191] report seven cases of fetoscopic release of amniotic bands resulting in limb anomalies in the human fetus, but with few resulting in functional improvement. Incidence of premature rupture of membrane was high, and with one case of intrauterine death. Currently, the risks of complications in fetoscopic intervention do not outweigh the proposed benefits, particularly as the underlying condition described is nonfatal.

Use of synthetic dermal substitutes may be another exciting avenue of future research with need for trials to assess their outcome when compared to traditional skin grafts and flaps.

References

1. Canale ST, Beaty JH. Campbell's operative orthopaedics, vol. 4. 11th ed. Philadelphia: Mosby Elsevier; 2008. p. 4403–4.
2. Green DP, Hotchkiss RN, Pederson WC, Wolfe SW. Green's operative hand surgery, vol. 2. 5th ed. Philadelphia, PA: Mosby Elsevier; 2005. p. 1381–2.
3. Burke FD, McGrouther DA, Smith PJ. Principles of hand surgery, chapter 15. Edinburgh: Churchill Livingstone; 1989. p. 256.
4. Eaton CJ, Lister GD. Syndactyly. Hand Clin. 1990;6(4):555.
5. Kozin SH. Syndactyly. J Am Soc Surg Hand. 2001;1:1–13.
6. Benson MKD, Fixen JA, Macnicol MF, Parsch K. Children's orthopaedics and fractures. 2nd ed. Edinburgh: Churchill Linigston; 2002. p. 306–307.

7. Netscher DT, Baumholtz MA. Treatment of congenital upper extremity problems. Plast Reconstr Surg. 2007;119(5):101e–29.
8. Hogan BL. Morphogenesis. Cell. 1999;96:225–33.
9. Oligny LL. Human molecular embryogenesis: an overview. Pedatr Dev Pathol. 2001;4:324–43.
10. Mariani FV, Martin GR. Deciphering skeletal patterning: clues from the limb. Nature. 2003;423:319–25.
11. Saunders JW. The proximo-distal sequence of origin of the parts of the chick wing and the role of the ectoderm. J Exp Zool. 1948;108(3):363–403.
12. Saunders JW, Gasseling MT. Ectodermal-mesodermal interactions in the origin of limb symmetry. In: Fleischmajer RE, Billingham R, editors. Epithelial-mesenchymal interactions. Baltimore: Williams & Wilkins; 1968. p. 78–97.
13. Todt WL, Fallon JF. Posterior apical ectodermal ridge removal in the chick wing bud triggers a series of events resulting in defective anterior pattern formation. Development. 1987;101(3):501–15.
14. Ahmed H, Akbari H, Emami A, Akbari MR. Genetic overview of syndactyly and polydactyly. Plast Reconstr Surg Glob Open. 2017;5(11):e1549.
15. Manouvrier-Hanu S, Holder-Espinasse M, Lyonnet S. Genetics of limb anomalies in humans. Trends Genet. 1999;15(10):409–17.
16. Ingham PW, McMahon AP. Hedgehog signalling in animal development. Genes Dev. 2001;15:3059–87.
17. Riddle RD, Johnson RL, Laufer E, Tabin C. Sonic hedgehog mediates the polarizing activity of the ZPA. Cell. 1993;75(7):1401–16.
18. Vortkamp A, Lee K, Lanske B, Segre GV, Kronenberg HM, Tabin CJ. Regulation of rate of cartilage differentiation by Indian hedgehog and PTH-related protein. Science. 1996;273(5275):613–22.
19. Naski MC, Omitz DM. FGF signalling in skeletal development. Front Biosci. 1998;3:D781–94.
20. Ohbayashi N, Shibayama M, Kurotaki Y, Imanishi M, Fujimori T, Itoh N, et al. FGF18 is required for normal cell proliferation and differentiation during osteogenesis and chondrogenesis. Genes Dev. 2002;16:870–9.
21. Chung UI, Schipani E, McMahon AP, Kronenberg HM. Indian hedgehog couples chondrogenesis to osteogenesis in endochondral bone development. J Clin Invest. 2001;107:295–304.
22. Klopocki E, Lohan S, Brancati F, Koll R, Brehm A, Seemann P, et al. Copy-number variations involving the IHH locus are associated with syndactyly and craniosynostosis. Am J Hum Genet. 2011;88(1):70–5. Epub 2010 Dec 17.
23. Gofflot F, Hars C, Illien F, Chevy F, Wolf C, Picard JJ, et al. Molecular mechanisms underlying limb anomalies associated with cholesterol deficiency during gestation: implications of hedgehog signalling. Hum Mol Genet. 2003;12(10):1187–98.
24. Litingtung Y, Dahn RD, Yina L, Fallon JF, Chiang C. Shh and Gli3 are dispensable for limb skeleton formation but regulate digit number and identity. Nature. 2002;418:979–83.
25. Welscher P, Zuniga A, Kuijper S, Drenth T, Goedemans HJ, Meijlink F, et al. Progression of vertebrate limb development through Shh-mediated counteraction of Gli3. Science. 2002;298(5594):827–30.
26. Chiang C, Litingtung Y, Harris MP, Simandl BK, Li Y, Beachy PA, et al. Manifestation of the limb prepattern: limb development in the absence of sonic hedgehog function. Dev Biol. 2001;236:421–35.
27. Kraus P, Fraidenraich D, Loomis CA. Some distal limb structures develop in mice lacking sonic hedgehog signalling. Mech Dev. 2001;100:45–58.
28. Drossopoulou G, Lewis KE, Sanz-Ezquerro JJ, Nikbakht N, McMahon AP, Hofmann C, et al. A model for anteroposterior patterning of the vertebrate limb based on sequential long and short range Shh signalling and bmp signalling. Development. 2000;127:1337–48.
29. Kawakami Y, Capdevilla J, Buscher D, Itoh T, Rodríguez Esteban C, Izpisúa Belmonte JC. WNT signals control FGF-dependent limb initiation and AER induction in the chick embryo. Cell. 2001;104:891–900.
30. Rankin J, Strachan T, Lako M, Lindsay S. Partial cloning and assignment of WNT6 to human chromosome band 2q35 by in situ hybridization. Cytogenet Cell Genet. 1999;84:50–2.
31. Parr BA, Shea MJ, Vassileva G, McMahon AP. Mouse WNT genes exhibit discrete domains of expression in the early embryonic CNS and limb buds. Development. 1993;119(1):247–61.
32. Khan S, Basit S, Zimri F, Ali N, Ali G, Ansar M, et al. A novel homozygous missense mutation in WNT10B in familial split-hand/foot malformation. Clin Genet. 2012;82(1):48–55.
33. Mori C, Nakamura N, Kimura S, Irie H, Takigawa T, Shiota K. Programmed cell death in the interdigital tissue of the fetal mouse limb is apoptosis with DNA fragmentation. Anat Rec. 1995;242:103–10.
34. Nishii K, Tsuzuki T, Kumai M, Takeda N, Koga H, Aizawa S, et al. Abnormalities of developmental cell death in Dad1-deficient mice. Genes. 1999;4(4):243–52.
35. Salas-Vidal E, Valencia C, Covarrubias L. Differential tissue growth and patterns of cell death in mouse limb autopod morphogenesis. Dev Dyn. 2001;220:295–306.
36. Merino R, Rodriguez-Leon J, Macias D, Gañan Y, Economides AN, Hurle JM. The BMP antagonist Gremlin regulates outgrowth, chondrogenesis and programmed cell death in the developing limb. Development. 1999;126:5515–22.
37. Crocoll A, Herzer U, Ghyselinck NB, Chambon P, Cato AC. Interdigital apoptosis and downregulation of BAG-1 expression in mouse autopods. Mech Dev. 2002;111:149–52.

38. Heymer J, Rüther U. Syndactyly of Ft/+mice correlates with an imbalance in bmp4 and fgf8 expression. Mech Dev. 1999;88(2):173–81.
39. Schwabe GC, Mundlos S. Genetics of congenital hand anomalies. Handchir Mikrochir Plast Chir. 2004;36:85–97.
40. Francis PH, Richardson MK, Brickell PM, Tickle C. Bone morphogenetic proteins and a signalling pathway that controls patterning in the developing chick limb. Development. 1994;120:209–18.
41. Lyons KM, Hogan BL, Robertson EJ. Colocalization of BMP 7 and BMP 2 RNAs suggests that these factors cooperatively mediate tissue interactions during murine development. Mech Dev. 1995;50:71–83.
42. Laufer E, Dahn R, Orozco OE, Yeo CY, Pisenti J, Henrique D, et al. Expression of radical fringe in limb-bud ectoderm regulates apical ectodermal ridge formation. Nature. 1997;386:366–73.
43. Ganan Y, Macias D, Duterque-Coquillaud M, Ros MA, Hurle JM. Role of TGF beta s and BMPs as signals controlling the position of the digits and the areas of interdigital cell death in the developing chick limb autopod. Development. 1996;122:2349–57.
44. Zuzarte-Luis V, Hurle JM. Programmed cell death in the developing limb. Int J Dev Biol. 2002;46:871–6.
45. Guha U, Gomes WA, Kobayashi T, Pestell RG, Kessler JA. In vivo evidence that BMP signalling is necessary for apoptosis in the mouse limb. Dev Biol. 2002;249(1):108–20.
46. Yokouchi Y, Sakiyama J, Kameda T, Iba H, Suzuki A, Ueno N, et al. BMP 2/4 mediate programmed cell death in chicken limb buds. Development. 1996;122:3725–34.
47. Zou H, Niswander L. Requirement for BMP signalling in interdigital apoptosis and scale formation. Science. 1996;272:738–41.
48. Arteaga-Solis E, Gayraud B, Lee SY, Shum L, Sakai L, Ramirez F. Regulation of limb patterning by extracellular microfibrils. J Cell Biol. 2001;154(2):275–81.
49. Dahn RD, Fallon JF. Interdigital regulation of digit identity and homeotic transformation by modulated BMP signalling. Science. 2000;289:438–41.
50. McCulloch DR, Nelson CM, Dixon LJ, Silver DL, Wylie JD, Lindner V, et al. ADAMTS metalloproteases generate active versican fragments that regulate interdigital web regression. Dev Cell. 2009;17(5):687–98.
51. Talamillo A, Delgado I, Nakamura T, de-Vega S, Yoshitomi Y, Unda F, et al. Role of Epiprofin, a zinc-finger transcription factor, in limb development. Dev Biol. 2010;337(2):363–74.
52. Ota S, Zhou ZQ, Keene DR, Knoepfler P, Hurlin PJ. Activities of N-Myc in the developing limb link control of skeletal size with digit separation. Development. 2007;134(8):1583–92.
53. Vortkamp A, Gessler M, Grzeschik KH. GLI3 zinc-finger gene interrupted by translocations in Greig syndrome families. Nature. 1991;352:539–40.
54. Johnston JJ, Sapp JC, Turner JT, Amor D, Aftimos S, Aleck KA, et al. Molecular analysis expands the spectrum of phenotypes associated with GLI3 mutations. Hum Mutat. 2010;31(10):1142–54.
55. Ricks CB, Masand R, Fang P, Roney EK, Cheung SW, Scott DA. Delineation of a 1.65 Mb critical region for hemihyperplasia and digital anomalies on Xq25. Am J Med Genet A. 2010;152A(2):453–8.
56. Schmidt K, Hughes C, Chudek JA, Goodyear SR, Aspden RM, Talbot R, et al. Cholesterol metabolism: the main pathway acting downstream of cytochrome P450 oxidoreductase in skeletal development of the limb. Mol Cell Biol. 2009;29(10):2716–29.
57. Lv D, Luo Y, Yang W, Cao L, Wen Y, Zhao X, et al. A novel single-base deletion in ROR2 causes atypical brachydactyly type B1 with cutaneous syndactyly in a large Chinese family. J Hum Genet. 2009;54(7):422–5.
58. Böse K, Nischt R, Page A, Bader BL, Paulsson M, Smyth N. Loss of nidogen-1 and -2 results in syndactyly and changes in limb development. J Biol Chem. 2006;281(51):39620–9.
59. Liu Y, Liu C, Yamada Y, Fan CM. Growth arrest specific gene 1 acts as a region-specific mediator of the Fgf10/Fgf8 regulatory loop in the limb. Development. 2002;129(22):5289–300.
60. Dauwerse JG, de Vries BB, Wouters CH, Bakker E, Rappold G, Mortier GR, et al. A t(4;6)(q12;p23) translocation disrupts a membrane-associated O-acetyl transferase gene (MBOAT1) in a patient with a novel brachydactyly-syndactyly syndrome. Eur J Hum Genet. 2007;15(7):743–51.
61. Jiang R, Lan Y, Chapman HD, Shawber C, Norton CR, Serreze DV, et al. Defects in limb, craniofacial, and thymic development in Jagged2 mutant mice. Genes Dev. 1998;12(7):1046–57.
62. Sidow A, Bulotsky MS, Kerrebrock AW, Bronson RT, Daly MJ, Reeve MP, et al. Serrate2 is disrupted in the mouse limb-development mutant syndactylism. Nature. 1997;389(6652):722–5.
63. Hwang SJ, Beaty TH, McIntosh I, Hefferon T, Panny SR. Association between homeobox-containing gene MSX1 and the occurrence of limb deficiency. Am J Med Genet. 1998;75(4):419–23.
64. Goodman FR. Limb malformations and the human HOX genes. Am J Med Genet. 2002;112(3):256–65.
65. McKusick VA. www.usfca.edu/Library/databases/OMIM/ and Mendelian inheritance in man. 12th ed. Baltimore: Johns Hopkins University Press; 1998.
66. Temtamy SA, McKusick VA. The genetics of hand malformations. New York, NY: Alan R. Liss New York; 1978. p. 301–22.
67. Goldstein DJ, Kambouris M, Ward RE. Familial crossed polysyndactyly. Am J Med Genet. 1994;50:215–23.
68. Malik S, Percin FE, Ahmad W, Percin S, Akarsu NA, Koch MC, et al. Autosomal recessive mesoaxial synostotic syndactyly with phalangeal reduction maps to chromosome 17p13.3. Am J Med Genet A. 2005;134(4):404–8.

69. Jordan D, Hindocha S, Dhital M, Saleh M, Khan W. The epidemiology, genetics and future management of syndactyly. Open Orthop J. 2012;6:14–27.
70. Percin EF, Percin S. Two unusual types of syndactyly in the same family; Cenani-Lenz type and "new" type versus severe type I syndactyly? Genet Couns. 2003;14(3):313–9.
71. Bosse K, Betz RC, Lee YA, Wienker TF, Reis A, Kleen H, et al. Localization of a gene for syndactyly type 1 to chromosome 2q34-q36. Am J Hum Genet. 2000;67(2):492–7.
72. Ghadami M, Majidzadeh-A K, Haerian BS, Damavandi E, Yamada K, Pasallar P, et al. Confirmation of genetic homogeneity of syndactyly type 1 in an Iranian family. Am J Med Genet. 2001;104(2):147–51.
73. Robin NH, Segel B, Carpenter G, Muenke M. Craniosynostosis, Philadelphia type: a new autosomal dominant syndrome with sagittal craniosynostosis and syndactyly of the fingers and toes. Am J Med Genet. 1996;62:184–91.
74. Jain M, Wallis D, Robin NH, De Vrieze FW, Hardy JA, Ghadami M, et al. Locus homogeneity between syndactyly type 1A and craniosynostosis Philadelphia type? Am J Med Genet A. 2008;146A:2308–11.
75. Rossant J. ENU mutants from the Center of Modeling Human Disease. MGI Direct Data Submission. 2004;Accession ID MGI:3032560.
76. Malik S, Schott J, Ali SW, Oeffner F, Amin-ud-Din M, Ahmad W, et al. Evidence for clinical and genetic heterogeneity of syndactyly type I: the phenotype of second and third toe syndactyly maps to chromosome 3p21.31. Eur J Hum Genet. 2005;13:1268–74.
77. Sarfarazi M, Akarsu AN, Sayli BS. Localization of the syndactyly type II (synpolydactyly) locus to 2q31 region and identification of tight linkage to HOXD8 intragenic marker. Hum Mol Genet. 1995;4:1453–8.
78. Dai L, Heng ZC, Zhu J, Cai R, Mao M, Wang H, et al. Mutation analysis of HOXD13 gene in a Chinese pedigree with synpolydactyly. Zhonghua Yi Xue Yi Chuan Xue Za Zhi. 2005;22(3):277–80.
79. Wajid M, Ishii Y, Kurban M, Dua-Awereh MB, Shimomura Y, Christiano AM. Polyalanine repeat expansion mutations in the HOXD13 gene in Pakistani families with synpolydactyly. Clin Genet. 2009;76(3):300–2.
80. Muragaki Y, Mundlos S, Upton J, Olsen BR. Altered growth and branching patterns in synpolydactyly caused by mutations in HOXD13. Science. 1996;272(5261):548–51.
81. Akarsu AN, Stoilov I, Yilmaz E, Sayli BS, Sarfarazi M. Genomic structure of HOXD13 gene: a nine polyalanine duplication causes synpolydactyly in two unrelated families. Hum Mol Genet. 1996;5:945–52.
82. Goodman FR, Majewski F, Collins AL, Scambler PJ. A 117-kb microdeletion removing HOXD9-HOXD13 and EVX2 causes synpolydactyly. Am J Hum Genet. 2002;70:547–55.
83. Goodman FR, Mundlos S, Muragaki Y, Donnai D, Giovannucci-Uzielli ML, Lapi E, et al. Synpolydactyly phenotypes correlate with size of expansions in HOXD13 polyalanine tract. Proc Natl Acad Sci U S A. 1997;94:7458–63.
84. Malik S, Girisha KM, Wajid M, Roy AK, Phadke SR, Haque S, et al. Synpolydactyly and HOXD13 polyalanine repeat: addition of 2 alanine residues is without clinical consequences. BMC Med Genet. 2007;8:78.
85. Zhao X, Sun M, Zhao J, Leyva JA, Zhu H, Yang W, et al. Mutations in HOXD13 underlie syndactyly type V and a novel brachydactyly-syndactyly syndrome. Am J Hum Genet. 2007;80(2):361–71.
86. Ghoumid J, Andrieux J, Sablonniere B, Odent S, Philippe N, Zanlonghi X, et al. Duplication of chromosome 2q31.1-q31.2 in a family presenting syndactyly and nystagmus. Eur J Hum Genet. 2011;19(11):1198–201.
87. Debeer P, Schoenmakers EF, Twal WO, Argraves WS, De Smet L, Fryns JP, et al. The fibulin-1 gene (FBLN1) is disrupted in a t (12;22) associated with a complex type of synpolydactyly. Med Genet. 2002;39(2):98–104.
88. Debeer P, Schoenmakers EF, De Smet L, Van de Ven WJ, Fryns JP. Co-segregation of an apparently balanced reciprocal t(12;22)(p11.2;q13.3) with a complex type of 3/3′/4 synpolydactyly associated with metacarpal, metatarsal and tarsal synostoses in three family members. Clin Dysmorphol. 1998;7(3):225–8.
89. Debeer P, Schoenmakers EF, Thoelen R, Holvoet M, Kuittinen T, Fabry G, et al. Physical map of a 1.5 mb region on 12p11.2 harbouring a synpolydactyly associated chromosomal breakpoint. Eur J Hum Genet. 2000;8(8):561–70.
90. Malik S, Abbasi AA, Ansar M, Ahmad W, Koch MC, Grzeschik KH. Genetic heterogeneity of synpolydactyly: a novel locus SPD3 maps to chromosome 14q11.2-q12. Clin Genet. 2006;69(6):518–24.
91. Malik S, Grzeschik KH. Synpolydactyly: clinical and molecular advances. Clin Genet. 2008;73(2):113–20.
92. Kuru I, Samli H, Yucel A, Bozan ME, Turkmen S, Solak M. Hypoplastic synpolydactyly as a new clinical subgroup of synpolydactyly. Hand Surg Br. 2004;29(6):614–20.
93. Ikegawa M, Han H, Okamoto A, Matsui R, Tanaka M, Omi N, et al. Syndactyly and preaxial synpolydactyly in the single Sfrp2 deleted mutant mice. Dev Dyn. 2008;237(9):2506–17.
94. Johnston O, Kirby VV. Syndactyly of the ring and little finger. Am J Hum Genet. 1955;7:80–2.
95. De Smet L, Mulier T, Fabry G. Syndactyly of the ring and small finger. Genet Couns. 1994;5:45–9.
96. Schrander-Stumpel CTRM, de Groot-Wijnands JBG, de Die-Smulders C, Fryns JP. Type III syndactyly and oculodentodigital dysplasia: a clinical spectrum. Genet Couns. 1993;4:271–6.
97. Gladwin A, Donnai D, Metcalfe K, Schrander-Stumpel C, Brueton L, Verloes A, et al. Localization

of a gene for oculodentodigital syndrome to human chromosome 6q22-q24. Hum Mol Genet. 1997;6(1):123–7.
98. Paznekas WA, Boyadjiev SA, Shapiro RE, Daniels O, Wollnik B, Keegan CE, et al. Connexin 43 (GJA1) mutations cause the pleiotropic phenotype of oculodentodigital dysplasia. Am J Hum Genet. 2003;72:408–18.
99. Richardson R, Donnai D, Meire F, Dixon MJ. Expression of Gja1 correlates with the phenotype observed in oculodentodigital syndrome/type III syndactyly. J Med Genet. 2004;41(1):60–7.
100. Dobrowolski R, Hertig G, Lechner H, Wörsdörfer P, Wulf V, Dicke N, et al. Loss of connexin43-mediated gap junctional coupling in the mesenchyme of limb buds leads to altered expression of morphogens in mice. Hum Mol Genet. 2009;18(15):2899–911.
101. Fenwick A, Richardson RJ, Butterworth J, Barron MJ, Dixon MJJ. Novel mutations in GJA1 cause oculodentodigital syndrome. Dent Res. 2008;87(11):1021–6.
102. Amador C, Mathews AM, Del Carmen MM, Laughridge ME, Everman DB, Holden KR. Expanding the neurologic phenotype of oculodentodigital dysplasia in a 4-generation Hispanic family. J Child Neurol. 2008;23(8):901–5.
103. Debeer P, Van Esch H, Huysmans C, Pijkels E, De Smet L, Van de Ven W, et al. Novel GJA1 mutations in patients with oculo-dento-digital dysplasia (ODDD). Eur J Med Genet. 2005;48(4):377–87.
104. Jamsheer A, Wisniewska M, Szpak A, Bugaj G, Krawczynski MR, Budny B, et al. A novel GJA1 missense mutation in a polish child with oculodentodigital dysplasia. Appl Genet. 2009;50(3):297–9.
105. Dobrowolski R, Sasse P, Schrickel JW, Watkins M, Kim JS, Rackauskas M, et al. The conditional connexin43G138R mouse mutant represents a new model of hereditary oculodentodigital dysplasia in humans. Hum Mol Genet. 2008;17(4):539–54.
106. Dobrowolski R, Sommershof A, Willecke K. Some oculodentodigital dysplasia-associated Cx43 mutations cause increased hemichannel activity in addition to deficient gap junction channels. J Membr Biol. 2007;219(1–3):9–17.
107. van Es RJ, Wittebol-Post D, Beemer FA. Oculodentodigital dysplasia with mandibular retrognathism and absence of syndactyly: a case report with a novel mutation in the connexin 43 gene. Int J Oral Maxillofac Surg. 2007;36(9):858–60.
108. Vreeburg M, de Zwart-Storm EA, Schouten MI, Nellen RG, Marcus-Soekarman D, Devies M, et al. Skin changes in oculo-dento-digital dysplasia are correlated with C-terminal truncations of connexin 43. Am J Med Genet A. 2007;143(4):360–3.
109. Wiest T, Herrmann O, Stögbauer F, Grasshoff U, Enders H, Koch MJ, et al. Clinical and genetic variability of oculodentodigital dysplasia. Clin Genet. 2006;70(1):71–2.
110. Haas SL. Bilateral complete syndactylism of all fingers. Am J Surg. 1940;50:363–6.
111. Sato D, Liang D, Wu L, Pan Q, Xia K, Dai H, et al. Syndactyly type IV locus maps to 7q36. J Hum Genet. 2007;52:561–4.
112. Rambaud-Cousson A, Dudin AA, Zuaiter AS, Thalji A. Syndactyly type IV/hexadactyly of feet associated with unilateral absence of the tibia. Am J Med Genet. 1991;40:144–5.
113. Gillessen-Kaesbach G, Majewski F. Bilateral complete polysyndactyly (type IV Haas). Am J Med Genet. 1991;38:29–31.
114. Wieczorek D, Pawlik B, Li Y, Akarsu NA, Caliebe A, May KJ, et al. A specific mutation in the distant sonic hedgehog (SHH) cis-regulator (ZRS) causes Werner mesomelic syndrome (WMS) while complete ZRS duplications underlie Haas type polysyndactyly and preaxial polydactyly (PPD) with or without triphalangeal thumb. Hum Mutat. 2010;31(1):81–9.
115. Sun M, Ma F, Zeng X, Liu Q, Zhao XL, Wu FX, et al. Triphalangeal thumb-polysyndactyly syndrome and syndactyly type IV are caused by genomic duplications involving the long range, limb-specific SHH enhancer. J Med Genet. 2008;45:589–95.
116. Wang ZQ, Tian SH, Shi YZ, Zhou PT, Wang ZY, Shu RZ, et al. A single C to T transition in intron 5 of LMBR1 gene is associated with triphalangeal thumb-polysyndactyly syndrome in a Chinese family. Biochem Biophys Res Commun. 2007;355(2):312–7.
117. Kemp T, Ravn J. Ueber erbliche Hand-und Fussdeformitaeten in einem 140-koepfigen Geschlecht, nebst einigen Bemerkungen ueber Poly- und Syndaktylie beim Menschen. Acta Psychiatr Neurol Scand. 1932;7:275–96.
118. Robinow M, Johnson GF, Broock GJ. Syndactyly type V. Am J Med Genet. 1982;11:475–82.
119. Kjaer KW, Hansen L, Eiberg H, Utkus A, Skovgaard LT, Leicht P, et al. A 72-year-old Danish puzzle resolved—comparative analysis of phenotypes in families with different-sized HOXD13 polyalanine expansions. Am J Med Genet. 2005;138A:328–39.
120. Cenani A, Lenz W. Totale Syndaktylie und totale radioulnare Synostose bie zwei Bruedern. Ein Beitrag zur Genetik der Syndaktylien Ztschr Kinderheilk. 1967;101:181–90.
121. Liebenam L. Ueber gleichzeitiges Vorkommen von Gliedmassendefekten und osteosklerotischer Systemerkrunkung. Ztschr Mensch Vererbungs-und Konstitutionslehre. 1938;21:697–703.
122. Borsky AJ. Congenital anomalies of the hand and their surgical treatment. Charles C Thomas: Springfield, IL; 1958.
123. Yelton CL. Certain congenital limb deficiencies occurring in twins and half siblings. Inter-Clinic Inform Bull. 1962;1:1–7.
124. Drögemüller C, Leeb T, Harlizius B, Tammen I, Distl O, Höltershinken M, et al. Congenital syndactyly in cattle: four novel mutations in the low density lipoprotein receptor-related protein 4 gene (LRP4). BMC Genet. 2007;8:5.

125. Simon-Chazottes D, Tutois S, Kuehn M, Evans M, Bourgade F, Cook S, et al. Mutations in the gene encoding the low-density lipoprotein receptor LRP4 cause abnormal limb development in the mouse. Genomics. 2006;87(5):673–7.
126. Li Y, Pawlik B, Elcioglu N, Aglan M, Kayserili H, Yigit G, et al. LRP4 mutations alter Wnt/beta-catenin signaling and cause limb and kidney malformations in Cenani-Lenz syndrome. Am J Hum Genet. 2010;86(5):696–706.
127. Bacchelli C, Goodman FR, Scambler PJ, Winter RM. Cenani-Lenz syndrome with renal hypoplasia is not linked to FORMIN or GREMLIN. Clin Genet. 2001;59:203–5.
128. Dimitrov BI, Voet T, De Smet L, Vermeesch JR, Devriendt K, Fryns JP, et al. Genomic rearrangements of the GREM1–FMN1 locus cause oligosyndactyly, radio-ulnar synostosis, hearing loss, renal defects syndrome and Cenani–Lenz-like non-syndromic oligosyndactyly. J Med Genet. 2010;47(8):569–74.
129. Harpf C, Pavelka M, Hussl H. A variant of Cenani-Lenz syndactyly (CLS): review of the literature and attempt of classification. Br J Plast Surg. 2005;58(2):251–7.
130. Orel H. Kleine Beitrage zur Vererbungswissenschaft. Synostosis Metacarpi Quarti et Quinti Z Anat. 1928;14:244–52.
131. Lonardo F, Della Monica M, Riccardi G, Riccio I, Riccio V, Scarano G. A family with X-linked recessive fusion of metacarpals IV and V. Am J Med Genet. 2004;124A:407–10.
132. Holmes LB, Wolf E, Miettinen OS. Metacarpal 4-5 fusion with X-linked recessive inheritance. Am J Hum Genet. 1972;24:562–8.
133. Lerch H. Erbliche Synostosen der Ossa metacarpalia IV und V. Z Orthop. 1948;78:13–6.
134. Faiyaz-Ul-Haque M, Zaidi SHE, King LM, Haque S, Patel M, Ahmad M, et al. Fine mapping of the X-linked split-hand/split-foot malformation (SHFM2) locus to a 5.1-Mb region on Xq26.3 and analysis of candidate genes. Clin Genet. 2005;67:93–7.
135. Percin EF, Percin S, Egilmez H, Sezgin I, Ozbas F, Akarsu AN. Mesoaxial complete syndactyly and synostosis with hypoplastic thumbs: an unusual combination or homozygous expression of syndactyly type I. J Med Genet. 1998;35(10):868–74.
136. Malik S, Arshad M, Amin-ud-Din M, Oeffner F, Dempfle A, Haque S, et al. A novel type of autosomal recessive syndactyly: clinical and molecular studies in a family of Pakistani origin. Am J Med Genet. 2004;126A:61–7.
137. Losch G, Duncker H. Acrosyndactylism. Transactions of the International Society of Plastic and Reconstructive Surgeons, 5th congress. Butterworth Pty: Melbourne; 1971.
138. Patterson T. Congenital ring constrictions. Br J Plast Surg. 1961;14:1–31.
139. Torpin R, Faulkner A. Intrauterine amputation with the missing member found in the fetal membranes. JAMA. 1966;198:185–7.
140. Upton J. Congenital anomalies of the hand and forearm. In: McCarthy JG, May Jr JW, Littler JW, editors. The hand, vol. 8. Plastic surgery. Philadelphia: WB Saunders; 1990. p. 5213–5398.
141. Walsh RJ. Acrosyndactyly. A study of twenty-seven patients. Clin Orthop. 1970;71:99–111.
142. Maisels D. Acrosyndactyly. Br J Plast Surg. 1962;15:166–72.
143. Poland A. Deficiency of the pectoral muscles. Guys Hosp Rep. 1841, VI:191–3.
144. Clarkson P. Poland's syndactyly. Guys Hosp Rep. 1962;111:335–46.
145. Bouvet J, Leveque D, Bernetieres F, Gros JJ. Vascular origin of Poland syndrome: a comparative rheographic study of the vascularisation of the arms in eight patients. Eur J Pediatr. 1978;128:17–26.
146. Fraser FC, Ronen GM, O'Leary E. Pectoralis major defect and Poland sequence in second cousins: extension of the Poland sequence spectrum. Am J Med Genet. 1989;33:468–70.
147. Bouwes-Bavinck J, Weaver D. Subclavian artery supply disruption sequence: hypothesis of a vascular etiology for Poland, Klippel-Feil, and Mobius anomalies. Am J Med Genet. 1986;23:903–18.
148. Wilson M, Louis DS, Stevenson TR. Poland's syndrome: variable expression and associated anomalies. J Hand Surg Am. 1988;13:880–2.
149. Karnak I, Tanyel FC, Tunçbilek E, Unsal M, Büyükpamukçu N. Bilateral Poland anomaly. Am J Med Genet. 1998;75(5):505–7.
150. Wilkie AOM, Slaney SF, Oldridge M, Poole MD, Ashworth GJ, Hockley AD, et al. Apert syndrome results from localized mutations of FGFR2 and is allelic with Crouzon syndrome. Nat Genet. 1995;9:165–72.
151. Howard TD, Paznekas WA, Green ED, Chiang LC, Ma N, Ortiz de Luna RI, et al. Mutations in TWIST, a basic helix-loop-helix transcription factor, in Saethre-Chotzen syndrome. Nat Genet. 1997;15:36–41.
152. Paznekas WA, Cunningham ML, Howard TD, Korf BR, Lipson MH, Grix AW, et al. Genetic heterogeneity of Saethre-Chotzen syndrome, due to TWIST and FGFR mutations. Am J Hum Genet. 1998;62:1370–80.
153. Muenke M, Schell U, Hehr A, Robin NH, Losken HW, Schinzel A, et al. A common mutation in the fibroblast growth factor receptor 1 gene in Pfeiffer syndrome. Nat Genet. 1994;8:269–74.
154. Rossi M, Jones RL, Norbury G, Bloch-Zupan A, Winter R. The appearance of the feet in Pfeiffer syndrome caused by FGFR1 P252R mutation. Clin Dysmorphol. 2003;12:269–74.
155. Jenkins D, Seelow D, Jehee FS, Perlyn CA, Alonso LG, Bueno DF, et al. RAB23 mutations in Carpenter

syndrome imply an unexpected role for hedgehog signaling in cranial-suture development and obesity. Am J Hum Genet. 2007;80:1162–70. Note: Erratum: Am. J. Hum. Genet. 81: 1114 only, 2007.
156. Cohen DM, Green JG, Miller J, Gorlin RJ, Reed JA. Acrocephalopolysyndactyly type II—Carpenter syndrome: clinical spectrum and an attempt at unification with Goodman and Summitt syndromes. Am J Med Genet. 1987;28:311–24.
157. McGregor L, Makela V, Darling SM, Vrontou S, Chalepakis G, Roberts C, et al. Fraser syndrome and mouse blebbed phenotype caused by mutations in FRAS1/Fras1 encoding a putative extracellular matrix protein. Nat Genet. 2003;34:203–8.
158. Shafeghati Y, Kniepert A, Vakili G, Zenker M. Fraser syndrome due to homozygosity for a splice site mutation of FREM2. Am J Med Genet. 2008;146A:529–31.
159. Carney TJ, Feitosa NM, Sonntag C, Slanchev K, Kluger J, Kiyozumi D, et al. Genetic analysis of fin development in zebrafish identifies furin and hemicentin1 as potential novel Fraser syndrome disease genes. PLoS Genet. 2010;6(4):e1000907.
160. Garagnani L, Smith GD. Syndromes associated with syndactyly. In: The pediatric upper extremity. New York: Springer; 2014. p. 1–31.
161. Malik S, Ahmad W, Grzeschik KH, Koch MC. A simple method for characterising syndactyly in clinical practice. Genet Couns. 2005;16:229–38.
162. Winter RM, Tickle C. Syndactylies and polydactilies: embryological overview and suggested classification. Eur J Hum Genet. 1993;1:96–104.
163. Man LX, Chang B. Maternal cigarette smoking during pregnancy increases the risk of having a child with a congenital digital anomaly. Plast Reconstr Surg. 2006;117(1):301–8.
164. Luo JY, Fu CH, Yao KB, Hu RS, Qy D, Liu ZY. A case-control study on genetic and environmental factors regarding polydactyly and syndactyly. Zhonghua Liu Xing Bing Xue Za Zhi. 2009;30(9):903–6.
165. Lorea P, Coessens BC. Evolution of surgical techniques for skin release. Eur J Plast Surg. 2001;24:275–81.
166. Oda T, Pushman AG, Chung KC. Treatment of common congenital hand conditions. Plast Reconstr Surg. 2010;126(3):121e–33.
167. Kettelkamp DB, Flatt AE. An evaluation of syndactylia repair. Surg Gynecol Obstet. 1961;113:471–8.
168. Dao K, Shin AY, Billings A. Surgical treatment of congenital syndactyly of the hand. J Am Acad Orthop Surg. 2004;12:39–48.
169. Hutchinson DT, Frenzen SW. Digital syndactyly release. Tech Hand Up Extrem Surg. 2010;14(1):33–7.
170. Deunck J, Nicolai JP, Hamburg SM. Long-term results of syndactyly correction: full-thickness versus split-thickness skin grafts. J Hand Surg Br. 2003;28(2):125–30.
171. Lumenta DB, Kitzinger HB, Beck H, Frey M. Long-term outcomes of web creep, scar quality and function after simple syndactyly surgical treatment. J Hand Surg Am. 2010;35(8):1323–9.
172. Kamath JB, Vardhan H, Naik DM, Bansal A, Rai M, Kumar A. A novel method of using mini external fixator for maintaining web space after the release of contracture and syndactyly. Tech Hand Up Extrem Surg. 2013;17(1):37–40.
173. Aydin A, Ozden BC. Dorsal metacarpal island flap in syndactyly treatment. Ann Plast Surg. 2004;52(1):43–8.
174. Sharma RK, Tuli P, Makkar SS, Parashar A. End-f-skin grafts in syndactyly release: description of a new flap for web resurfacing and primary closure of finger defects. Hand. 2009;4(1):29–34.
175. Gao W, Yan H, Zhang F, Jiang L, Wang A, Yang J, et al. Dorsal pentagonal local flap: a new technique of web reconstruction for syndactyly without skin graft. Aesthet Plast Surg. 2011;35(4):530–7.
176. Wang S, Zheng S, Li N, Feng Z, Liu Q. Dorsal hexagon local flap without skin graft for web reconstruction of congenital syndactyly. J Hand Surg Am. 2020;45(1):63.e1–9.
177. Yao JM, Shong JL, Sun H. Repair of incomplete simple syndactyly by a web flap on a subcutaneous tissue pedicle. Plast Reconstr Surg. 1997;99:2079–81.
178. Tadiparthi S, Mishra A, Mcarthur P. A modification of the Chinese island flap technique for simple incomplete syndactyly release. J Hand Surg Eur Vol. 2009;34(1):99–103.
179. Greuse M, Coessens BC. Congenital syndactyly: defatting facilitates closure without skin graft. J Hand Surg Am. 2001;26:589–94.
180. Jose RM, Timoney N, Vidyadharan R, Lester R. Syndactyly correction: an aesthetoc reconstruction. J Hand Surg Eur Vol. 2010;35(6):446–50.
181. Buck-Gramcko D. Congenital malformations: syndactyly and related deformities. In: Higst H, Buck-Gramcko D, Millesi H, et al., editors. Hand surgery. New York: Thieme Medical Publishers; 1988.
182. Wall LB, Velicki K, Roberts S, Goldfarb CA. Outcomes of pediatric syndactyly repair using synthetic dermal substitute [published online ahead of print, 2020 Feb 12]. J Hand Surg Am. 2020;S0363-5023(19):31544–8.
183. Jung JJ, Woo AS, Borschel GH. The use of Integra bilaminar dermal regeneration template in Apert syndactyly reconstruction: a novel alternative to simplify care and improve outcomes. J Plast Reconstr Aesthet Surg. 2012;65(1):118e121.
184. Duteille F, Truffandier MV, Perrot P. 'Matriderm' dermal substitute with split-thickness skin graft compared with full-thickness skin graft for the coverage of skin defects after surgical treatment of congenital syndactyly: results in 40 commissures. J Hand Surg Eur Vol. 2016;41(3):350–1.

185. Landi A, Garagnani L, Leti Acciaro A, Lando M, Ozben H, Gagliano MC. Hyaluronic acid scaffold for skin defects in congenital syndactyly release surgery: a novel technique based on the regener- ative model. J Hand Surg Eur. 2014;39(9):994–1000.
186. Niranjan NS, Azad SM, Fleming ANM, Liew SH. Long-term results of primary syndactyly correction by the trilobed flap technique. Br J Plast Surg. 2005;58:14–21.
187. Vekris MD, Lykissas MG, Soucacos PN, Korompilias AV, Beris AE. Congenital syndactyly: outcome of surgical treatment in 131 webs. Tech Hand Up Extrem Surg. 2010;14:2–7.
188. Goldfarb CA, Steffen JA, Stutz CM. Complex syndactyly: aesthetic and objective outcomes. J Hand Surg Am. 2012;37:2068–73.
189. Miyamoto J, Nagasao T, Miyamoto S. Biomechanical analysis of surgical correction of syndactyly. Plast Reconstr Surg. 2010;125(3):963–8.
190. Cromblehome TM, Dirkes K, Whitney TM, Alman B, Garmel S, Connelly RJ. Amniotic band syndrome in fetal lambs: I. Fetoscopic release and morphometric outcome. J Pediatr Surg. 1995;30:974.
191. Husler MR, Wilson RD, Horri SC, Bebbington MW, Adzick NS, Johnson MP. When is fetoscopic release of amniotic bands indicated? Review of outcome of cases treated in utero and selection criteria for fetal surgery. Prenat Diagn. 2009;29:457–63.

Apert Syndrome

15

Brian C. Pridgen and James Chang

Introduction

History and Brief Description of Clinical Features

Apert syndrome is a rare congenital disorder characterized by craniosynostosis, midface hypoplasia, and bilateral syndactyly of the hands and feet, as well as a constellation of more variable findings in other organ systems [1]. In the late nineteenth century, a series of case reports, primarily in the French literature, described what would come to be known as Apert syndrome. The initial description was by Robert Troquart in 1886 [2]. Eugene Apert made his initial observation in 1896 while working as an intern at Hôpital des Enfants-Malade, the children's hospital in Paris, where he saw a patient with a constellation of findings that he would later term acrocephalosyndactyly. In 1906, he described the syndrome of acrocephalosyndactyly based on eight case reports dating to 1886 with a cluster of malformations similar to the patient he saw as an intern [3]. He also described associated symptoms including cleft palate, ankylosis of the elbows, synonychia, and a spared trunk and proximal limbs. Apert's initial clinical descriptions remain accurate and have been complemented by advances in imaging that have expanded the morphological characterization of the disease.

In a landmark study by Blank in 1959, he reviewed 54 cases of acrocephalosyndactyly, 34 of which he observed firsthand [4]. He divided his cases into two subtypes—typical acrocephalosyndactyly with complete bilateral syndactyly as described by Apert (type I) and atypical acrocephalosyndactyly with partial syndactyly (type II). He referred to typical type I acrocephalosyndactyly as "Apert syndrome," thereby coining the term. Blank proposed that type I and type II acrocephalosyndactyly were likely unrelated but that type I syndrome was caused by a mutation of a single gene.

He suggested that sporadic instances of Apert syndrome, which constituted the majority of cases, resulted from mutations in paternal germ cells and that there was a significant relationship between incidence of Apert syndrome and advanced paternal age [4]. However, the precise cause of Apert syndrome remained elusive until Wilkie et al. discovered a molecular basis involving two highly specific genetic mutations in fibroblast growth factor receptor 2 (*FGFR2*) [5]. Thereafter, studies using modern biochemical techniques continued to elucidate the molecular mechanisms underlying Apert syndrome, as will be discussed in the section on molecular etiology later in this chapter.

Prior to the discovery of the genetic basis of Apert syndrome, much of the work on the disease

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focused on the surgical management of the multiple associated anomalies [2]. An early focus of surgical intervention was to manage increased intracranial pressure in patients exhibiting craniosynostosis initially by decompression techniques and later by more advanced reconstructive techniques. Paul Tessier, in particular, considered Apert syndrome a prototype for other craniofacial deformities [6]. His methods for reconstructing hypertelorism and midface retrusion found in Apert patients pioneered the field of craniofacial surgery.

Correction of complex bilateral syndactyly was another area of emphasis for surgeons. In 1970, Hoover published the first study focusing specifically on surgical techniques for the Apert hand, as will be discussed later in this chapter [7].

Genetics and Embryology

Molecular Etiology

Apert syndrome can be inherited in an autosomal dominant pattern, but de novo mutations of paternal origin are the most common cause [8]. Ninety-eight percent of cases are due to one of two missense in fibroblast growth factor receptor 2 (FGFR2): Pro253Arg and Ser252Trp [5]. FGFR is a member of the tyrosine kinase receptor family and is involved in normal limb bud patterning and connective tissue development during embryogenesis.

Of the 98% of Apert cases caused by the two FGFR2 mutations, the Pro253Arg mutation constitutes one-third of cases, and the Ser252Trp mutation constitutes two-thirds of cases [8]. Patients with a Pro253Arg missense mutation generally present with more severe forms of syndactyly and more impaired cognitive function than patients with a Ser252Trp mutation; however, the incidence of cleft palate is more common in patients with the Ser252Trp mutation [9].

Historically, the advanced age of fathers of Apert children has suggested that Apert syndrome is influenced by the paternal age effect (PAE) [4]. The PAE posits that the incidence of certain genetic disorders increases with increasing paternal age owing to an increased number of accumulated germline mutations and an increased mutation rate in the sperm of older males [10]. Goriely et al. suggested that the Ser252Trp mutation may confer a selective advantage to sperm stem cells [11]. This mechanism could more fully explain the increased incidence of Apert births to older fathers.

Prenatal Diagnosis

Suspected Apert syndrome is confirmed prenatally by amniocentesis [12]. However, screening for Apert syndrome remains challenging because the pathognomonic facial and skeletal changes of Apert syndrome are difficult to visualize through ultrasound before the third trimester. David et al. report cases in which craniofacial and extremity abnormalities detected in the second trimester through careful 2D and 3D ultrasound examination were later confirmed as prenatal signs of Apert syndrome by amniocentesis [13]. Quintero-Rivera et al. point to fetal CNS abnormalities, such as agenesis of the corpus callosum and ventriculomegaly, as early indicators of Apert syndrome that can be detected through MRI before pathognomonic morphologies can be discerned [12].

Epidemiology

Apert syndrome is a rare disorder that historically has been challenging to track because most cases occur due to sporadic mutations rather than due to familial inheritance; only 11 Apert patients have been documented to have had children [14]. Diagnosis and documentation of Apert syndrome have improved with the development of better birth defect surveillance systems and greater awareness of the disorder in the medical community. Cohen et al. published the first extensive multi-site epidemiological study of Apert syndrome in 1992 in which they defined an Apert case as a patient exhibiting craniosynostosis,

midface hypoplasia, and symmetric syndactyly of the hands and feet [15]. Based on data from seven sites, they calculated an Apert birth prevalence of 15.5 cases per million live births. They estimated Apert syndrome to constitute 4.5% of all craniosynostosis cases.

A more recent study that drew samples from the California Birth Defects Monitoring Program (CBDMP) calculated an Apert birth prevalence of 12.4 cases per million births with an approximately similar incidence between males and females [14]. In almost half of tracked cases, the age of the father was 35 or older, supporting the theory of the PAE.

Clinical Features

Apert syndrome is clinically diagnosed based on the presence of craniosynostosis, midface hypoplasia, bilateral syndactyly, and specific genetic mutations. As mentioned previously, patients also present with a highly variable collection of features that affect multiple organ systems. The pathogenetic mechanisms underlying many of these features remain largely unknown. Clinical features associated with Apert syndrome can be broadly categorized into craniofacial, CNS, visceral, skeletal, and dermatological pathologies.

Craniofacial Anomalies

Fearon and Podner categorize Apert skulls into type I skulls, which have a split metopic sutures without anterior turricephaly and soft nonbulging dura; type II skulls, which have a closed metopic suture with moderate turribrachycephaly; and type III skulls, which are Pfeiffer-type and exhibit severe turricephaly [16]. In type I skulls, which are most common, the coronal suture is fused at birth, but other sutures and fontanelles are patent. Patients are born with a wide midline calvarial defect formed from the metopic and sagittal sutures extending from the glabella to the posterior fontanelle. Bony islands form and coalesce to close the defect by age 2 to 4. This defect allows some early growth of the brain. In contrast, the midline defect closes earlier in type II skulls, leading to constriction of anterior skull growth and turricephaly. The rare type III skulls have pansutural fusions, leading to a towering skull that presents like the skulls of Pfeiffer syndrome patients.

The primary goals for craniofacial surgical treatment of Apert patients are to preempt preventable developmental delays, minimize the number and risks of procedures, and help to improve aesthetic appearance by the time of skeletal maturity [16]. When optimizing timing and extent of cranial vault remodeling for each skull type, clinicians must weigh the benefits of intracranial decompression and improved appearance with the risks of causing iatrogenic skull growth inhibition. Fearon and Podner advocate a guiding principle of later surgery for less severe type I skulls (15 months) and earlier intervention for type II (9–12 months) and type III (6 months) skulls.

In addition, patients frequently present with a cleft palate and maxillary hypoplasia [17]. Shallow orbits and ocular proptosis predispose Apert patients to injury to unprotected eyes, exposure keratitis, and corneal abrasions. Patients may exhibit exotropia, hyperopia, or astigmatism. Increased ocular pressure can lead to blindness [18].

CNS Abnormalities

Several CNS anomalies are associated with Apert syndrome. Most patients exhibit corpus callosum and limbic structure malformation [19]. Cohen and Kreiborg also reported frequent occurrence of gyral abnormalities, cerebral white matter hypoplasia, and heterotopic grey matter.

Cognitive function among Apert patients ranges widely. The impact of timing of first surgical intervention on IQ is contested. Renier et al. found that initial skull surgery before 1 year of age was the main factor that correlated with increased IQ, with some contribution from septum pellucidum morphology [20]. However,

Fearon and Podner did not find a significant correlation between IQ and timing of surgery, severity of turricephaly, type of genetic mutation, or corpus callosum and septum pellucidum morphology [16]. Similarly Yacubian et al. did not find significant correlations between IQ and timing of surgery or intervention via strip craniectomy and instead attribute differences in mental development to family environment and parents' education level [21].

Visceral Anomalies

Apert patients can present with cardiac, genitourinary, and, less frequently, respiratory and gastrointestinal pathologies [22]. Cohen and Kreiborg report up to 10% of autopsied Apert patients presented with various, often concurrent, congenital heart abnormalities such as atrial and ventricular septal defects, dextrocardia, and pulmonic stenosis. Complex heart defects were associated with early mortality. They also report that 9.6% of patients presented with genitourinary anomalies, including cryptorchidism in males and hydronephrosis.

Cohen and Kreiborg report a much lower frequency of respiratory (1.5%) and gastrointestinal (1.5%) symptoms. The most serious lower respiratory defect was a completely or partially solid cartilaginous trachea that restricted tracheal distensibility and caused respiratory insufficiency. Upper respiratory problems stemmed from nasopharyngeal and oropharyngeal space constraints due to craniofacial bone displacement and resulted in sleep apnea, cor pulmonale, and sudden death in patients [1].

Skeletal Abnormalities

Apart from changes in the skull and bony skeleton of the hands and feet, Apert patients can also exhibit cervical spine fusion, with 68% of cases presenting with a fusion of vertebrae C5 and C6 [1]. Cohen and Kreiborg report cases of progressive limitation of shoulder, elbow, and knee joint mobility; pectus excavatum; irregular pelvic girdles; subacromial and elbow dimpling; winged scapulae; and abnormally short humeri.

Dermatological Anomalies

Skin anomalies such as increased sweat and sebaceous glands, oily skin, and acneiform lesions can be found in Apert patients [23]. Other symptoms include hypopigmentation, wrinkling of the forehead, and hyperhidrosis; mothers of Apert patients frequently report that the children sweat excessively while crying, breastfeeding, or even sleeping.

Upper Extremity Anomalies

Upper extremity involvement of Apert syndrome includes a short thumb with radial clinodactyly; involvement of the first web space with varying degrees of syndactyly between the thumb and index finger; complex syndactyly between the index, middle, and ring fingers typically at the level of the distal interphalangeal joints or beyond; and variable degrees of syndactyly between the ring and small fingers. Additional findings include aberrant anatomy of the intrinsic muscles, extrinsic tendon insertions, neurovascular bundles, and absent proximal interphalangeal joints with the only functional interphalangeal joint typically being the distal interphalangeal joint of the small finger [24]. Van Heest and Reckling proposed a classification system based on the radiographic appearance of hands in Apert syndrome patients [25]. However, the more widely used classification system was described by Upton and includes three types of hands [24]. Type I hands, or "spade" hands, are defined by a complex syndactyly between the index, middle, and ring fingers and a simple syndactyly between the ring and small fingers. The thumb and index finger are separated, although the first web space may be shallow. Type II hands, or "spoon" or "mitten" hands, are defined by the features of type I hands plus a partial or complete simple syndactyly between the thumb and index finger and a more complete simple syndactyly between

Table 15.1 Reported incidence of Upton-type hands

Reference	Number of patients	Type I Number (percent)	Type II Number (percent)	Type III Number (percent)
Upton (1991) [24]	68	28 (41%)	24 (35%)	16 (24%)
Cohen et al. (1995) [26]	44	20 (45%)	18 (39%)	6 (16%)
Holten et al. (1997) [27]	45	29 (64%)	10 (22%)	6 (13%)
Chang et al. (2002) [28]	10	5 (50%)	1 (10%)	4 (40%)
Fearon (2003) [29]	17	11 (65%)	2 (12%)	4 (24%)
Guero (2005) [30]	52	11 (21%)	19 (37%)	22 (42%)
Raposo-Amaral (2018) [31]	41	20 (49%)	10 (24%)	11 (27%)
Totals	277	124 (45%)	84 (30%)	69 (25%)

the ring and small fingers. Type III hands, or "rosebud" hands, are defined by a complex syndactyly between the thumb, index, middle, and ring fingers and a complete simple syndactyly between the ring and small fingers. The type III deformity is often so severe that it can be difficult to distinguish the thumb from the index finger. Table 15.1 shows the reported incidence of each of the Upton-type hands in several groups' series.

Treatment

Reconstruction of the hand in patients with Apert syndrome is an evolving technique that presents a significant challenge to hand surgeons, and the treatment of the numerous hand anomalies encountered in Apert syndrome requires a complex operative plan with multiple stages through childhood and into adolescence. There has been a lively discussion in the literature over the past several decades, adding to the prior body of literature, in which a variety of reconstructive plans have been described. Several factors account for the lack of a clear consensus on the management of these patients, including the rarity of this syndrome, the presentation of each patient with a unique cluster of anomalies with varying degrees of severity, the role of surgeon preference and surgeon comfort in determining a reconstructive plan, and the difficulty in having the long-term follow-up needed to evaluate the durability of the reconstruction. Despite this lack of consensus, the common goals between most of the proposed reconstructive plans include minimizing the number of procedures, maximizing the functional outcome of the hand, and providing a favorable cosmetic result, which includes preserving as many digits as possible through judicious use of amputations.

It should be noted that in the past, there was some question about the utility of offering hand reconstruction to Apert syndrome patients due to mental impairment that can be quite severe. However, we want to echo the sentiment of other authors [7, 30] who also specifically have emphasized the point that, regardless of the degree of mental impairment of the patient, the functional gains and cosmetic improvements following reconstruction offer significant quality of life improvements, both for the patient and for the family, that should not be withheld from Apert syndrome patients.

The technical goals for reconstruction of the Apert hand address syndactyly and symphalangism, thumb radial clinodactyly, and later secondary deformities requiring revision. These goals have been organized by several authors into a reconstructive plan. Considerations that must be made in the formulation of a reconstructive plan include age of the patient at the time of the initial operation, timing, and sequence of the release of border digits, providing soft tissue coverage, need for digital amputation, thumb lengthening and straightening, and secondary revisions.

Patient Age

Ideally, patients with Apert syndrome should be referred shortly after birth to a center with the

multidisciplinary expertise necessary to treat the hand and craniofacial anomalies associated with Apert syndrome. However, due to a variety of reasons, including patients who were born in parts of the world without the multidisciplinary teams available for reconstruction, Apert syndrome patients are often seen well after infancy. This can present a challenge and requires modifications to the reconstructive sequence in these patients.

The age of the patient is particularly relevant to the decision of whether both hands are operated on simultaneously or whether the same operation for each hand is delayed in a staged manner. Following each reconstruction, the patients are typically placed in casts or splint, which is variable from group to group. In patients who require bilateral upper extremity restraints, this can cause significant distress for the patient, depending how independent and interactive he or she is, and place a significant burden on the parents, again, depending on how dependent the patient is on the parents for assistance with basic tasks of daily care. The age below which operations are performed concurrently on bilateral upper extremities simultaneously varies from 12 [28, 30, 32] to 18 [33] to 24 months [7] among authors who specified. In patients who underwent the same procedure on each hand individually, the delay between procedures on each hand ranged from as short as 2 weeks [30] up to 3 [28] to 6 months [30, 32].

Syndactyly, Symphalangism, and Border Digits

Timing of release of the border digits is a source of controversy. Some authors suggest that postponing separation of the digits will lead to angular growth deformities due to differential growth of each of the digits [7, 24, 34], while others state that in their experience, this is not the case [29]. Another consideration in the timing of the release of the digits is to provide early mobility to promote earlier motor development. Earlier release of the thumb and the small finger, the border digits, allows the patient to begin development of a grasp. Hoover recommends performing a border digit release by 1 year of age [7]. Fearon, however, did not observe these problems in his patients that did not undergo early border digit release [29].

For those authors who prioritize the release of the border digits in Upton type II and III hands, two additional procedures are required to release the remaining syndactylies. This is the case because the remaining syndactylies after release of the border digits are the index-middle and middle-ring finger syndactylies. Releasing both of these syndactylies in the second and third web spaces requires operating on both sides of the middle finger. Operating on both sides of the middle finger during the same operation theoretically risks compromising the vascular supply to the middle finger and having a shortage of flap skin [25, 29, 32]. To minimize this risk, the middle finger syndactyly release is typically staged as two separate operations, which increases to three the number of operations a patient must undergo and increases the time spent by a patient without full release of all of his or her fingers. To reduce the number of operations, some surgeons release alternating web spaces, including releasing one side of the middle finger syndactyly during the first operation while neglecting one of the two border digit syndactylies during the first operation [29, 31].

The concern for vascular compromise dictates operative staging and forces surgeons to choose between prioritizing border digit release and limiting the number of operations to two. Even with careful consideration of the vascular supply to the digits, the aberrant anatomy of the neurovascular bundles increases the risk of inadvertent disruption of the blood supply to the digits. To address these problems, Harvey et al. examined the role of CT angiogram to assist with mapping of the vascular supply to each digit [35]. This imaging was done concurrently with CT imaging performed for operative planning for craniofacial reconstruction. After mapping the vascular supply to the hand and planning the surgical approach, they attempted to perform a single-stage syndactyly release guided by the vascular anatomy seen on CT angiogram. In both hands of

all five patients in this study, they were able to perform successfully a single-stage syndactyly release without any major complications.

We have not adopted this approach because another problem with release of adjacent fingers is the shortage of dorsal skin that can be used for dorsal flap coverage of the webs. Therefore, in our experience, the risks and limitations of adjacent finger release outweigh the benefit of a single-stage approach.

Separation of the syndactyly in the fingers is typically performed with a zigzag incision. This results in interdigitating triangular flaps along the sides of the newly released digits. The purpose of this pattern is to avoid a straight-line scar along the sides of the fingers due to the concern for scar contracture. Syndactyly release in Apert syndrome is different because the fingers have some degree of symphalangism, with resultant stiff joints that will not deviate with scarring of the skin incisions [29]. Straight-line syndactyly release incisions will prevent the zigzag incisions from extending onto the dorsal and volar surface of the fingers and will allow application of a single skin graft to each side of the finger (Fig. 15.1). However, Upton suggests the small finger should be treated with extra caution with regard to the use of straight-line incisions due to variability in symphalangism.

Because many syndactylized fingers in Apert syndrome are complete and complex, two specific operative maneuvers are critical. Zigzag fingertip flaps, attributed to Buck-Gramcko, are useful for recreating the nailfolds [36] (Fig. 15.2). Also, intraoperative fluoroscopy is used to visualize the bony fusion prior to osteotomy. A fine-gauge needle is placed slightly off center to the proposed longitudinal osteotomy, and the osteotome is slid on top of the needle to allow precise sectioning of the bone (Fig. 15.3).

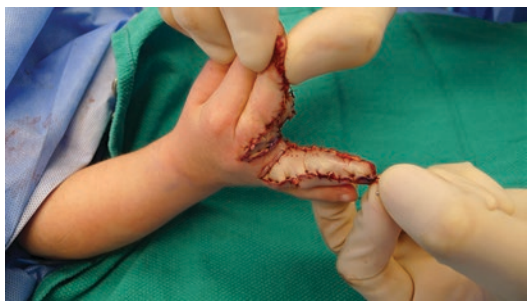

Fig. 15.1 Full-thickness skin grafting after straight-line syndactyly release

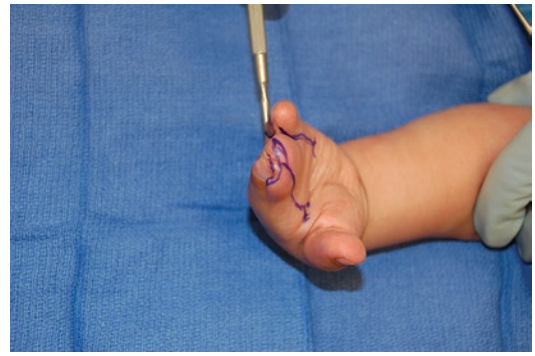

Fig. 15.2 Markings for zigzag fingertips for recreating the nailfolds

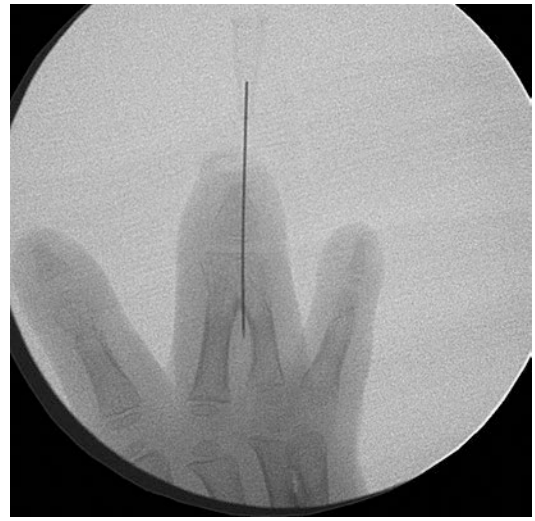

Fig. 15.3 Fluoroscopy image demonstrated needle positioning used to guide longitudinal osteotomy

Several flaps have been described for reconstruction of the second, third, and fourth web spaces. Barot and Caplan describe a dorsal rectangular flap that they inset into a volar T-incision [32]. Guero describes an omega-shaped dorsal flap [30]. Other authors perform a similar long dorsal flap for reconstruction of the web space. Fearon, however, uses equal-length triangular dorsal and volar flaps [29]. This results in a length-to-width ratio that provides more favor-

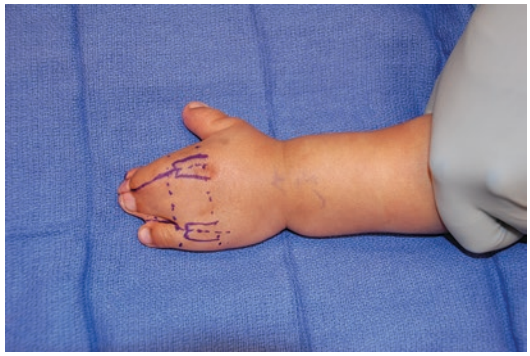

Fig. 15.4 Rectangular dorsal advancement flaps for web space reconstruction

able blood supply to the distal tip of the flap. He attributes this technique as the reason for his very low reported rate of 3% for secondary syndactylies requiring reoperation. He designs the base of his dorsal flap proximal to the base of the volar flap to recreate the normal slope of the web space. In Upton's commentary on Fearon's article, Upton agrees with the Fearon's triangular flaps, but he cautions that the second web space may require a future secondary release due to increased metacarpal growth [29]. To accommodate for this, Upton recommends considering a wide rectangular flap being used initially, which can then more easily be readvanced if needed later in life. This is the flap design that we usually choose to use (Fig. 15.4).

For areas not covered by the skin flaps raised during release of the syndactyly, full-thickness skin grafts are typically applied. Split thickness skin grafts rarely are used due to graft contraction leading to web space contracture and risk of recurrent syndactyly. Full-thickness skin grafts often are harvested from the groin crease, avoiding the future hair-bearing skin. Skin harvested from circumcisions should never be used due to darkening of the harvested skin with time, which provides a poor cosmetic result that patients often request to be revised. In cases with small areas of exposed bone without overlying vascularized tissue in the distal half of the released digits, Fearon did not provide coverage with skin grafts or tissue flaps [29]. This reduced the need for full-thickness skin graft tissue but without increasing wound healing complications. In addition to skin grafts, several other techniques have been suggested for providing soft tissue coverage, including pedicled groin flaps [34], tissue expanders, and silastic sheets [37]. Although these were not used in the more recent large series, the reconstructive surgeon should remain mindful of these techniques should additional soft tissue coverage be needed.

The role of digital amputation is a controversial topic with multiple practices described in the literature. Hoover recommended routine amputation of the middle finger to provide additional soft tissue for coverage of the remaining index and ring fingers [7]. However, since Hoover's work in 1970, further discretion and nuance have been applied when deciding whether to amputate a digit. Guero attempts to achieve a five-digit hand in Upton type I and type II hands and only plans for a fourth ray amputation in Upton type III hands with radiographic evidence of severe deformities including synostosis between the fourth and fifth metacarpals or misalignment between the third and fourth metacarpals [30]. Chang et al., too, recommended routine amputation only in Upton type III hands, and if one digit was markedly smaller than the others [28]. Van Heest et al. created a new classification system for hands in Apert syndrome based on the radiographic appearance of the hands [25]. One of their justifications for the new classification system was to guide hand surgeons in determining if an amputation is necessary and, if so, which ray should be resected. Details of the classification system can be found in their paper, but their recommendations for amputation, briefly, are amputation of the third ray for complex syndactyly of the index, middle, and ring fingers; amputation of the second ray for marked pronation and apex radial angulation of the index finger; and amputation of the fourth ray for marked supination and apex ulnar angulation of the ring finger. In general, all attempts should be made to achieve a five-digit hand, even in Upton type III hands. This is achievable, as described by Theman et al., who achieved a five-digit hand in 11 of 12 (92%) Upton type III hands [38], and as

described by Raposo-Amaral et al., who achieved a five-digit hand in 8 of 11 (73%) Upton type III hands [31].

First Web Space Release, Thumb Radial Clinodactyly, and Short Thumb

In addition to releasing the small finger, which is typically the most normal and functional finger, reconstructing the thumb to allow opposition is one of the most important aspects of reconstructing the hand of an Apert patient. The anomalies of the thumb include a contracted first web space and syndactyly with the index finger, particularly in Upton type II and III hands, thumb radial clinodactyly, and a shortened thumb. Ensuring patients have an adequate first web space allows maximal function from a shortened and radially deviated thumb. Preferred management of this first web space includes a four-flap z-plasty, a dorsal rotation-advancement flap for more severe syndactylies, or full-thickness skin grafting for severe type III hands in which local flaps do not provide adequate soft tissue coverage [29, 30]. Zuker et al. also describe the contribution of restrictive bands of palmar fascia across the first web space and a contracted adductor pollicis muscle that may also need to be released to achieve a more mobile first web space [34].

Upton, in his commentary on Fearon's article, describes his preferred method for facilitating thumb to small finger opposition [29]. He performs an open-wedge osteotomy of the thumb, which can be performed through a radial z-plasty to address the shortening and the radial clinodactyly. He then excises the fourth-fifth metacarpal synostosis in order to mobilize the small finger. To prevent the frequent recurrent synostosis between the metacarpal bases, he has tried various methods including interposition of a palmaris longus tendon graft or silicone sheeting, though without much success. Instead, he has found that fascia lata, whether autologous or allogeneic, wrapped around the fifth metacarpal works well to prevent recurrent synostosis. Guero prefers to interpose interosseous muscles [30]. The excised bone from the synostosis may be used to fill an opening wedge osteotomy defect. Chang et al., alternatively, suggested using bone harvested from the ulna as an alternative if digital bone is not available [28].

Fereshetian and Upton emphasized the important of creating an adequate first web space during the first year of life to prevent delays in musculoskeletal and coordination development [33]. They felt that the first web space should be released during the first 6 months of life but that the radial clinodactyly does not need to be treated with an opening wedge osteotomy until age 4–7. In describing their technique for releasing the first web space, they noted several anatomic abnormalities, including an extensive and restrictive palmar aponeurosis, tight fascial connections between the metacarpals, distal branching of the princeps pollicis artery, and aberrant anatomy of several intrinsic muscles.

A significant departure from the paradigm of treating the thumb radial clinodactyly and shortening was described by Dao et al. [39]. The radial clinodactyly of the thumb had been attributed to a delta phalanx of the thumb [32] and a longitudinally bracketed diaphysis [24]. However, Dao took note of Fereshetian and Upton's description of an anomalous insertion of the abductor pollicis brevis (APB) onto the radial aspect of the distal phalanx [33] and used this aberrant anatomy as an explanation for the thumb anomalies in Apert syndrome. They cite Fereshetian and Upton's observation that thumb radial angulation recurs with growth in some patients [33]. They postulated that the recurrence of the thumb radial clinodactyly following a closing wedge or opening wedge osteotomy is not primarily a result of a delta phalanx or a longitudinally bracketed diaphysis but, rather, due to the abnormal radial force of the APB tendon that persists following a wedge osteotomy.

Dao et al. review the technique for APB release in detail in their paper [39]. They had only two patients in their series, who they saw for follow-up for 1.5 and 5.6 years. Both patients had excellent results without recurrence of radial angulation at the end of follow-up. In

their practice, they perform the APB release concurrently with other reconstructive procedures, as the release is performed extraosseously and avoids the physis. This means that the APB release can be performed at a very early age before the deforming effects of the anomalous APB insertion have a chance to take effect. Upton, in his review of Fearon's paper, commented that he now favors Dao et al.'s approach and has changed his practice based on their work [29].

Oishi and Ezaki expanded on Dao et al.'s work to describe additional techniques in the management of the Apert thumb [40]. They note a paucity of skin along the radial aspect of the thumb that is typically addressed by a z-plasty by other groups, although they believe this leads to a soft tissue defect and a concave appearance. Instead, they described a V-to-Y and Y-to-V flap design encircling the thumb, which is nicely illustrated in their paper. They feel this offers improved mobilization of the skin for better exposure and a more aesthetic result. They agree with Dao et al.'s management of the anomalous APB insertion. Lastly, they perform an osteotomy of the proximal phalanx to address any radial angulation. This may be necessary in their series because they prefer to wait until after 4 years of age, by which time the anomalous insertion of the APB has had time to have a deforming effect. They typically perform an opening wedge osteotomy to preserve length in the thumb because it is usually short.

Secondary Revisions

Patients with Apert syndrome develop progressively stiff interphalangeal joints. Fearon addressed this deformity with phalangeal osteotomies [29]. At the ages of 9–12, he performs an opening phalangeal osteotomy on the dorsal surface of the fingers at the midpoint of the fused proximal and middle phalanges where the proximal interphalangeal joint typically would be. He initially attempted to do the phalangeal osteotomies at ages 7–9, but he observed that this was associated with lateral scissoring of the digits.

Additional secondary revisions include excision of pigmented skin at sites of skin grafting, readvancement of the first web space flap, release of recurrent syndactylies, performing longitudinal ostectomies for widened digits, and correction of deviated digits that may occur with growth.

Postoperative Care and Complications

Immobilization

The importance of postoperative immobilization has been emphasized by many groups due to the risk for recurrent syndactyly or wound breakdown. Upton observed that patients with a persistent or recurrent syndactyly often had been splinted for only a short period or had their cast or splint come off prematurely [33]. The recommended duration for postoperative splinting ranges from 2 to 3 weeks [28, 29, 32]. The goal for each of these immobilization regimens is to minimize motion and friction at the sites of grafts and flaps while balancing this against the risks of maceration from prolonged splinting and the inconvenience from prolonged splinting in young children.

Hyperhidrosis

Most patients with Apert syndrome have hyperhidrosis [41]. The excessive sweating can lead to maceration. This is of particular concern along fresh sutures lines, which may be disrupted with excessive maceration, possibly leading to a secondary syndactyly. Several authors go so far as to avoid reconstructive hand operations in Apert patients in the warm summer months to avoid the effects of excessive sweating [30, 33].

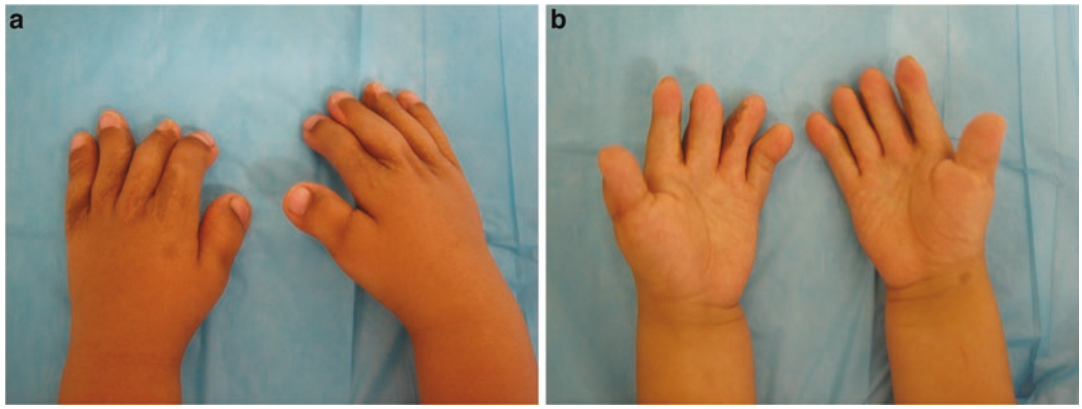

Fig. 15.5 Dorsal (**a**) and volar (**b**) views of a patient with a type II Apert hand, 5 years after Apert syndactyly release and skin grafting

Secondary Syndactyly

Web space creep and recurrence of syndactyly are reported in most authors' series. This often requires revision at a later date ranging from 3% to 40% in different authors' series [28, 29, 31, 32]. Most cases of recurrent syndactyly have been attributed to insufficient postoperative immobilization. Thus, careful attention should be paid to splinting postoperatively.

Outcomes

Quantifiable outcomes have been difficult to measure in Apert syndrome patients owing to heterogeneity in the functional status of these patients, the young age at which they receive their reconstruction, and the unreliable follow up that they receive. Anecdotal reports from authors describe variable functional improvements after reconstruction, although most patients do achieve opposition between the thumb and the most ulnar digit. The most comprehensive evaluation of functional outcomes in adults with Apert syndrome was reported in a recent study by Taghinia et al. [42]. In this study, they found that patients had high self-reported health outcome scores despite upper extremity functional testing times being significantly lower than population norms. With regard to the aesthetic outcomes, parents and patients are generally satisfied with the appearance of their hands in most authors' series and rarely request further operations in late adolescence and early adulthood (Fig. 15.5).

References

1. Cohen MMJ, Kreiborg S. An updated pediatric perspective on the Apert syndrome. Am J Dis Child 1960. 1993;147:989–93.
2. Perlyn CA, Nichols C, Woo A, Becker D, Kane AA. Le premier siècle: one hundred years of progress in the treatment of Apert syndrome. J Craniofac Surg. 2009;20:801–6.
3. Apert E. De l'acrocephalosyndactlie. Bull Mem Soc Med Hop Paris. 1906;23:1310.
4. Blank CE. Apert's syndrome (a type of acrocephalosyndactyly)-observations on a British series of thirty-nine cases. Ann Hum Genet. 1960;24:151–64.
5. Wilkie AO, Slaney SF, Oldridge M, Poole MD, Ashworth GJ, Hockley AD, et al. Apert syndrome results from localized mutations of FGFR2 and is allelic with Crouzon syndrome. Nat Genet. 1995;9:165–72.
6. Lee DS, Chung KC. Eugène Apert and his contributions to plastic surgery. Ann Plast Surg. 2010;64:362–5.

7. Hoover GH, Flatt AE, Weiss MW. The hand and Apert's syndrome. J Bone Joint Surg Am. 1970;52:878–95.
8. Au PKC, Kwok YKY, Leung KY, Tang LYF, Tang MHY, Lau ET. Detection of the S252W mutation in fibroblast growth factor receptor 2 (FGFR2) in fetal DNA from maternal plasma in a pregnancy affected by Apert syndrome. Prenat Diagn. 2011;31:218–20.
9. Lajeunie E, Cameron R, El Ghouzzi V, de Parseval N, Journeau P, Gonzales M, et al. Clinical variability in patients with Apert's syndrome. J Neurosurg. 1999;90:443–7.
10. Glaser RL, Broman KW, Schulman RL, Eskenazi B, Wyrobek AJ, Jabs EW. The paternal-age effect in Apert syndrome is due, in part, to the increased frequency of mutations in sperm. Am J Hum Genet. 2003;73:939–47.
11. Goriely A, McVean GAT, Röjmyr M, Ingemarsson B, Wilkie AOM. Evidence for selective advantage of pathogenic FGFR2 mutations in the male germ line. Science. 2003;301:643–6.
12. Quintero-Rivera F, Robson CD, Reiss RE, Levine D, Benson C, Mulliken JB, et al. Apert syndrome: what prenatal radiographic findings should prompt its consideration? Prenat Diagn. 2006;26:966–72.
13. David AL, Turnbull C, Scott R, Freeman J, Bilardo CM, van Maarle M, et al. Diagnosis of Apert syndrome in the second-trimester using 2D and 3D ultrasound. Prenat Diagn. 2007;27:629–32.
14. Tolarova MM, Harris JA, Ordway DE, Vargervik K. Birth prevalence, mutation rate, sex ratio, parents' age, and ethnicity in Apert syndrome. Am J Med Genet. 1997;72:394–8.
15. Cohen MMJ, Kreiborg S, Lammer EJ, Cordero JF, Mastroiacovo P, Erickson JD, et al. Birth prevalence study of the Apert syndrome. Am J Med Genet. 1992;42:655–9.
16. Fearon JA, Podner C. Apert syndrome: evaluation of a treatment algorithm. Plast Reconstr Surg. 2013;131:132–42.
17. Kreiborg S, Cohen MMJ. Is craniofacial morphology in Apert and Crouzon syndromes the same? Acta Odontol Scand. 1998;56:339–41.
18. Oberoi S, Hoffman WY, Vargervik K. Craniofacial team management in Apert syndrome. Am J Orthod Dentofacial Orthop. 2012;141:S82–7.
19. Cohen MMJ, Kreiborg S. The central nervous system in the Apert syndrome. Am J Med Genet. 1990;35:36–45.
20. Renier D, Arnaud E, Cinalli G, Sebag G, Zerah M, Marchac D. Prognosis for mental function in Apert's syndrome. J Neurosurg. 1996;85:66–72.
21. Yacubian-Fernandes A, Palhares A, Giglio A, Gabarra RC, Zanini S, Portela L, et al. Apert syndrome: factors involved in the cognitive development. Arq Neuropsiquiatr. 2005;63:963–8.
22. Cohen MMJ, Kreiborg S. Visceral anomalies in the Apert syndrome. Am J Med Genet. 1993;45:758–60.
23. Cohen MMJ, Kreiborg S. Cutaneous manifestations of Apert syndrome. Am J Med Genet. 1995;58:94–6.
24. Upton J. Apert syndrome. Classification and pathologic anatomy of limb anomalies. Clin Plast Surg. 1991;18:321–55.
25. Van Heest AE, House JH, Reckling WC. Two-stage reconstruction of Apert acrosyndactyly. J Hand Surg. 1997;22:315–22.
26. Cohen MMJ, Kreiborg S. Hands and feet in the Apert syndrome. Am J Med Genet. 1995;57:82–96.
27. Holten IW, Smith AW, Bourne AJ, David DJ. The Apert syndrome hand: pathologic anatomy and clinical manifestations. Plast Reconstr Surg. 1997;99:1681–7.
28. Chang J, Danton TK, Ladd AL, Hentz VR. Reconstruction of the hand in Apert syndrome: a simplified approach. Plast Reconstr Surg. 2002;109:465–70; discussion 471.
29. Fearon JA. Treatment of the hands and feet in Apert syndrome: an evolution in management. Plast Reconstr Surg. 2003;112:1–12; discussion 13–19.
30. Guero SJ. Algorithm for treatment of apert hand. Tech Hand Up Extrem Surg. 2005;9:126–33.
31. Raposo-Amaral CE, Denadai R, Furlan P, Raposo-Amaral CA. Treatment of Apert hand syndrome: strategies for achieving a five-digit hand. Plast Reconstr Surg. 2018;142:972–82.
32. Barot LR, Caplan HS. Early surgical intervention in Apert's syndactyly. Plast Reconstr Surg. 1986;77:282–7.
33. Fereshetian S, Upton J. The anatomy and management of the thumb in Apert syndrome. Clin Plast Surg. 1991;18:365–80.
34. Zucker RM, Cleland HJ, Haswell T. Syndactyly correction of the hand in Apert syndrome. Clin Plast Surg. 1991;18:357–64.
35. Harvey I, Brown S, Ayres O, Proudman T. The Apert hand--angiographic planning of a single-stage, 5-digit release for all classes of deformity. J Hand Surg. 2012;37:152–8.
36. Golash A, Watson JS. Nail fold creation in complete syndactyly using Buck-Gramcko pulp flaps. J Hand Surg Edinb Scotl. 2000;25:11–4.
37. Stefansson GM, Stilwell JH. Use of silastic sheet in Apert's syndactyly. J Hand Surg Br Eur Vol. 1994;19:248–9.
38. Theman TA, Upton J, Taghinia AH, Firriolo JM, Nuzzi LC, Labow BI. Central coalition osteotomy of phalangeal synostoses in the management of the Type III apert hand. J Hand Surg. 2018;43:1042.e1–8.
39. Dao KD, Shin AY, Kelley S, Wood VE. Thumb radial angulation correction without phalangeal osteotomy in Apert's syndrome. J Hand Surg. 2002;27:125–32.
40. Oishi SN, Ezaki M. Reconstruction of the thumb in Apert syndrome. Tech Hand Up Extrem Surg. 2010;14:100–3.
41. Solomon LM, Fretzin D, Pruzansky S. Pilosebaceous abnormalities in Apert's syndrome. Arch Dermatol. 1970;102:381–5.
42. Taghinia AH, Yorlets RR, Doyle M, Labow BI, Upton J. Long-term functional upper-extremity outcomes in adults with Apert syndrome. Plast Reconstr Surg. 2019;143:1136–45.

Central Deficiency (Cleft Hand)

16

Toshihiko Ogino

Definition

Central deficiency of the hand is called cleft hand, split hand, lobster claw, or central oligodactyly. Barsky defined cleft hand as a form of congenital absence of one or more digits in which the central rays of the hand are affected [1]. According to his definition, there are two types of cleft hand, typical and atypical. Typical cleft hand is characterized by a deep V-shaped or funnel-shaped defect in the central part of the hand; atypical cleft hand is a more severe anomaly in which the three central rays are missing and is associated with various degrees of hypoplasia of the thumb and little finger. In atypical cleft hand, there are often rudiments of the missing fingers along the web between the thumb and little finger (Fig. 16.1). Atypical cleft hand has the common characteristic features of other types of symbrachydactyly: all cases were unilateral; various degrees of hypoplasia existed not only in the affected finger but also in the adjacent fingers and in the proximal part of the limbs and are associated with pectoral muscle absence [2, 3]. Atypical cleft hand is considered to be a moderate grade of symbrachydactyly, and the Congenital Committee of the International Federation of Societies for Surgery of the Hand (IFSSH) has urged not to use the term atypical cleft hand in order to prevent confusion of terminology [4]. This chapter only deals with typical cleft hand.

Editor's Note Toshihiko Ogino was a diligent and passionate researcher into congenital anomalies of the upper extremity. His contribution to this book reflects his scholarship and his contribution to the Japanese Modification of Swanson's Classification of hand anomalies. This chapter is published in the second edition of this book largely unaltered in his memory. He remained somewhat skeptical of newer classification systems; I have therefore added the section "The Cleft Hand in The Oberg-Manske-Tonkin (OMT) Classification."

DL

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Incidence and Genetics

Birch-Jensen [5] estimated the ratio of occurrence of typical cleft hand as 1 in 90,000 births. The incidence of cleft hand among all anomalies of the upper extremity is 2.3% of 1476 patients in Flatt's Iowa series [6] and 2.6% of 943 patients in Ogino's Sapporo series [7].

Regular autosomal dominant inheritance was evident in about 34% of reported pedigrees. In other pedigrees, there are some different types of inheritance, such as lack of penetrance of autosomal dominant inheritance and markedly irregular

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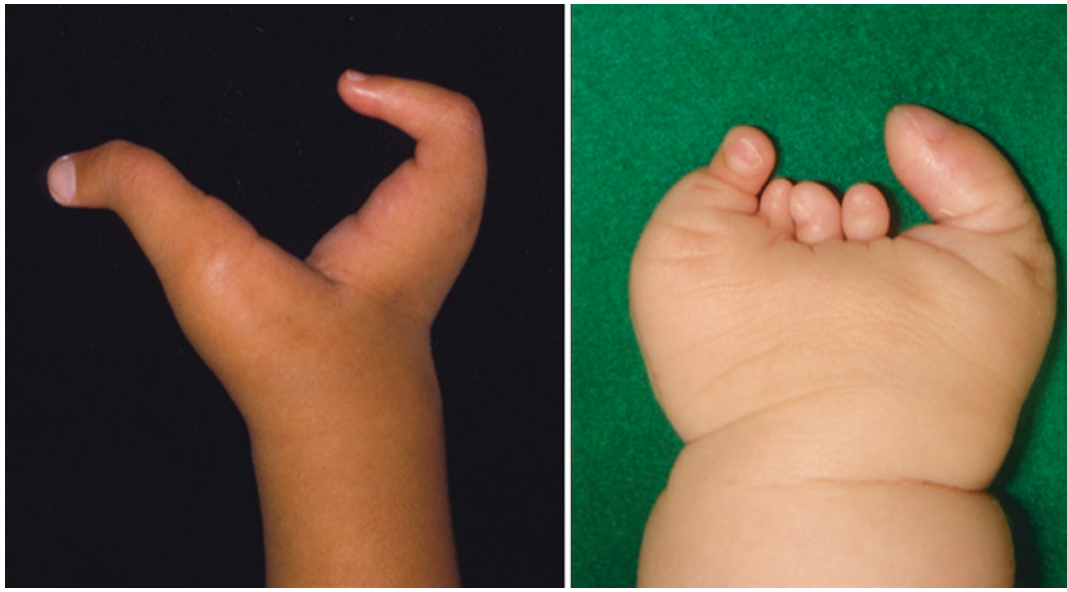

Fig. 16.1 Typical cleft hand (left) and atypical cleft hand (right)

dominant inheritance [8]. Vogel classified cleft hand into two types from the genetic aspect [9]. In type 1 pedigree, affected members showed constant involvement of feet and had a consistent autosomal dominant inheritance. In type 2 pedigrees, affected members showed variable involvement of the feet and irregular inheritance.

Split hand/foot malformation (SHFM) is a congenital absence of the central rays of the hands and feet. Some authors use ectrodactyly to denote any absence deformity of the distal limbs and reserve SHFM for the typical malformation; others use ectrodactyly synonymously with SHFM [10]. The Human Genome Organization Nomenclature Committee determined in 1994 that split hand/foot malformation should be denoted SHFM. SHFM may present with syndactyly, median clefts of the hands and feet, as well as aplasia or hypoplasia of the phalanges, metacarpals, and metatarsals. In severe cases, the hands and feet have a lobster claw-like appearance [11]. However, the severity of SHFM is highly variable. In mildly affected patients, SHFM may be limited to syndactyly, and several instances of non-penetrance have been documented. Clinical variability exists not only between patients but also between limbs of a single individual [12]. The most common mode of inheritance is autosomal dominant with variable penetrance. Autosomal-recessive and X-linked forms occur more rarely and other cases of SHFM and may be caused by chromosomal deletions and duplications. Abnormality of six SHFM loci has been found [13, 14].

Difference Between Cleft Hand and Other Types of Longitudinal Deficiency

The Swanson classification, which has been adopted as the IFSSH classification, has two major categories of congenital absence of digits [15, 16]: transverse deficiency (symbrachydactyly) and longitudinal deficiency. Atypical cleft hand is best classified as transverse deficiency or symbrachydactyly. In longitudinal deficiency, the congenital absence of digits is confined to the long axis of the upper limb and is classed as ulnar deficiency, radial deficiency, or central deficiency (cleft hand). In ulnar deficiency, there are various degrees of defects of ulnar fingers, such as the hypoplastic little finger, absence of the little finger, absence of the little and ring fingers, absence

of the ulnar three digital rays, and absence of the ulnar four digital rays [17]. In radial deficiency, the mildest form of the hand deformity is hypoplasia of the thenar muscles, and the most severe form is total absence of the thumb [18]. Non-opposable triphalangeal thumb, which is called five-fingered hand, is also one of the types of hypoplastic thumb. In some cases, the thumb and index finger are absent. In both radial and ulna deficiencies, there may be hypoplasia or aplasia of the forearm bones, and syndactyly and central polydactyly are not often seen.

Cleft hand is central deficiency, and the severe form is the absence of central three fingers, but in some cases thumb or little finger is also absent. The forearm bones are never involved, although defect or fusion of the carpal bones in distal carpal row may be seen in severe cleft hand. There are many cases in which central polydactyly, syndactyly, and cleft hand are associated in various combinations in an affected hand or in both hands of a patient [19, 20]. These anomalies also may occur in the members of the same family in various combinations. Manske [21] reported three cleft hands and one central polydactyly in four hands of identical twins. Satake et al. [22] reported a family of a mother with bilateral cleft hands, an elder daughter with the right cleft hand and the left central polydactyly, and young daughter with the left osseous syndactyly of the middle and ring fingers associated with cross bone between the middle and index fingers. There are some cases in which the middle finger is apparently missing, but on X-ray, the middle and ring fingers are fused [23]. On the other hand, Müller [24] reported cases, which seemed to be cleft hands apparently, but skeletal changes were more consistent with a polydactyly of the middle finger. This issue has not been discussed in the literature for many years. Some authors reported that there were some cases in which the middle finger appears to be missing, but the metacarpus of the middle finger is duplicated [19, 25]. It is difficult or impossible to classify these cases into central polydactyly, syndactyly, or cleft hand. By these observations, cleft hand is seen to be an anomaly closely related to central polydactyly and syndactyly [19, 20, 26–29] (Fig. 16.2). When one looks at the radiographs of patients with osseous syndactyly between the middle and ring fingers, or polydactyly of the middle finger, if the defect occurs sufficiently proximal, then an appearance of cleft hand is seen (Figs. 16.3 and 16.4a, b) [28]. These observations support the concept that a common etiological mechanism is involved in the development of central polydactyly, cleft hand, and syndactyly. They also support that a common teratogenic mechanism might be the abnormal induction of finger rays in the process of formation of the fingers in the hand plate [20, 29]. From this point of view, cleft hand is one phenotype of abnormal induction of digital rays of the hand plate in which the central fingers are missing [29].

The Teratogenic Mechanisms of Formation of Cleft Hand and Other Types of Longitudinal Deficiency

In order to have a better understanding of the classification, it is necessary to clarify the development of longitudinal deficiency and cleft hand. The authors developed animal models of these deformities using cleft foot as a model of cleft hand [17, 30–33]. The antineoplastic drug busulfan is given to pregnant rats, and radial deficiency and ulnar deficiency have been induced [19, 30]. The skeletal changes in busulfan-induced ulnar and radial deficiencies were similar to those of clinical cases. The critical period of ulnar deficiency in rats is about 1 day earlier than that of radial deficiency, and the critical period of radial deficiency in rats is just before limb buds appear [17, 30]. It was found that the dead mesenchymal cells were distributed evenly and there was no localized cell deficiency inside the limb bud [33]. It was clear that the absence of digits in longitudinal deficiency was not caused by the localized deficiency of the limb bud.

A single cause affecting the limb bud in a certain receptive period of the development of the limb bud can induce central polydactyly, cleft hand, and syndactyly. When busulfan was given to rat fetuses at a critical period of these anoma-

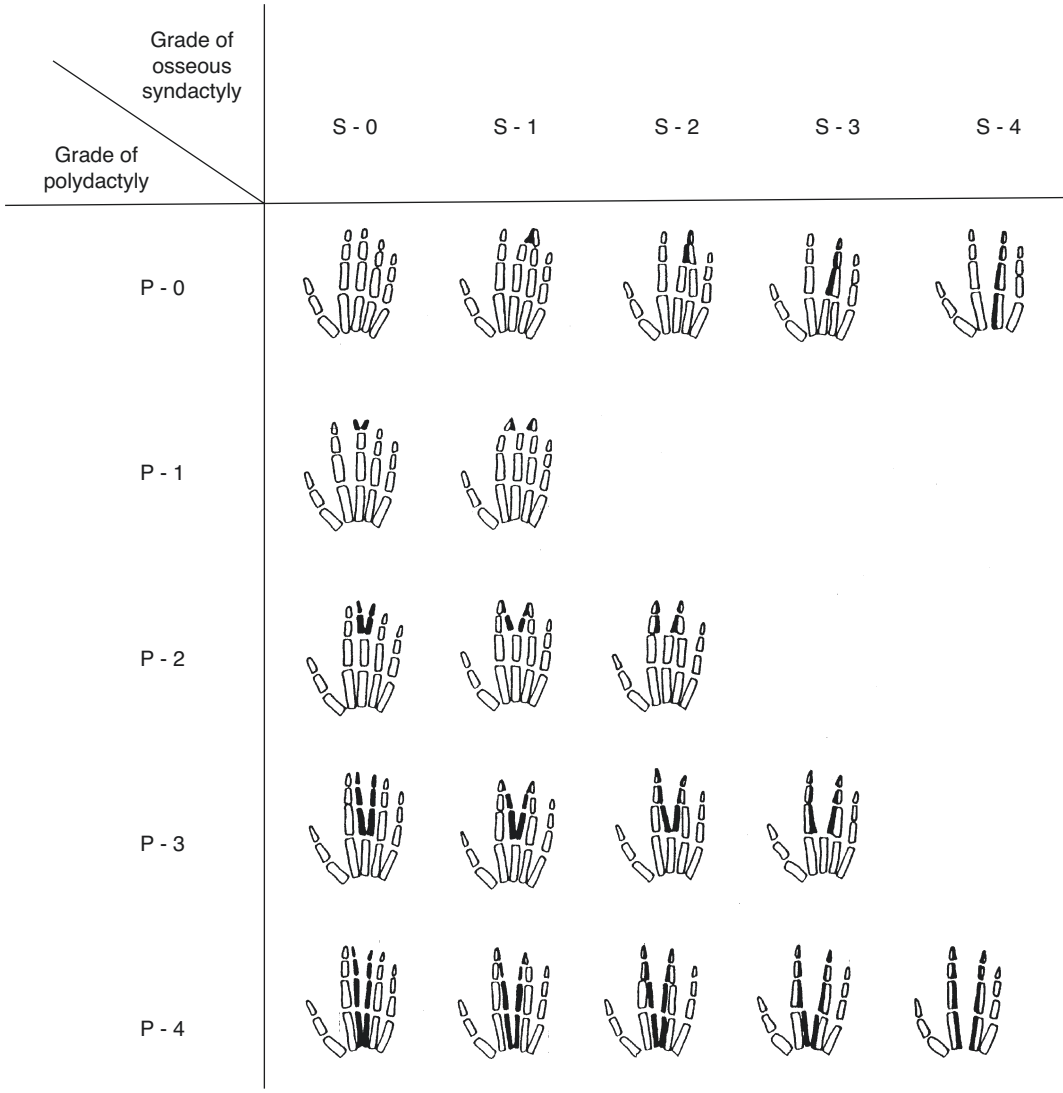

Fig. 16.2 Cleft hand formation processes from central polydactyly and/or osseous syndactyly. (Reprinted with permission from Ogino [20])

lies, later than that of longitudinal deficiency, cleft hand, central polydactyly, and osseous syndactyly were induced. The deformities were seen in varying stages of severity of osseous fusion. It was postulated that cleft hand was induced by the same etiology as osseous syndactyly and central polydactyly [29].

In order to examine the underlying mechanism of busulfan-induced cleft hand, central polydactyly, and syndactyly, the authors evaluated localized apoptosis by Nile Blue staining and TdT-mediated dUTP nick end labeling (TUNEL) assays in treated rat embryos [34]. The authors further evaluated the potential disruption of major developmental pathways linked to digit number and syndactyly using Fgf8, Bmp4, and Shh as markers of these pathways. In busulfan-treated embryos, there was no difference of expression of Fgf8, BMp4, and Shh in the limb bud and footplate. The early morphological changes leading to

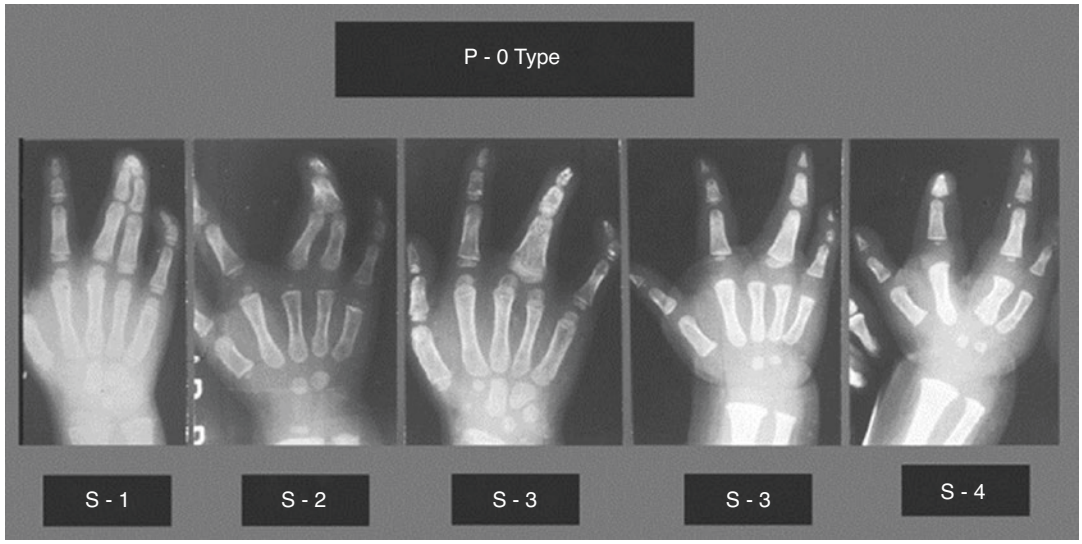

Fig. 16.3 The skeletal changes of P-0 type of anomalies in clinical cases. They seem to show that cleft hand formation proceeds from osseous syndactyly. (Reprinted with permission from Ogino [28])

central polydactyly, syndactyly, and cleft hand or foot were growth reduction and abnormal clefts in the central parts of the footplates. The abnormal cleft was induced without precedent cell death, and the cleft became deeper also without cell death [34]. If the abnormal cleft were induced on the edge of digital radiation, it might induce polydactyly or cleft hand or foot. If the abnormal cleft were induced on the interdigital tissue, it might induce syndactyly or cleft hand or foot. The authors conclude that the abnormal cleft formation without precedent cell death was an early change leading to central polydactyly, syndactyly, and cleft hand or foot by a teratogen (Fig. 16.5, [35]). Abnormal cleft formation without precedent cell death might be caused by localized inactivation of the apical ectodermal ridge (AER) in the central part of the footplate [36].

Results of recent studies on split-hand/split-foot malformation (SHFM) using murine Dactylaplasia mutant (Dac) have shown that the central segment of the AER degenerates, leaving the anterior and posterior segments intact [37]. From this observation, it was suggested that localized failure of ridge maintenance activity was the fundamental developmental defect in Dac and it might also be suggested in SHFM [10]. Therefore, the teratogenic mechanism of formation of cleft hand/foot is the same both in drug-induced cleft hand in rats and in mutant mice with cleft hand.

Position of Cleft Hand in Japanese Modification of Swanson's Classification

Based on the clinical and experimental studies, the author modified the IFSSH classification in 1986 and added a fourth new category—abnormal induction of digital rays [38, 39]. In IFSSH classification, brachysyndactyly is classified into undergrowth and transverse deficiency into failure of formation of parts, and there is no item of cleft of the palm. However, analysis of clinical cases showed that brachysyndactyly, atypical cleft hand, or transverse deficiency seemed to be morphological variants of symbrachydactyly [2, 3]. Therefore, these deformities are included in a similar concept to transverse deficiency in failure of formation of parts in modified classification.

On the other hand, central polydactyly is classified as duplication, syndactyly as failure of differentiation of parts, and typical cleft hand as failure of formation of parts in the IFSSH classification. However, these congenital deformities

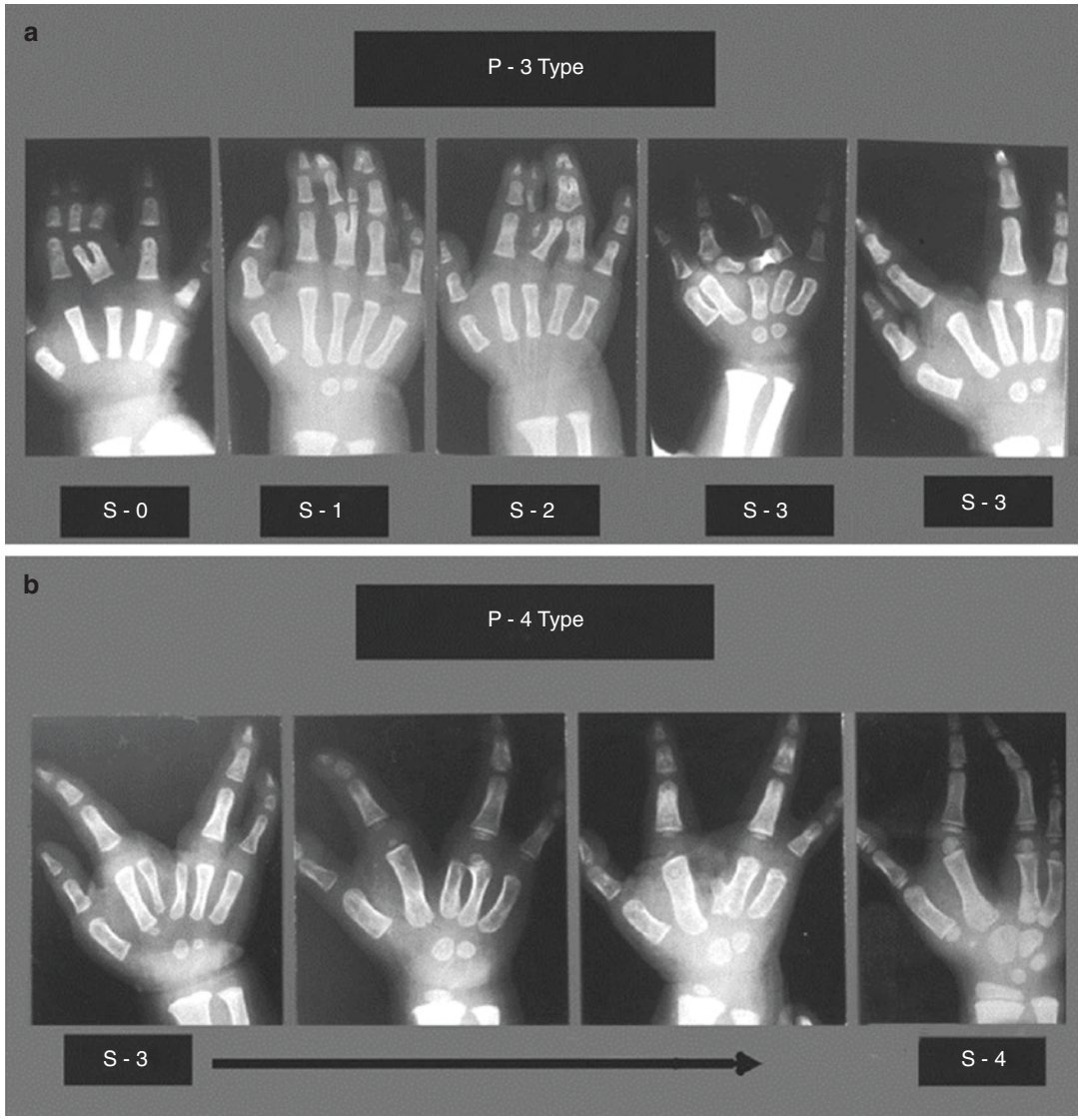

Fig. 16.4 (**a**, **b**) The skeletal changes of P-3 and P-4 types of polysyndactyly in clinical cases. They seem to show the cleft hand formation proceeds from central polydactylies. (Reprinted with permission from Ogino [28])

appear when the same teratogenic factor acts on embryo at the same developmental period. Because they have a similar causation, central deficiency, osseous syndactyly, central polydactyly, and cleft of the palm may be grouped together and are included in the same category of abnormal induction of digital rays in modified classification [38, 39] (Table 16.1). Recent literature has reported that chromosome abnormality and also abnormalities of the positional gene may cause these anomalies [40–42].

The Japanese Society for Surgery of the Hand adopted our modification of the IFSSH classification in 1996, and it is now called the Japanese modification [43]. As a skin manifestation, there are syndactyly and cleft of the palm. As a skeletal manifestation, there are osseous syndactyly, central polydactyly, and absence of central finger rays (cleft hand), and triphalangeal thumb associated with cleft hand.

The author reviewed his own cases of abnormal induction of digital rays affecting 186 hands

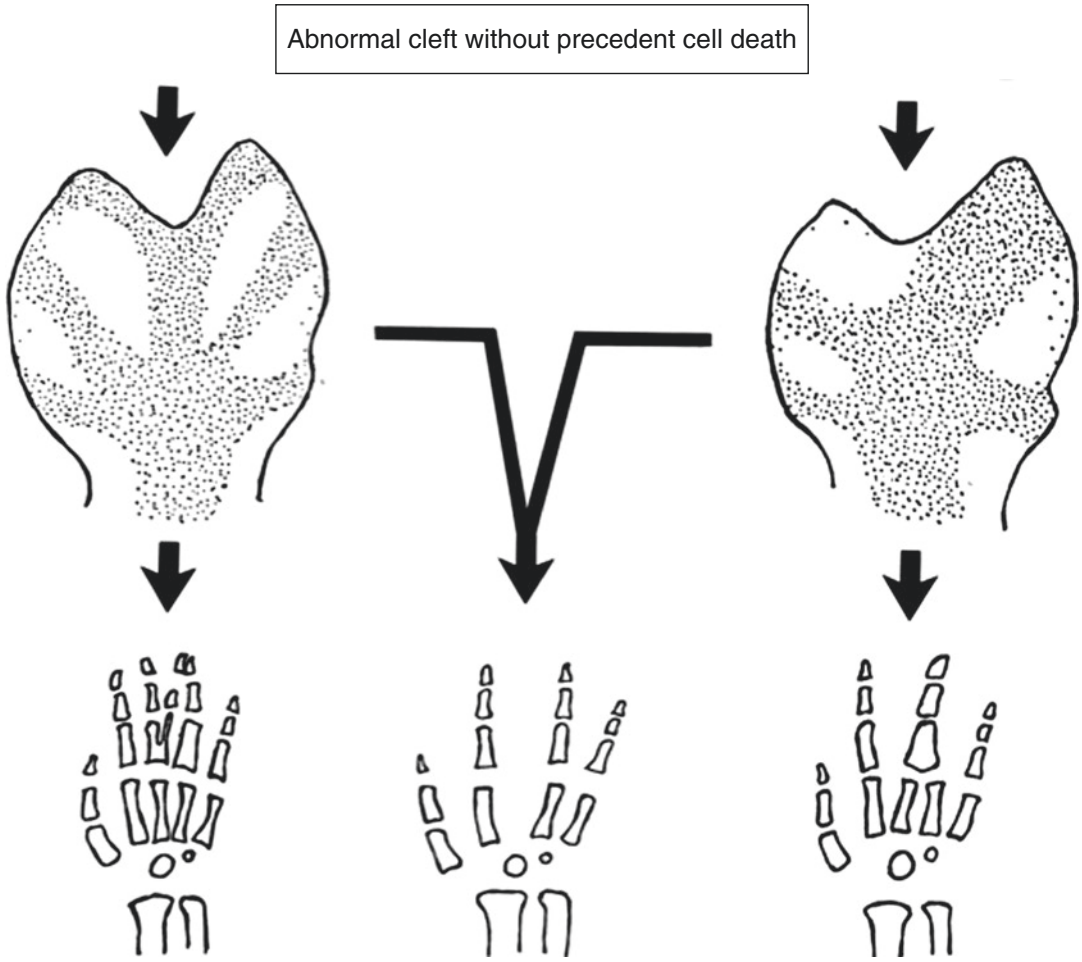

Fig. 16.5 Abnormal induction of digital rays. The early morphological changes leading to central polydactyly, syndactyly, and cleft hand were growth reduction and abnormal clefts in the central parts of the hand plates. The abnormal cleft was induced without precedent cell death, and the cleft became deeper without cell death. If the abnormal cleft is induced on the edge of digital radiation, it might induce polydactyly or cleft hand. If the abnormal cleft is induced on the interdigital tissue, it might induce syndactyly or cleft hand. (Reprinted with permission from Ogino [35])

in 125 patients. Eighty-three cases were male and 42 female. The right side was affected in 47 cases, the left in 17 cases, and both in 61 cases. The deformities of the affected hand were expressed by the combination of cleft on the palm, cutaneous syndactyly, osseous syndactyly, absence of central digit(s), which is absence of all phalanges of the digital ray(s), and central polydactyly. Of the 186 abnormal hands, a single deformity appeared in 86 hands: cutaneous syndactyly alone in 65 hands, osseous syndactyly alone in 17 hands, and cleft on the palm without absence of digit in 4 hands. In 100 hands, multiple deformities appeared in the same hand of a patient. Polydactyly and syndactyly were present in the same hand in 16 cases; a combination of cleft on the palm and syndactyly in 6 cases; a cleft, polydactyly, and syndactyly in 1 case; an absence of central digit and cleft on the palm in 37 cases; an absence of central digit, cleft on the palm, and syndactyly in 34 cases; an absence of central digit, cleft on the palm, and polydactyly in 1 case; and an absence of central digit, a cleft on the palm, central polydactyly, and syndactyly

Table 16.1 The Japanese Society for Surgery of the Hand Modification of the IFSSH classification revised by Ogino (2013)

I. Failure of formation of parts (arrest of development)
A. Transverse deficiency
1. Peripheral hypoplasia type
2. Short webbed finger type
3. Tetradactyly type
4. Tridactyly type
5. Didactyly type
6. Monodactyly type
7. Adactyly type
8. Metacarpal type
9. Carpal type
10. Wrist type
11. Forearm type
12. Above elbow type
B. Longitudinal deficiencies
1. Radial deficiencies:
(a) Dysplasia of the radius
(b) Deformities of the hand
(c) Dysplasia of the elbow
2. Ulnar deficiencies:
(a) Dysplasia of the ulna
(b) Deformities of the hand
(c) Dysplasia of the elbow
C. Phocomelia
D. Tendon or muscle dysplasia
E. Nail dysplasia
1. Aplasia/hypoplasia of the nail
2. Nail defect with brachytelephalangia
II. Failure of differentiation of parts
A. Synostosis
B. Radial head dislocation
C. Symphalangism
D. Contracture
1. Soft tissue
(a) Arthrogryposis multiplex
(b) Webbed elbow (pterygium cubitale)
(c) Clasped thumb
(d) Windblown hand
(e) Camptodactyly
(f) Aberrant muscles
(g) Nail deformities:
(i) Nail deformity with clinodactyly
(ii) Nail deformity with hypoplasia of the distal phalanx
(iii) Nail deformity or palmar nail with hypoplastic digit and symphalangism
2. Bone
(a) Kirner deformity
(b) Delta bone (longitudinal epiphyseal bracket)
(c) Madelung deformity
3. Others
E. Tumorous conditions
III. Duplication
A. Thumb polydactyly
B. Central polydactyly (it should be category IV)
C. Polydactyly of little finger
D. Opposable triphalangeal thumb
E. Other hyperphalangism
F. Mirror hand
G. Dorsal and palmar duplication
1. Double dorsal limited in the digit
2. Double dorsal including the hand
3. Double palmar limited in the digit
4. Double palmar including the hand
IV. Abnormal induction of digital rays
A. Soft tissue:
(1) Cutaneous syndactyly, (2) cleft of the palm
B. Bone:
(1) Osseous syndactyly, (2) central polydactyly, (3) absence of central finger ray(s), (4) triphalangeal thumb with cleft hand
C. Ulnar cleft hand:
(1) Cleft of the fourth web space: (a) with absent ring finger, (b) without absent ring finger
(2) Stiff finger: (a) symphalangism, PIP and/or DIP joint; (b) partial ankylosis, PIP and/or DIP joint
(3) Nail deformity: (a) clam nail, (b) claw nail, (c) circumferential nail
D. Abnormal induction of digital rays with hypoplastic hand:
(1) Polydactyly, (2) syndactyly, (3) central finger absence
V. Overgrowth
A. Macrodactyly
B. Hemihypertrophy
VI. Undergrowth
A. Microcheiria (hypoplastic hand)
B. Brachydactyly
C. Clinodactyly
VII. Constriction band syndrome
(1) Constriction ring, (2) lymphedema, (3) acrosyndactyly, (4) amputation type
VIII. Generalized skeletal abnormalities and a part of syndrome
IX. Others (including unclassifiable cases)

in 5 cases. In these cases there were eight hands with triphalangeal thumb associated with absence of the index finger, and there was one hand with a floating little finger. In bilaterally affected cases, same type of expression was evident in both the right and left hands in 47 cases. Different abnormalities occurred in the right and left hands in 14 cases. Hand deformities were expressed by com-

binations of cutaneous syndactyly, cleft on the palm, osseous syndactyly, central polydactyly, absence of central digit, and triphalangeal thumb with cleft hand with absence of the index finger. This review suggested that abnormal induction of digital rays may explain simultaneous occurrence of differing abnormalities within the same hand. The concept of abnormal induction of digital rays seemed useful for classification of congenital hand differences.

In this chapter, the author has revised the Japanese modification of the IFSSH (see Table 16.1). The abnormality of the nail has not been clearly classified, and the abnormalities of the dorsoventral plane of the hand also have not been described in the previous Japanese modification.

Firstly, "E. Nail dysplasia" in I. Failure of formation of parts was subdivided into:

- Aplasia/hypoplasia of the nail
- Nail defect with brachytelephalangia
- Others

Secondly, II. Failure of differentiation of parts had (g) nail deformities added as a subcategory, and it is subclassified into:

- Nail deformity with clinodactyly
- Nail deformity with hypoplasia of the distal phalanx
- Nail deformity or palmar nail with hypoplastic digit and symphalangism (this is the same deformity observed in "ulnar cleft hand: VI. C")
- Others

Thirdly, III. Duplication had "G. dorsal and palmar duplication" added and is subclassified into:

- Double dorsal limited in the digit
- Double dorsal including the hand
- Double palmar limited in the digit
- Double palmar including the hand
- Others

Fourthly, the categories IV. Abnormal induction of digital rays added the categories:

C. Abnormal induction of digital rays and ulnar cleft hand

D. Abnormal induction of digital rays with hypoplastic hand

After these changes, it becomes easier to differentiate true typical cleft hand described by Barsky and other cleft handlike deformities.

The Cleft Hand in the Oberg-Manske-Tonkin (OMT) Classification

The underlying etiology of split hand and foot malformations, cleft hand, has been better characterized by both clinical genetics and developmental biology over the past few years [44]. Of the seven subcategories of split hand and foot malformations, six have a known genetic basis, and all are linked to disruption in apical ectodermal ridge formation or function, which results in variable loss of proximodistal growth in the central hand plate [45, 46]. Current genetic technologies confirm the underlying etiology first noted by Ogino several decades ago [17, 30–35]. For this reason, cleft hand has moved from its previous position of malformation hand plate, unspecified axis [44] to malformation hand plate proximal-distal axis (OMT 2020, IB1iv) [47].

Clinical Characteristics

Blauth and Falliner's reported incidence of cleft hand: they found bilateral involvement in 50%, and in unilateral involvement, the ratio of right hand to left hand is 60–40%. The ratio of male to female is 60–40% [48]. In approximately one out of three cases of cleft hand, there was associated cleft foot.

Defect of the central finger rays varies [49]: there are hands with deep cleft formation on the palm without absence of the finger rays. This is a type of central deficiency and therefore a form of cleft hand (Type 0) [50]. There are cleft hands with one finger absent, two fingers absent, three fingers absent, or four digits absent. In one finger absence type (Type 1), the middle finger is most commonly absent. In that case, the ring finger

often will have camptodactyly. This deformity is not actually true camptodactyly but a claw finger deformity due to abnormal lumbrical and interosseous muscles. Most often, the affected ring finger has no joint contracture when the child is young. If the metacarpophalangeal joint of the ring finger is passively flexed to neutral, the patient can actively extend the PIP and DIP joints of the affected finger.

Some cases with mild excessive cleft and absence of the middle finger will have normal looking third metacarpal bone radiologically. However, in some cases, the third metacarpal bone deviates ulnarly and has a common MP joint with the fourth metacarpal bone and proximal phalanx of the ring finger. Alternately, third metacarpal bone will deviate radially and have a common MP joint with the second metacarpal bone and proximal phalanx of the index finger. In the former case, the ring finger is wider than normal, and in the latter case, the index finger is wider than normal. When middle finger ray including the third metacarpal is absent, the cleft is deeper than usual. The deeper the cleft is, the more often syndactyly of the first web space and the fourth web space occur. In some rare cases of deep cleft, hypoplasia of the little finger, or the fusion of the fourth and fifth metacarpals, is seen. In type 1 cleft hand, the index finger or ring finger also may be absent [51, 52]. When the index finger is absent, the thumb is often triphalangeal and will deviate radially, in contrast to most triphalangeal thumbs, which deviate ulnarly. A "Y"-shaped second metacarpal bone between the thumb and middle finger, or two thumb metacarpal bones, may be seen on X-ray. When the ring finger is absent, the little finger is small and stiff, and this may be called "ulnar cleft hand." When the finger is not absent and the cleft is in the fourth web apace, this is often associated with stiffness of the IP joints, palmar nail, and the dorsal skin on the palmar side of the little finger. This may be called "double dorsal deformity of the finger." The etiology of this deformity is considered to be different from other types of cleft hand (see below).

In two-finger absence type (Type 2), the index and middle fingers are absent more commonly than the middle and ring fingers. When the index and middle fingers are absent, the thumb is usually triphalangeal. In three-finger absence type (Type 3), if the thumb is opposable, then pinch is possible between the thumb and the little finger. If the thumb is in the plane of the hand, however, pinch between the thumb and little finger is impossible [53]. In four-digit absence type (Type 4), the radial four digits are absent in most commonly, but very rarely the ulnar four digits will be absent and only the thumb remains [50]. In radial-four-digits absence type, the metacarpals of the thumb and affected fingers are usually only partially absent or not involved.

A cross bone is a transverse or oblique bone lying in the base of the cleft. It is regarded as the displaced remnant of the metacarpal or proximal phalanx of the missing digit, and it bridges between the end of the metacarpal bones of the missing digit and the proximal phalanx, MP joint, or the metacarpal bone of the adjacent finger. There may be two cross bones which might be duplicated proximal phalanges of the missing digit and are located between missing digit and adjacent fingers between the end of the metacarpal bones of the missing digit and the proximal phalanx, MP joint, or the metacarpal bone of the adjacent finger. There may be two cross bones, which might be duplicated proximal phalanges of the missing digit and are located between missing digit and adjacent fingers. There may be solid bone union or cartilaginous continuity between the cross bone and the proximal phalanx of the adjacent finger in the skeletally immature patient. In some cases, the proximal phalanx of the adjacent finger will have a delta phalanx (longitudinal epiphyseal bracket). X-ray films may show two metacarpals supporting one-digit, side-to-side fusion of the neighboring metacarpals, broad metacarpals, or duplicated metacarpals.

Surgical Classification of the Cleft Hand

Saito et al. [49] classified typical cleft hand into four types on the basis of the number of defective finger rays:

- Type 1: deep cleft formation on the palm without missing finger
- Type 2: defect of a single finger ray
- Type 3: defect of two finger rays
- Type 4: defect of three finger rays

Watari and Tsuge [27] classified typical cleft hand according to the same idea. In their classification, there is no type without absence of the finger but a type in which four finger rays are absent. They divided single ray defect type of cleft hand into proximal and distal types. In the proximal type, all phalanges and the metacarpus are missing, and in the distal type, only phalanges are missing. The author modified these classifications as follows (Fig. 16.6):

- Type 0: cleft hand without missing finger
- Type 1: defect of a single finger ray
- Type 2: defect of two finger rays
- Type 3: defect of three finger rays
- Type 4: defect of four digital rays

In every type, when the index finger is absent, the thumb is mostly triphalangeal and deviated radially.

Manske et al. [54] proposed surgical classification for cleft hand based on the characteristics of the thumb web space, because he thought the thumb web was more important to the function of the hand than the central deficiency. According to his report, cleft hand is classified into five types:

- Type 1: normal first web
- Type 2A: mildly narrowed first web
- Type 2B: severely narrowed first web
- Type 3: syndactylized first web
- Type 4: merged web in which index ray suppressed and thumb web space is merged with the cleft

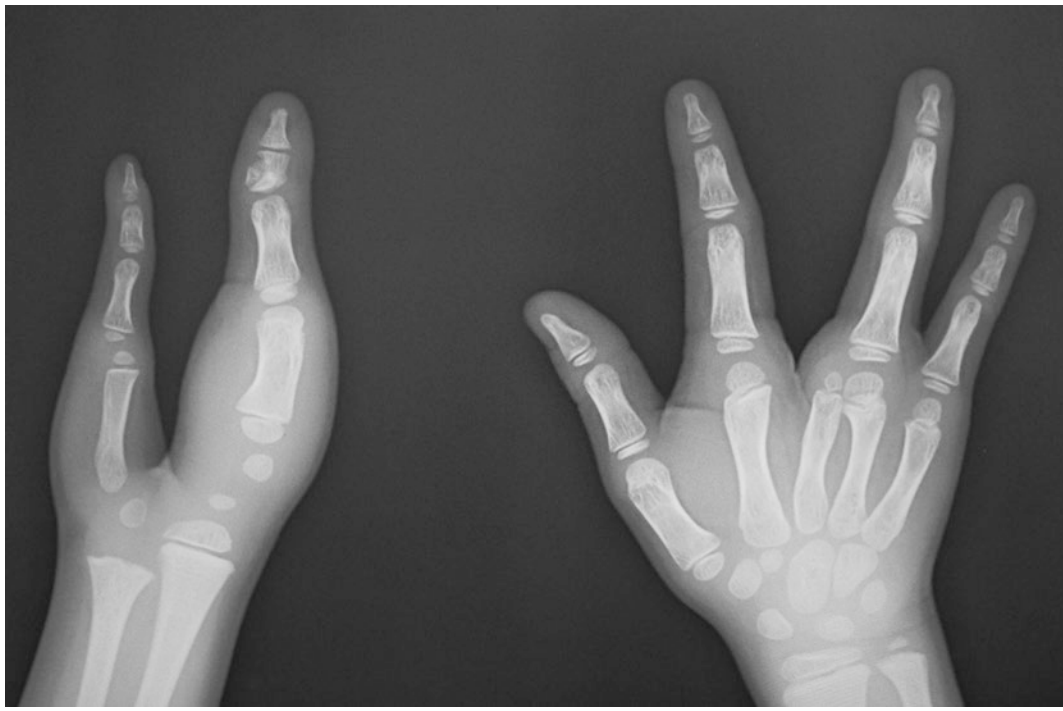

Fig. 16.6 Different degree of absence of the fingers associated in both hand of a patient. Left: type 3 cleft hand with central three-finger absence and triphalangeal thumb with radial deviation of the IP joint. Right: type 1 cleft hand with absence of the middle finger

- Type 5: absent web, in which thumb elements suppressed, ulnar rays remain, and thumb web space no longer present

One benefit of subclassification of the congenital hand deformities is that one can better picture the deformity of the hand, from description with the classification. For example, when told or read: "Type 4 thumb polydactyly in Wassel's classification [55]" or "Type 3 hypoplastic thumb in Blauth's classification [18]," one can clearly image the deformities of the hand and the possible associated deformities. Both hypoplastic thumb and thumb polydactyly may have the narrowing of the first web. This is an important factor not only when treating cleft hand but also hypoplastic thumb and thumb polydactyly. Manske reported that the progressive narrowing of the thumb web correlated with progressive severity of the central defect. The author also observed the same findings and published it in 1977 [19]. Therefore, one can imagine the possible condition of the first web associated with cleft hand, using Saitou's classification based on the number of defective finger rays. Surgical treatment is directed not only to the first web but also to the deep or wide cleft. I feel that subclassification should be valuable not only for the patient but also for the communication of the people who are treating these deformities. Based on this viewpoint, Saitou's classification based on the number of defective finger rays seems more valuable for subclassification of the cleft hand. If one uses Manske's classification [55], it would be more useful if combined with Satou's classification [49]. Falliner [56] classified cleft hand into three types as follows:

Radial cleft hand
- Hand deformities including osseous syndactyly of the thumb and index finger
- Absence of the index finger
- Absence of the thumb and index finger
- Absence of the radial three or four digits

Central cleft hand
- Central defect with absence of the middle finger
- Central defect with absence of the central two fingers
- Central defect with absence of the central three fingers
- Cleft hand with only the thumb and little finger present

Ulnar cleft hand
- Absence of the ring finger
- Absence of the ring and middle fingers, with or without of hypoplasia of the little finger

This classification seems to be too simple for clinical use. Moreover, ulnar cleft hand has characteristic clinical features such as deep cleft in the fourth web space, absence of the ring finger, and/or hypoplastic little finger associated with stiffness of the PIP joint and palmar nail, and it is considered to differentiate it from other types of cleft hand. When one uses Japanese modification of the IFSSH classification [47], in abnormal induction of finger rays, the hand deformities are expressed with combination of the cleft, syndactyly, and other phenotypes. Therefore, if one describes deformities combined with the degree and the location, one can expresses the deformity of the cleft hand and other combined deformities precisely.

Cleft of the Fourth Web Space of the Hand

Cleft of the fourth web space of the hand is associated with or without absence of the ring finger. These deformities are called ulnar cleft hand [52]. However, its clinical features are different from various types of abnormal induction of digital rays including cleft hand. Moreover, characteristic clinical features of cleft of the fourth web space with absence of the ring finger are different from those without absence of the ring finger, although the little finger is hypoplastic in both conditions [51, 57]. There is no appropriate terminology and precise classification for the sequence of these congenital hand deformities. Ulnar cleft hand without absence of the ring finger is characterized with combination of various

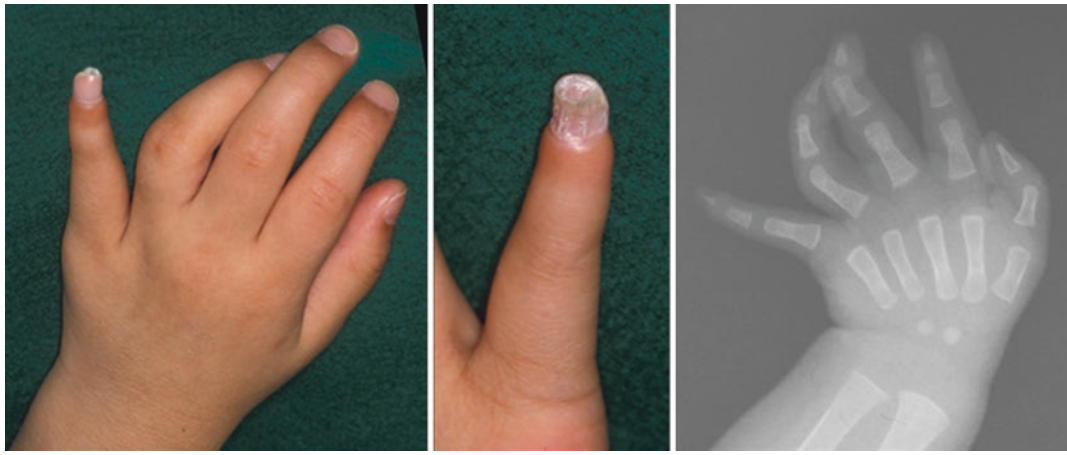

Fig. 16.7 Cleft of the fourth web space without absence of the finger. Left: cleft of fourth web space associated with stiff PIP joint (symphalangism) and hypoplastic little finger. Center: circumferential nail and dorsal skin on the palmar side of the little finger. Right: synchondrosis of the PIP joint of the little finger

degrees of cleft of the ring and little finger, hypoplasia of the little finger, hypoplasia of hypothenar muscles, extension contracture or symphalangism of the little finger and clam nail, claw nail or circumferential nail deformity, and dorsal skin of the palmar little finger [57] (Fig. 16.7). In the opposite hand, the same deformity, polydactyly of the little finger, ulnar deficiency, or partial duplicated distal phalanx of the ring finger may be seen. In this anomaly, there are various associated deformities of the hand. Hand and nail deformities in this anomaly are similar to those of ulnar-mammary syndrome or Schinzel syndrome [58]. The teratologic sequence of the variety of hand deformities with ulnar cleft of the fourth web without absence of digits is most likely a different entity from abnormal induction of finger rays.

Abnormal Induction of Digital Rays (Including Cleft Hand) Associated with Hypoplastic Hand

Abnormal induction of digital rays in the hand plate means induction of abnormal number of the digital rays in the hand plate. Therefore, excessive or decreased number of inductions of digital ray occurs, but nearly all of the hands with deformities of abnormal induction of digital rays do not seem to have hypoplasia of the hand. However, there are hand deformities, with combinations of syndactyly, cleft of the palm, central polydactyly, osseous syndactyly, or absence of the central fingers associated with hypoplasia of the affected hand. This deformity is most often unilateral. This condition seems to have both the characteristic features of transverse deficiency (hypoplasia of the affected hand and unilateral involvement) and those of abnormal induction of digital rays (central polydactyly, syndactyly, and cleft hand). This condition is not associated with polydactyly, syndactyly, and/or central deficiency of the opposite hand and the feet. In the affected hand, thenar and hypothenar muscles are relatively well formed, and it is sometimes difficult to say which finger rays are missing in the central finger rays, although the thumb and the little finger are never absent [59, 60] (Fig. 16.8).

Associated Anomalies

As regional association, syndactyly of the thumb and index finger or that of the ring and little fingers and brachydactyly of the little finger are most common. Triphalangeal thumb often occurs in cleft hand associated when the index finger is absent. Polydactyly of the thumb and side-to-side

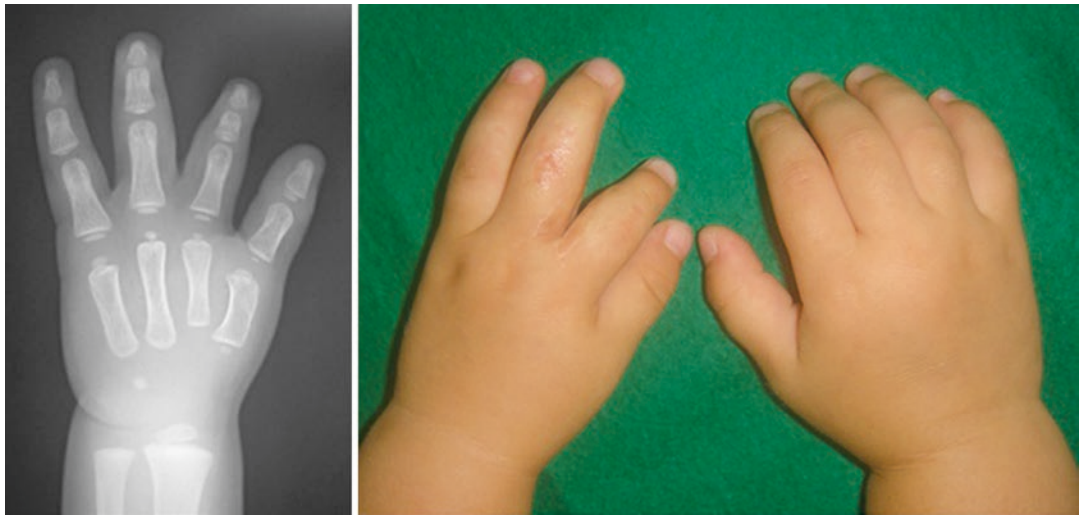

Fig. 16.8 Abnormal induction of the finger rays associated with hypoplasia of the affected hand. The characteristic features of this condition seem to be those of transverse deficiency, which are unilateral involvement and hypoplasia of the whole affected hand compared to the opposite hand, and those of abnormal induction of digital rays, which are that the hand has cleft of the palm, syndactyly, central polydactyly, osseous syndactyly, and/or absence of the central fingers. It is difficult to say which finger rays are missing in the X-ray film

synostosis of the fourth and fifth metacarpals are rarely seen. Occasionally, some patients will be affected bilaterally in which there is a cleft hand on one side and on the other, another type of anomaly, such as cutaneous syndactyly, osseous syndactyly, or central polydactyly. The central deficiency in SHFM patients may also be accompanied by other distal limb anomalies including central polydactyly and/or syndactyly [61].

Foot deformities, such as cleft foot, syndactyly, central polydactyly, and tibial ray deficiency, are also associated with cleft hand.

Cleft hand appeared as a part of syndrome, such as ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome, de Lange syndrome, split hand/split foot with mandibulo-facial dysostosis, split hand with perceptive deafness, split hand with congenital nystagmus, fundal changes and cataract, anonychia with ectrodactyly, and the acrorenal syndrome.

As mentioned above, split hand/foot malformation (SHFM), or central ray deficiency, can occur as an isolated malformation or as a part of syndrome, such as in the EEC syndrome. Rüdiger et al. in 1970 [62] named an anomaly complicated three malformations the EEC syndrome, based on their initials, namely, ectrodactyly, ectodermal dysplasia, and clefting syndrome. The main clinical signs, in order of frequency observed in Rodini and Richieri-Costa [63] reported group, were ectodermal dysplasia (100%), ectrodactyly (78%), tear duct anomaly (71%), cleft lip/plate (58%), genito-urinary anomalies (15%), deafness (9%), and mental retardation (2%). The clinical expression of the EEC syndrome is quite variable; any one of the above signs may be absent except ectodermal signs. Ectrodactyly may occur only in hands (25%) or in both hands and feet (65%). Ten percent of the patients had no limb involvement. Cleft hands and feet are characteristic anomalies of this syndrome, but syndactyly and polydactyly of the central digital ray may be associated with this syndrome [61, 64, 65]. Majewski and Küster [66] stated that ectrodactyly is not an obligatory symptom. Skin anomalies related to ectodermal dysplasia are fine, thin smooth skin, hyperkeratosis, and dermatoglyphic alterations. Trichodysplasia, dental defects, onychodysplasia, and dyshidrosis may be associated. In EEC syndrome, most cases have *p63* gene mutations. In contrast, *p63* mutations were detected in only

a small proportion of patients with isolated SHFM [67].

Treatment of Cleft Hand

Indication and Timing of Surgery

Cleft hand has several associated deformities. The goals of surgical treatment for cleft hand may need to address:

- Reduction of the excessive deep or wide interdigital space
- Separation of syndactyly of the first web or the interdigital space between the ring and little fingers
- Correction of claw finger deformity of the ring finger
- Correction of the deviation of the thumb due to triphalangeal thumb
- Correction of the deviation of the index finger due to trapezoidal shape of middle phalanx

Many authors stated that surgery of cleft hand is mainly performed for esthetic reasons. Reduction of the interdigital space is in fact performed mainly for the cosmetic reasons in cleft hand without missing finger (Type 0) and cleft hand with defect of a single finger ray (Type 1). However, correction of thumb deformities including the first web contracture and that of the deviation of the thumb due to triphalangeal thumb gives significant functional improvement. Such procedures may be performed simultaneously in order to prevent multiple surgeries. Reduction of the interdigital space, separation of syndactyly of the first web space, and correction of the deviation of the thumb and that of claw finger deformity of the ring finger are usually performed at initial surgery. Claw finger deformity of the ring finger is corrected by reconstruction of the MP joint flexor with FDS tendon of the missing finger as in lasso procedure. It is easily done at initial surgery, as the flexor tendons are exposed in the palm, and it is easy to select the transferred tendon before the cleft is closed. Alternatively, this procedure may be performed later as a second stage surgery, if the deformity is not corrected spontaneously after closing the cleft. The combination of the surgical procedures is different in each case according to the associated deformities. Reduction of the interdigital space should not be performed for some kind of cleft hand that is cleft hand with missing index finger, that with missing index and middle fingers, and cleft hand with defect of central three finger rays (Type 4). If reduction of the interdigital space is performed in these cases, the patient will have difficulty in grasping a large object. On the other hand, in cleft hand with trapezoidal proximal phalanx of the ring finger, the proximal phalanx is a delta phalanx, and the ring finger has ulnar deviation. It may be corrected in some extent by physiolysis with free fat graft, if the surgery is performed in a young patient [68]. However, a secondary corrective osteotomy may be needed if satisfactory correction has not been achieved after physiolysis.

Closure of the excessive interdigital space (cleft) for cleft hand without missing finger (Type 0) or that with absence of a single finger (Type 1), separation of syndactyly between thumb and index finger and removal of the delta phalanx of the thumb, and correction of the claw finger deformity of the ring finger are performed at the age of 1 year. The author prefers to perform these surgeries simultaneously. Separation of syndactyly of the ring and little fingers is usually carried out at the second stage surgery, since the level of the interdigital web to be corrected can be more easily determined at that time. Separation of the side-to-side fusion of the metacarpals and arthrodesis of the finger should be performed at a later stage as needed. Physiolysis with free fat graft should be performed around the age of 3–4 years. All necessary surgery should be completed by the time the child enters school at the age of 6 years.

Preoperative Care

Usually no preoperative care is needed. The author asks the parents to close the cleft of the hand manually by pushing the border digits at

least one a day, when the simple closure of the cleft is indicated. If the cleft hand is associated with claw finger deformity of the ring finger, the author asks them also to prevent contracture of the finger with manual correction.

When the interdigital space is wide or deep and simple closure of the cleft is indicated, static splint may be applied in order to close the cleft until surgery. When we examine a patient, the first web contracture associated with cleft hand at the age of 1 or 2 years, sometimes the patient does not use the thumb for pinch but uses two fingers adjacent to the cleft for pinch. When the splint is applied to close the wide cleft soon after birth, the patient can learn normal pinch pattern. While the literature has generally not recommended splinting prior to surgery for cleft, the author believes that the splint may establish proper muscle balance in a corrected position and prevent secondary skeletal deformities in selected cases. Preoperative splinting facilitates correction of the deformity during surgery.

Closure of the Excessive Interdigital Space

In order to make natural slope of the interdigital web after closing the cleft, many procedures have been reported: Barsky [1] used a diamond-shaped flap based on one digit, Kelikian [69] used a rectangular flap from across the apex of the palmar cleft of the hand, and Tsuge [70] used a triangular flap. The author prefers to use small triangular flap [50] (Fig. 16.9). Before skin incision, the second and fifth metacarpals are pushed toward each other and cleft is manually closed. The cleft can be closed easily, since the parents have been manually closing it for certain period before surgery. Then zigzag incisions may then be designed in expectation of an interdigitating closure. However, dorsal zigzag suture line may not give the best aesthetic result. In that case, the author uses dorsal straight incision instead of zigzag incision. An ulnar-based small triangular flap is raised by this incision. Excessive skin of a wide or deep interdigital space may then be removed. After necessary treatment of bone, tendon, and ligament, the skin incision is closed.

Treatment of Metacarpus and Cross Bone

There are different types of metacarpal bone deformities. In some cases, two metacarpals shift each other and support one digit. For example, in cleft hand with absent middle finger, the third metacarpal bone deviates ulnarward and has common MP joint among fourth metacarpal bone and proximal phalanx of the ring finger, or it deviates radialward and has common MP joint among second metacarpal bone and proximal phalanx of the index finger. If the third metacarpal bone prevents to close the cleft manually in these types of deformities, the shortening or partial removal of the metacarpal shaft is indicated (Fig. 16.10a, b), but it was not necessary in most cases. There are also side-to-side fusion of the neighboring metacarpals, broad metacarpus, and duplicated metacarpals. In the cleft hand with absent index finger, the Y-shaped second metacarpal bone is located between the thumb and middle finger, or two metacarpal bones exist in the thumb. These metacarpal deformities usually do not disturb hand function nor induce secondary deformities. Therefore, it is not necessary to treat them surgically.

On the other hand, many authors advocate removal of the cross bones and osteotomy of one or both of the adjacent metacarpals. Some authors thought that osteotomy is not essential. If the metacarpal remnants or cross bone prevents to draw the metacarpals together, these bone should be removed. If the second and fourth metacarpals could not be put into parallel after removing the third metacarpal, osteotomy of the second metacarpal or metacarpal transfer of the second metacarpal to the third one is recommended, but it is not essential. When these bones are removed, extensor hood and capsule of the metacarpophalangeal joint of the absent finger ray and/or adjacent finger ray must be incised. In such cases, repair of extensor hood and joint capsule are necessary to prevent deformity after surgery.

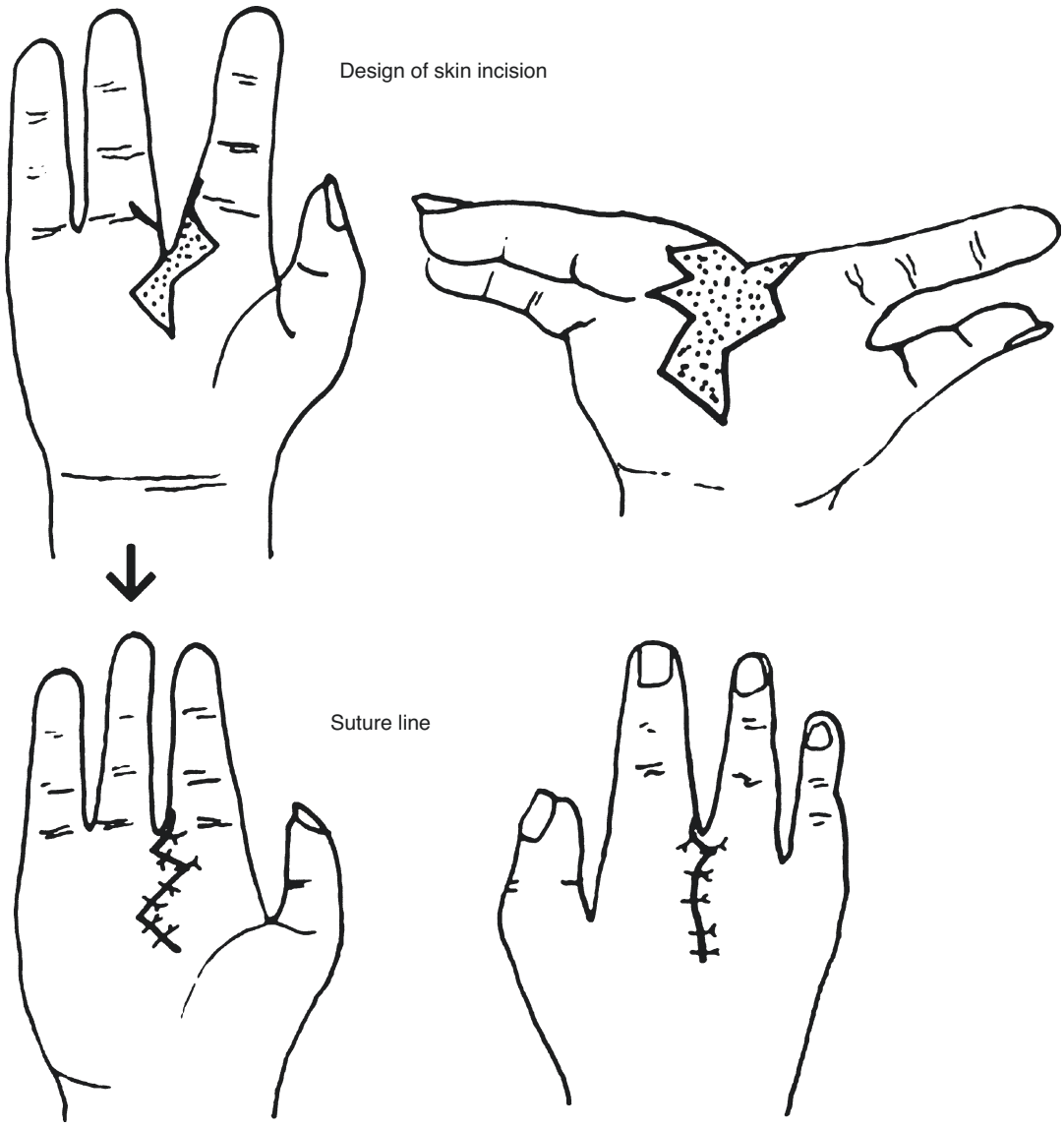

Fig. 16.9 Skin incision for reduction of the interdigital space using small triangular flap for the web. The *dotted area* of the skin will be excised

However, the tight soft tissue on the radial side does not allow the metacarpal to transfer ulnarward easily.

Reconstruction of the Deep Transverse Metacarpal Ligament

The deep transverse metacarpal ligament connects the anterior surfaces of the adjacent metacarpal heads. It normally blends with the volar plates of the metacarpophalangeal joints and prevents spreading of the fingers [71]. In cleft hand, the deep transverse metacarpal ligament is absent in the cleft where the finger is missing.

In order to obtain a satisfactory commissure and to prevent later spreading of the fingers, reconstruction of the deep transverse metacarpal ligament is necessary. Barsky makes two drill holes through both metacarpals adjacent to the

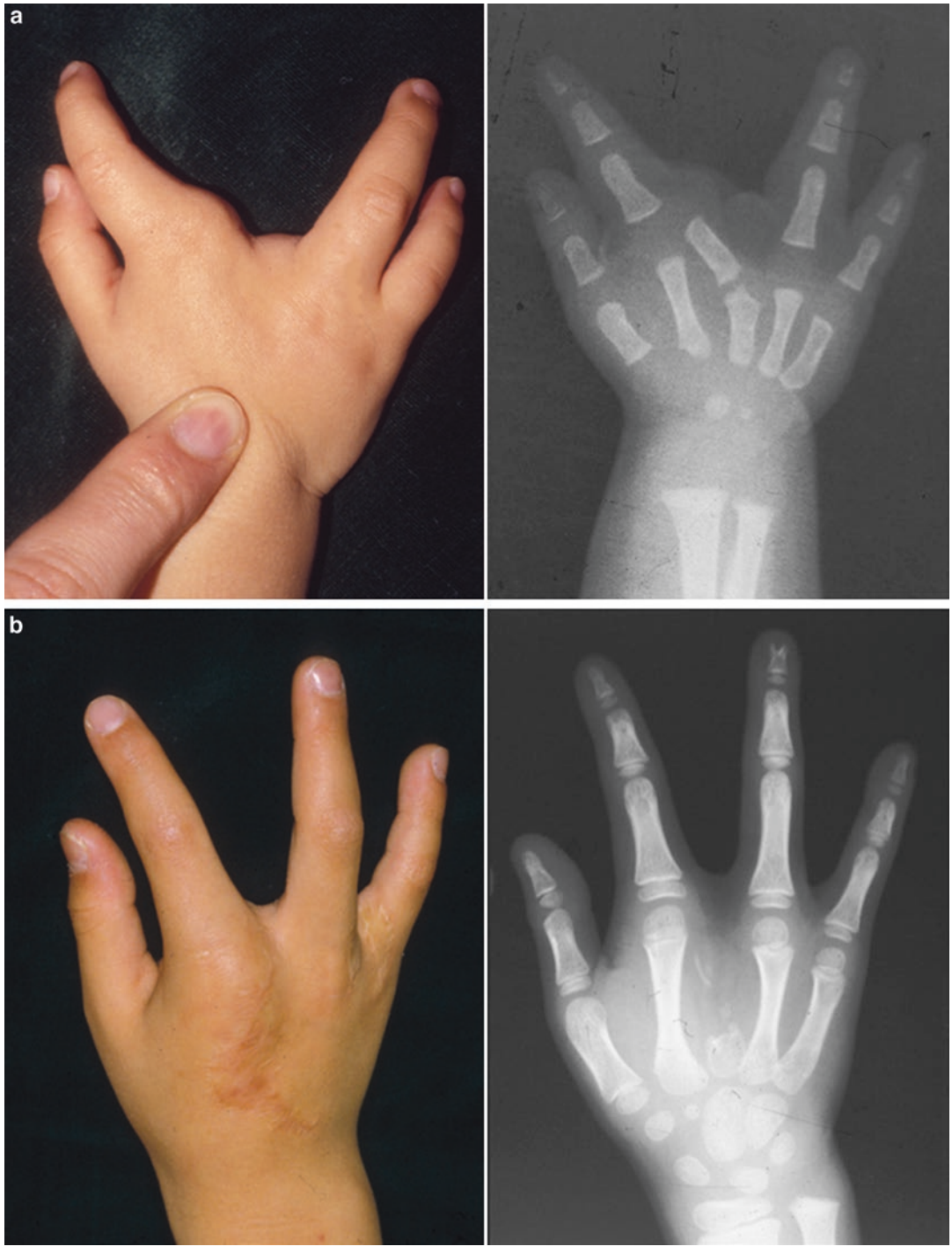

Fig. 16.10 Excision of the cross bone. (**a**) Preoperative appearance and roentgenogram. At the age of 1 year 2 months, the cross bone and the third metacarpal were resected. Osteotomy of the second metacarpal base was performed and the cleft was close. (**b**) Postoperative appearance and roentgenogram: after surgery, good alignment has been achieved

cleft just proximal to the heads. Chromic catgut sutures are passed through these holes and tightened to approximate the diverging metacarpals on each side of the cleft. Flatt [6] used to fashion some sort of ligament out of the adjacent soft tissues, but he used also catgut or silk sutures in a technique similar to that reported by Barsky. Free tendon graft can be also used for tethering the adjacent metacarpals. However, one should know that excessive tethering of the metacarpals causes rotation of the metacarpals and cross over the fingers during grasping. Excessive force should be avoided to coapting the two metacarpal together. If excessive force is necessary to coapt the two metacarpal together, metacarpal osteotomy or metacarpal shift is recommended. In order to reconstruct the deep transverse metacarpal ligament, the author uses ligamentous flaps made out of the flexor tendon sheaths of the index and ring fingers (Fig. 16.11). The advantage of this method is that the reconstructed deep transverse metacarpal ligament is located in anatomical position and it is possible to avoid excessive tethering or rotation of the metacarpals. The index finger and ring finger are drawn together. If there is slackening of the extensor hood, it should be repaired by plication or tendon transfer. Then the deep transverse metacarpal ligament is reconstructed by flexor tendon sheath. If osteotomy or metacarpal shift is necessary, it should be carried out before reconstruction of the ligament.

Widening of the Thumb Web Space or Syndactyly Release of the Thumb and Index Finger

When the cleft of the hand is deep, the thumb web space is narrow. In this type of cleft hand, cleft closure and release of the adduction con-

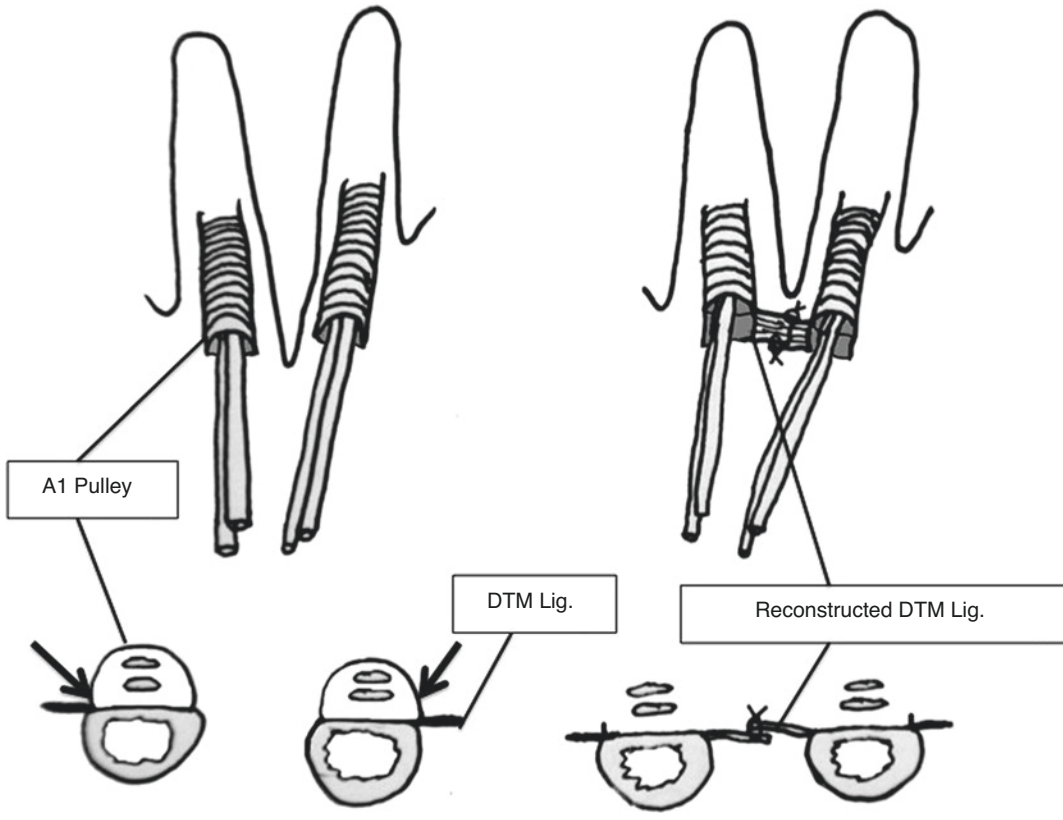

Fig. 16.11 Reconstruction of the deep transverse metacarpal ligament using flexor tendon sheath. Ligamentous flexor tendon sheaths are cut and ligamentous flaps are made. They are turned over and sutured each other

tracture of the thumb are necessary. Various procedures have been reported to treat the cleft and syndactyly simultaneously. In every procedure, a rotation flap fashioned from the skin of the cleft is used to separate the web between the thumb and index finger, and ulnar transposition of the index finger is performed to close the cleft. Snow and Littler used a palmar-based flap from the cleft, and Takahashi and Yabe [68, 72] used dorsal and palmar flaps from the cleft. Miura et al. [73], Ueba [74, 75], and Upton and Taghinia [76] solved this problem by transposition of the index finger ray to the ulnar side of the cleft by using skin incision around the base of the index finger. In all these procedures, an osteotomy is performed at the base of the second metacarpal, or the index finger metacarpal is transferred to an ulnar finger ray. In these procedures, care must be taken to preserve adductor pollicis muscle and prevent injury of the ulnar nerve to the adductor pollicis.

On the other hand, Foucher et al. [77] stated that none of surgical techniques reported previously is easily applied to the treatment of very deep clefts accompanied by a significant divergence of the metacarpal bones. In such cases, the results of current techniques are disappointing. They proposed a new technique of "Translocation in the Radial Direction of the Ulnar Finger(s)" (TRUF) by intracarpal osteotomy. The reported cases were limited. The TRUF operation allowed closing of the cleft, alignment of the metacarpal bones, and preservation of carpometacarpal mobility. They transfer the little finger or the little and ring fingers with carpometacarpal joint(s) and hamate radially after intracarpal osteotomy. They put the hamate and ulnar fingers on the capitate. The best indication of this procedure is in the case of good alignment of the second metacarpal with the radius and no stump of the middle metacarpal but divergence of the ulnar finger(s). If the second metacarpal has severe radial inclination, a closing wedge osteotomy of the ulnar base of the index metacarpal should be performed.

Previously, the author used a dorsally based flap from the cleft to widen the first web. The skin incision outlines the sides of the cleft on the palmar surface of the index and ring fingers forming a zigzag incision with a proximal V-shaped apex. At the sides of the adjacent metacarpal heads, an ulnarly based small triangular flap is raised by this incision. As the incisions curve back onto the dorsal aspect, they run almost parallel the index finger to the cleft side of the midline of the two fingers. Additional incision starts on the palm of the thumb and index web at the same level as the V-shaped cleft incision. It runs distally parallel with the index finger, curves back onto the dorsal aspect of the thumb-index web, and runs proximally and across in an ulnar direction to meet the dorsal index cleft incision. Fibrous bands between the thumb and index finger and fascia of the adductor pollicis and first dorsal interosseous muscle have to be released. Care must be taken to avoid the injuries to the neurovascular bundles. The index finger and ring finger are drawn together, and deep transverse metacarpal ligament is reconstructed by a flap of the flexor tendon sheath. Osteotomy of the metacarpal may be performed, if it is necessary. The flap raised from the cleft is transposed to the thumb-index web, and wound is closed in layers. However, the dorsal zigzag scar is not esthetically acceptable, and in some cases, necrosis of the distal tip of the flap due to poor circulation occurred. The author has used palmar rotation flap from the cleft to widen the first web (Snow-Littler procedure) for the past 25 years. The procedure is nearly the same as dorsal rotation flap [78, 79] (Figs. 16.12 and 16.13a, b). The digital artery is not included in the flap, but necrosis of the distal tip of the flap has never occurred.

When the cleft is very deep or there is complete syndactyly between the thumb and index finger, the Snow-Littler procedure is not indicated, as it is not easy to adapt the rotation flap from the cleft to the first web and the created deep V-shaped first web is not as esthetically acceptable. If there is complete or nearly complete syndactyly between the thumb and index finger, a palmar rotation flap from the cleft can be used but usually is not enough to cover the raw surface of the first web, and a full-thickness skin graft is necessary. In such cases, dorsal and palmar triangular flaps from the first web with free

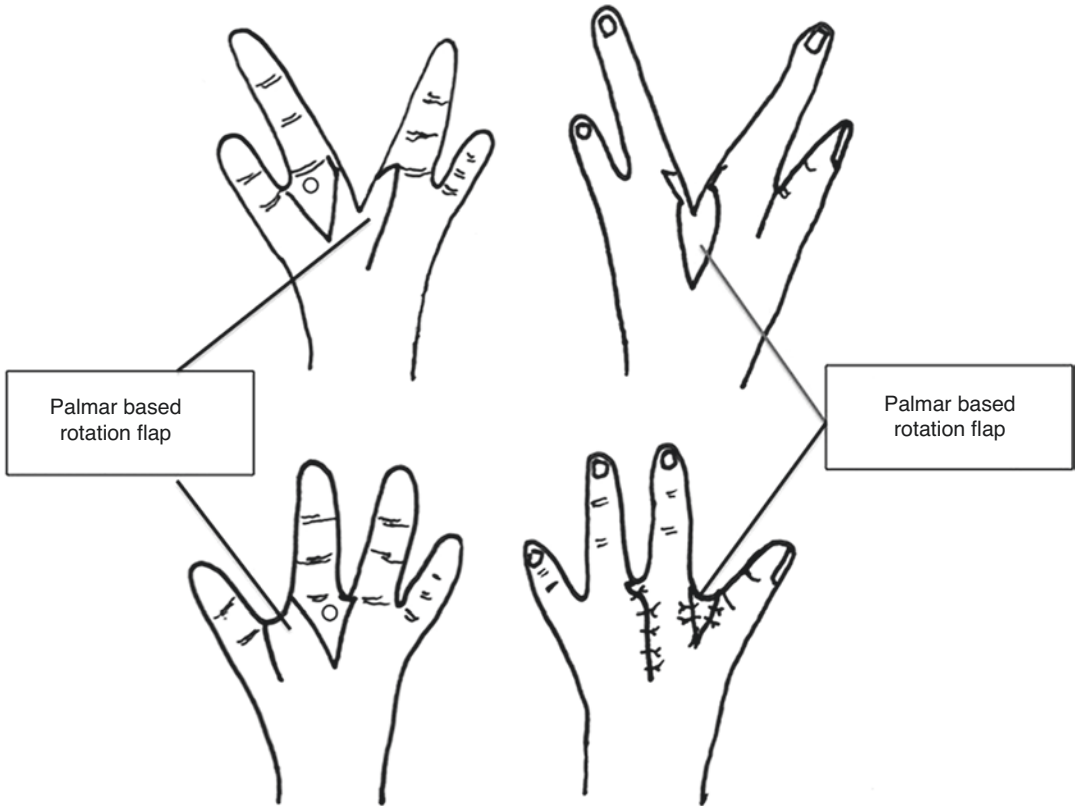

Fig. 16.12 Widening of the narrow first web by Snow-Littler procedure

skin graft are better than Snow-Littler procedure in order to obtain functionally and esthetically good first web.

Syndactyly Release Between Ring and Little Finger

Separation of syndactyly between ring and little fingers is carried out by using dorsal rectangular flap combined with free skin graft. This surgery is usually performed when the patient is about 2 years old. Sometimes author performs cleft closure and separation of syndactyly between the ring and little fingers simultaneously. In such cases, there is a benefit to be able to use skin removed from the cleft for the free skin graft, if rotation skin from the cleft to the first web is not needed. If cleft hand is associated with the fourth and fifth metacarpal fusion, and partial cutaneous syndactyly between the ring and little fingers, deepening of the web space improves the appearance and the length of the fingers. In such cases, syndactyly release is indicated electively.

Correction of the Deviation of the Thumb

Deviation of the thumb in cleft hand is often caused by triphalangeal thumb with a delta phalanx or rectangular extra phalanx [80]. Deviation of the thumb is corrected by removing the delta phalanx when the patient is less than 5 years. If the child is older than 5 years, the PIP joint or the DIP joint, where angulation occurs, is shortened and fused.

In removal of the delta phalanx, a short midlateral incision over the convex side of the thumb is used. The capsular structure including the collateral ligament is incised longitudinally and split. The delta phalanx is removed, and the IP

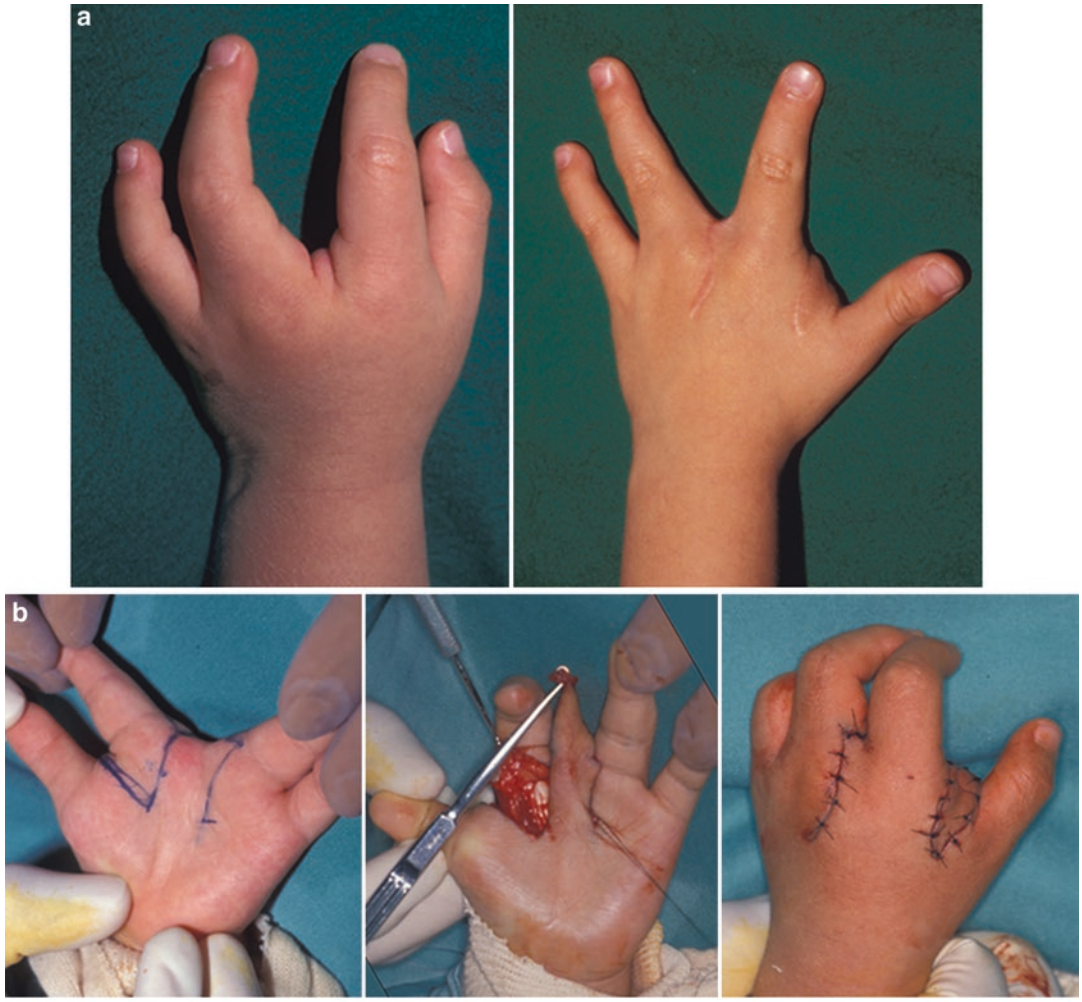

Fig. 16.13 (**a**) Snow-Littler procedure. Left: preoperative. Right: postoperative. (**b**) Snow-Littler procedure: during surgery. Left: design of skin incision. Center: palmar flap from the cleft. Right: transferred flap into the thumb web space and skin closure

joint is fixed with a Kirschner wire for approximately 6 weeks. The collateral ligament is shortened and repaired, but the redundant skin is not excised, as it recovers spontaneously.

Correction of the Deviation of the Index Finger

Deviation of the index finger in cleft hand is caused by inclination of the DIP joint due to the rectangular middle phalanx. Most patients have no complaint due to this deformity. However, some patients will strongly desire correction of this deformity, when they reach adolescence. In such cases, corrective closing wedge osteotomy at the distal third of the middle phalanx is indicated.

Osteotomy of the phalanx: Longitudinal dorsal skin incision is carried out, and middle of the extensor tendon is cut longitudinally. Closed wedge osteotomy is performed after subperiosteal exposure; fixation is carried out by crossed Kirschner wires or modified interosseous wiring.

Correction of Claw Finger Deformity of the Ring Finger

If the middle finger is absent, the ring finger may have a claw finger deformity. This deformity is described as camptodactyly associated with cleft hand in many papers. The PIP joint becomes rigid when the patient ages and if passive correction of the PIP joint flexion deformity is not performed. This is not a true camptodactyly because the patient is able to extend the PIP joint actively when the hyperextension of the MP joint of the affected finger is corrected to a neutral or slightly flexed position. Passive stretching and continuous splinting may correct this contracture. When cleft is closed around 1 year of age, spontaneous correction of the flexion deformity is sometimes observed, as hyperextension of the MP joint is usually corrected by the tension of the closed palmar skin. However, flexion deformity of the PIP joint or claw finger deformity should be corrected with tendon transfer at the initial surgery. In order to close a deep cleft, the structures including tendon and bone under the cleft are exposed. It is at this time that the surgeon has the best chance to select a tendon for transfer. In most cases of cleft hand, flexion of the PIP joint is caused by the dysfunction of the intrinsic muscles. During surgery, we can often observe the extra flexor digitorum superficialis tendons of the ring finger or middle finger. One of them can be detached from the membranous insertion at the end of the stump of the missing finger. It is then transferred to the base of the proximal phalanx or the proximal end of the ligamentous flexor tendon sheath of the ring finger [81] (Fig. 16.14). If claw finger deformity is associated with divergence of the index and ring fingers, the detached flexor digitorum superficialis tendon may be divided into two slips. One slip is transferred to the radio-palmar periosteum of the base of the proximal phalanx of the ring finger, and the other slip is transferred to the palmar periosteum of the ulnar base of the proximal phalanx of the index finger. The same type of procedure may be performed for extensor side. Extrinsic extensor tendon to the ring finger is transferred to the dorso-ulnar side of the expansion hood of the index finger, and the extensor digitorum communis to the index finger is transferred to the dorso-radial side of the expansion hood of the ring finger. These procedures may prevent divergence deformity of the index and ring fingers when the fingers are extended.

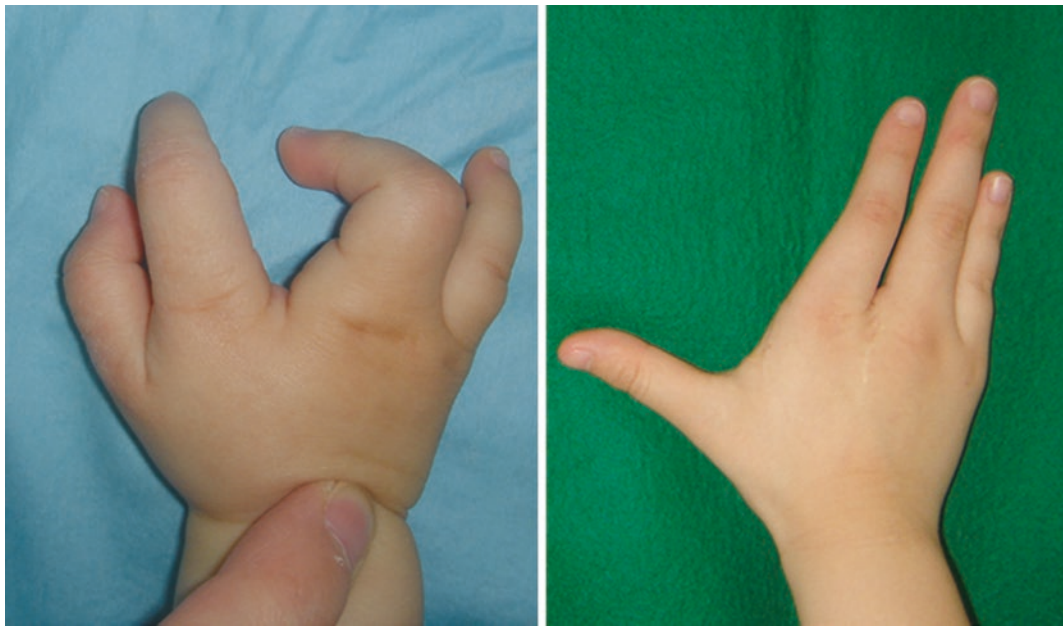

Fig. 16.14 Correction of the claw finger associated with cleft hand

Summary

Cleft hand is often associated with other deformities, which are phenotypes of abnormal induction of the finger ray numbers in the hand plate. When one classifies the congenital hand deformities, one has to face the problems how to classify the cases associated with cleft hand, central polydactyly, and syndactyly. It is easy to understand the association of these anomalies, once the concept of abnormal induction of the finger ray numbers in the hand plate has been accepted. The situation is the same as in congenital constriction band syndrome. One can easily understand the association among constriction band, acrosyndactyly, and amputation, if one has accepted the concept of congenital constriction band syndrome.

As I mentioned before, many authors think surgery of cleft hand is mainly performed for esthetic reasons, but some of the procedures have been performed for functional improvement. As in other congenital hand deformities, patient with cleft hand should use their hand skillfully when they become old, even if they have not surgically treated. Prof. P.C. Leung in Hong Kong, who is a respected hand surgeon and a person, delivered a lecture and told us as follows. Surgeons should be ambitious for treating the child with congenital hand problems. However, over ambitions may lead miserable surgeon and miserable patient. Surgery has its limitation, and never forget, "Don't make it worse!"

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References

1. Barsky J. Cleft hand: classification, incidence, and treatments. J Bone Joint Surg. 1964;46A:1707–20.
2. Blauth W, Gekeler J. Symbrachydaktylien; Beitrag zur Morphologie, Klassifikation und Therapie. Handchirurgie. 1973;5:121–74. (in German).
3. Ogino T, Minami A, Kato H. Clinical features and roentgenograms of symbrachydactyly. J Hand Surg. 1989;14B:303–6.
4. Manske PR. Symbrachydactyly instead of atypical cleft hand. Plast Reconstr Surg. 1993;91:196.
5. Birch-Jensen A. Congenital deformities of the upper extremities. Ejnar Munksgaart: Copenhagen; 1949.
6. Flatt AE. The care of congenital hand anomalies. St. Louis: CV Mosby; 1977. p. 50.
7. Ogino T, Minami A, Fukuda K, Kato H. Congenital anomalies of the upper limb among the Japanese in Sapporo. J Hand Surg. 1986;11B:364–71.
8. Temtamy SA, McKusick V. The genetics of hand malformations. New York: Alan R Liss; 1978. p. 53.
9. Vogel IF. Verzogerte mutation bei menschen? Ann Hum Genet. 1957/1958;22:132 (in German).
10. Duijf PHG, van Bokhoven H, Brunner HG. Pathogenesis of split-hand/split-foot malformation. Hum Mol Genet. 2003;12:51–60.
11. Elliott AM, Evans JA. Genotype-phenotype correlations in mapped split hand foot malformation (SHFM) patients. Am J Med Genet. 2006;140A:1419–27.
12. Elliott AM, Reed MH, Roscioli T, Evans JA. Discrepancies in upper and lower limb patterning in split hand foot malformation. Clin Genet. 2005;68:408–23.
13. Scherer SW, Poorkaj P, Massa H, Soder S, Allen T, Nunes M, et al. Physical mapping of the split hand/split foot locus on chromosome 7 and implication in syndromic ectrodactyly. Hum Mol Genet. 1994;3:1345–54.
14. Basel D, Kilpatrick MW, Tsipouras P. Research review. The expanding panorama of split hand foot malformation. Am J Med Genet. 2006;140A:1359–65.
15. Swanson AB. A classification for congenital limb malformations. J Hand Surg. 1976;1A:8–22.
16. Swanson AB, Swanson GG, Tada K. A classification for congenital limb malformations. J Hand Surg. 1983;8:693–702.
17. Ogino T, Kato H. Clinical and experimental studies on ulnar ray deficiency. Handchir Mikrochir Plast Chir. 1988;20:330–7.
18. Blauth W. Der hypoplastische Daumen. Arch Orthop Unfallchirur. 1967;62:225–46. (in German).
19. Ogino T, Ishii S, Minami M, Usui M, Muramatsu I, Miyake A. Roentgenological and clinical analyses of cleft hand, polydactyly of the middle finger. Seikeigeka. 1977;28:1508–11. (in Japanese).
20. Ogino T. A clinical and experimental study on teratogenic mechanism of the cleft hand, polydactyly and syndactyly. Nihon Seikeigeka Gakkai Zasshi. 1979;53:535–43. (in Japanese).
21. Manske PR. Cleft hand and central polydactyly in identical twins: a case report. J Hand Surg. 1983;8A:906–8.
22. Satake H, Ogino T, Takahara M, Kikuchi N, Muramatsu I, Muragaki Y, et al. Occurrence of central polydactyly, syndactyly, and cleft hand in a single family: report of five hands in three cases. J Hand Surg. 2009;34A:1700–3.
23. Miura T. Syndactyly and split hand. Hand. 1976;8:125–30.

24. Müller W. Die angeborenen Fehlbildungen der menschlechen Hand. Liepzig: Georg Thieme; 1937. (in German).
25. Jones NF, Kono N. Cleft hands with six metacarpals. J Hand Surg. 2004;29A:720–6.
26. Egawa T, Horiki A, Senrui H, Tada K. Characteristic anatomical findings of the cleft hand—its significance and classification. Handchirurgie. 1978;10:3–8. (in German).
27. Watari S, Tsuge K. A classification of cleft hands, based on clinical findings. Plast Reconstr Surg. 1979;64:381–9.
28. Ogino T. Teratogenic relation between central polydactyly, osseous syndactyly and cleft hand. J Hand Surg. 1990;15B:201–9.
29. Ogino T. Clinical features and teratogenic mechanisms of congenital absence of digits. Develop Growth Differ. 2007;49:523–31.
30. Kato H, Ogino T, Minami A, Ohshio I. Experimental study on radial ray deficiency. J Hand Surg. 1990;15B:470–6.
31. Ogino T, Kato H. Histological analysis of myleran induced oligodactyly of longitudinal deficiency in rats. Handchirurgie. 1988;20:271–4.
32. Ogino T, Kato H. Clinical and experimental studies on teratogenic mechanisms of congenital absence of digits in longitudinal deficiencies. Congenit Anom. 1993;33:187–96.
33. Otsuji M, Takahara M, Naruse T, Guan D, Harada M, Zhe P, et al. Developmental abnormalities in rat embryos leading to tibial ray deficiencies induced by busulfan. Birth Defects Res A Clin Mol Teratol. 2005;73:461–7.
34. Naruse T, Takahara M, Takagi M, Ogino T. Early morphological changes leading to central polydactyly, syndactyly, and central deficiencies: an experimental study in rats. J Hand Surg. 2007;32A:1413–7.
35. Ogino T. Teratogenic mechanisms of congenital absence of digits. Locomotor System Adv Res Diagn Ther. 2011;18:173–93.
36. Naruse T, Takahara M, Takagi M, Oberg KC, Ogino T. Busulfan-induced central polydactyly, syndactyly and cleft hand or foot: a common mechanism of disruption leads to divergent phenotypes. Develop Growth Differ. 2007;49:533–41.
37. Ianakiev P, Kilpatrick MW, Toudjarska I, Basel D, Beighton P, Tsipouras P. Split-hand/split-foot malformation is caused by mutations in the p63 gene on 3q27. Am J Hum Genet. 2000;67:59–66.
38. Ogino T. Congenital anomalies of the upper limb in our clinic—an application of modified Swanson's classification. J Jpn Soc Surg Hand. 1986;2:909–16. (in Japanese).
39. Ogino T. Current classification of congenital hand deformities based on experimental research. In: Saffar P, Amadio CP, Foucher G, editors. Current practice in hand surgery. London: Martin Dunitz; 1997. p. 337–41.
40. Muragaki T, Mundlos S, Upton J, Olsen BR. Altered growth and branching pattern in synpolydactyly caused by mutations in HOXD 13. Science. 1996;272:548–51.
41. Debeer P, Bacchelli C, Scambler PJ, De Smet L, Fryns JP, Goodman FR. Severe digital abnormalities in a patient heterozygous for both a novel missense mutation in HOXD13 and a polyalanine tract expansion in HOXA13. J Med Genet. 2002;39:852–6.
42. Kjaer KW, Hedeboe J, Bugge M, Hansen C, Friis-Henriksen K, Vestergaard MB, et al. HOXD13 polyalanine tract expansion in classical synpolydactyly type Vordingborg. Am J Med Genet. 2003;110:116–21.
43. Congenital Hand Committee of the Japanese Society for Surgery of the Hand. Manual for classification of congenital hand anomalies. J Jpn Soc Surg Hand. 1996;13:455–67 (in Japanese).
44. Kantaputra PN, Carlson BM. Genetic regulatory pathways of splithand/foot malformation. Clin Genet. 2019;95(1):132e139.
45. Restelli M, Lopardo T, Lo Iacono N, et al. DLX5, FGF8 and the Pin1 isomerase control DeltaNp63alpha protein stability during limb development: a regulatory loop at the basis of the SHFM and EEC congenital malformations. Hum Mol Genet. 2014;23(14):3830e3842.
46. Sowinska-Seidler A, Socha M, Jamsheer A. Split-hand/foot malformation—molecular cause and implications in genetic counseling. J Appl Genet. 2014;55(1):105e115.
47. Goldfarb CA, Ezaki M, Wall LB, Lam WL, Oberg KC. The Oberg-Manske-Tonkin (OMT) classification of congenital upper extremities: update for 2020 [published online ahead of print, 2020 Feb 21]. J Hand Surg Am. 2020;S0363-5023(20):30007–1. https://doi.org/10.1016/j.jhsa.2020.01.002.
48. Blauth W, Falliner AA. Zur Morphologie und Klassifikation von Spalthanden. Handchirurgie. 1986;18:161–95.
49. Saito H, Seki T, Suzuki Y, Fujino K. Operative treatments for various types of the cleft hand. Seikeigeka. 1978;29:1551–3. (in Japanese)
50. Ogino T. Cleft hand. Hand Clin. 1990;6:661–71.
51. Kato S, Ishii S, Ogino T, Shiono H. Anomalous hands with cleft formation between the fourth and fifth digits. J Hand Surg. 1983;8:909–13.
52. Tonkin MA, Nanchahal J, Kwa S. Ulnar-sided cleft hand. J Hand Surg. 2002;27A:493–7.
53. Langer JS, Manske PR, Steffen JA, Hu C, Goldfarb C. Thumb in the plane of the hand: characterization and results of surgical treatment. J Hand Surg. 2009;34A:1795–801.
54. Manske PR, Halikis MN. Surgical classification of central deficiency according to the thumb web. J Hand Surg. 1995;20A:687–97.
55. Wassel HD. The result of surgery for polydactyly of the thumb, a review. Clin Orthop Relat Res. 1969;64:175–93.
56. Falliner AA. Analysis of anatomic variations in cleft hands. J Hand Surg. 2004;29A:994–1001.

57. Kikuchi N, Ogino T, Takahara M, Ito K, Kato Y. Cleft of the 4th web space of the hand without finger defect. J Jpn Soc Surg Hand. 2005;22:635–8. (in Japanese).
58. Schinzel A. Ulnar-mammary syndrome. J Med Genet. 1987;24:778–81.
59. Ogino T, Minami A, Fukuda K, Nakazato T, Sakuma T, Kato H. Cleft hand complex with mirocheiria. J Jpn Soc Surg Hand. 1986;3:847–52. (in Japanese).
60. Buck-Gramcko D, Ogino T. Congenital malformation of the hand: non-classifiable cases. Hand Surg. 1996;1:45–61.
61. Küster W, Majewski F, Meinecke P. EEC syndrome without ectrodactyly? Clin Genet. 1985;28:130–5.
62. Rüdiger RA, Haase W, Passarge E. Association of ectrodactyly, ectodermal dysplasia and cleft lip-palate. Am J Dis Child. 1970;120:160–3.
63. Rodini ESO, Richieri-Costa A. EEC syndrome: report on 20 new patients, clinical and genetic considerations. Am J Med Genet. 1990;37:42–53.
64. Christodoulou J, McDougall P, Sheffield LJ. Choanal atresia as a feature of ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome. J Med Genet. 1989;26:576–89.
65. Fryns JP, Legius E, Dereymaeker AM, Van den Berghe H. EEC syndrome without ectrodactyly: report of two new families. J Med Genet. 1990;27:165–8.
66. Majewski F, Küster W. EEC syndrome sine sine? Clin Genet. 1988;33:69–72.
67. van Bokhoven H, Hamel BCJ, Bamshad M, Sangiorgi E, Gurrieri F, Duijf PH, et al. p63 gene mutations in EEC syndrome, limb–mammary syndrome, and isolated split hand split foot malformation suggest a genotype-phenotype correlation. Am J Hum Genet. 2001;69:481–92.
68. Vickers D. Clinodactyly of the little finger: a simple operative technique for reversal of the growth abnormality. J Hand Surg. 1987;12-B:335–42.
69. Kelikian H. Split hand complex. In: Congenital deformities of the hand and forearm. Philadelphia: WB Saunders Company; 1974. p. 467–95.
70. Tsuge K, Sanada Y, Yamamoto M. Treatment of cleft hand. Seikeigeka. 1965;16:854–6. (in Japanese).
71. Al-Qattan MM, Robertson GA. An anatomical study of the deep transverse metacarpal ligament. J Anat. 1993;182:443–6.
72. Takahashi M, Yabe Y. Treatment for cleft hand with syndactyly; a case report of a new skin incision. Seikeigeka. 1978;29:1554–7. (in Japanese).
73. Miura T, Komada T. Simple method for reconstruction of the cleft hand with an adducted thumb. Plast Reconstr Surg. 1979;64:65–7.
74. Ueba Y. Plastic surgery for the cleft hand. J Hand Surg. 1981;6A:557–60.
75. Ueba Y. Cleft hand. In: Buck-Gramcko D, editor. Congenital malformation of the hand and forearm. London: Churchill Livingstone; 1998. p. 199–215.
76. Upton J, Taghinia AH. Correction of the typical cleft hand. J Hand Surg. 2010;35A:480–5.
77. Foucher G, Lorea P, Hovius S, Pivato G, Medina J. Radial shift of the ulnar fingers: a new technique for special cases of longitudinal central deficiency. J Hand Surg. 2006;31:156–61.
78. Buck-Gramcko D. Cleft hands: classification and treatment. Hand Clin. 1985;1:467–73.
79. Rider MA, Grindel SI, Tonkin MA, Wood VE. An experience of the Snow-Littler procedure. J Hand Surg. 2000;25B:376–81.
80. Ogino T, Ishii S, Kato H. Opposable triphalangeal thumb, clinical features and results of treatment. J Hand Surg. 1994;19-A:39–47.
81. Zancolli EA. Structure and dynamic bases of hand surgery. 2nd ed. Philadelphia: JB Lippincott; 1978.

Camptodactyly and Clinodactyly

17

Erin A. Miller and Raymond W. Tse

Camptodactyly

Camptodactyly (Greek: kamptos = bend, daktylos = finger) is a non-traumatic progressive flexion deformity of the proximal interphalangeal (PIP) joint that typically involves one or two ulnar digits and is usually noted during infancy or adolescence [1] (Fig. 17.1). It is classified as a failure of differentiation of parts under the International Federation of Societies for Surgery of the Hand classification of congenital hand anomalies.

Ever since Tamplin's description in 1846 [1], the definition, etiology, and treatment have varied in the literature. Almost every structure around the PIP joint has been implicated, and reconciliation of these pathologic observations has been debated. While the definitive cause of camptodactyly remains elusive, it appears to be multifactorial and treatment with a staged approach can be successful.

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Incidence and Classification

Camptodactyly affects less than 1% of the population and is usually asymptomatic [2, 3], although significant contractures can limit instrument playing and typing. Patients may also complain of difficulty wearing gloves. The anomaly usually occurs sporadially; however, it can be inherited in an autosomal dominant pattern with variable expressivity and incomplete penetrance.

Bilateral deformities occur in approximately two-thirds of cases. The small finger is most frequently involved (~55% in the literature), followed in incidence by the ring and finally middle fingers [4]. Multiple digits on the same hand may be affected, with less frequent involvement of the radial digits. Camptodactyly of the thumb has not been reported. Metacarpophalangeal (MCP) joint hyperextension can accompany PIP flexion contractures, and an intrinsic minus posture or bouttinere deformity may be seen if the contracture is significant.

When the initial presentation is during infancy, males and females are equally affected. Females are more commonly affected when the initial presentation is during adolescence.

Benson classified patients into three types [5]. Type I camptodactyly presents in infancy (<2 years of age) with the clinical features described above, and type II presents in preadolescence (>10 years). Type III, or syndromic camptodactyly, is a more severe presentation

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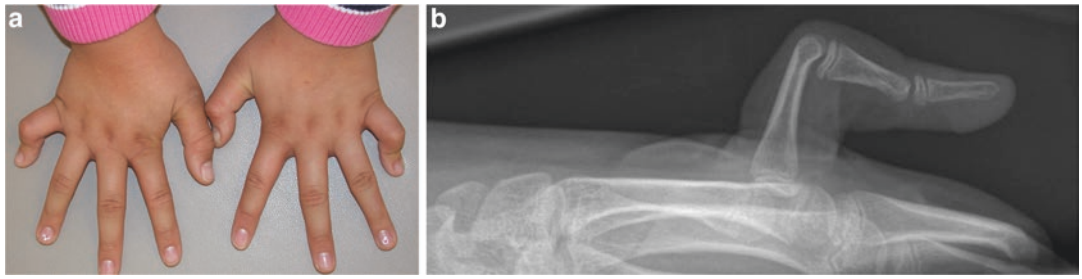

Fig. 17.1 Camptodactyly. (**a**) Non-traumatic progressive flexion deformity typically involving the ulnar digit(s), often with an intrinsic minus posture. (**b**) Radiologic appearance

Table 17.1 Generalized conditions associated with camptodactyly

	Conditions
Craniofacial	Orofaciodigital syndrome
	Craniocarpotarsal dystrophy (Freeman–Sheldon syndrome)
	Oculodentodigital dysplasia
Chromosomal	Trisomy 13–15
Short stature	Campomelic dysplasia I
	Mucopolysaccharidosis
	Facial–digital–genital (Aarskog–Scott syndrome)
Others	Osteo-onychodysostosis (turner–Kieser syndrome)
	Cerebrohepatorenal (Zellweger's syndrome)
	Jacob-Downey syndrome

Adapted from [3]

characterized by significant contractures, bilateral involvement, multiple digits and other associated congenital anomalies; it is present at birth and is seen as a manifestation of a more generalized condition (Table 17.1).

The bimodal age presentation of type I and type II camptodactyly at infancy and preadolescence, respectively, may be related to growth spurts during which flexor–extensor imbalances manifest [6, 7].

The PIP flexion deformity may be fixed or passively correctible, which has important treatment implications. Foucher proposed subclassifying type I and II camptodactyly into "stiff" or "correctable" categories to guide his treatment approach [8].

Etiology

Abnormalities of almost every structure around the PIP joint have been described as the cause for camptodactyly, including volar skin, flexor tendon, intrinsic ligament, lateral bands, extensor mechanism and bony structure of the joint. Some authors believe all these structures are involved in varying degrees [8, 9]. Others believe that all cases of camptodactyly arise from an isolated abnormality of the flexor digitorum superficialis (FDS) or the intrinsic musculature, and cause secondary distortion with time and growth [10–12].

The earliest cited theory is a tight, contracted, or underdeveloped FDS tendon [1] that causes an imbalance of flexor and extensor forces leading to the deformity. Aberrant FDS tendon origins in the absence of a normal muscle belly have been described, and include the A2 pulley, palmar aponeurosis, flexor tendon sheath, and transverse carpal ligament [13].

Surgical explorations by Courtemanche and McFarlane have identified consistent abnormalities of lumbrical muscles, suggesting that these may be the primary etiology of camptodactyly [10–12], although several surgical series note completely normal lumbricals [7, 14]. Aberrant lumbrical insertions include the FDS tendon [10–12, 15, 16] and MCP joint capsule [10–12]. An aberrant lumbrical origin from the flexor retinaculum has also been described [17].

Other soft tissue abnormalities include extensor incompetence, collateral ligament contracture, volar plate contracture, and volar skin deficiency [1, 8, 9]. Bony changes can be seen with long-standing deformities and are consistent with growth in the setting of a chronically flexed joint. The head of the proximal phalanx is narrowed in the dorsovolar plane with loss of the normal volar convexity; this loss appears as flattening of the phalangeal head. There may also be abnormal flexion of the head. The articular surface of the middle phalanx base may develop a shallow dorsal groove and middle phalanx may subuluxate palmarly [11]. Radiographic changes were seen in approximately 15% of patients in McFarlane and Smith's series [1, 11]. Smith argues that all of these abnormalities are common to all cases of camptodactyly, but to varying degrees [1]. McFarlane argues that aberrations of lumbrical muscle insertion are the unifying cause and all other changes occur secondary to chronic motor imbalance. He points out how previous anatomic studies have demonstrated that normal anatomic variations of the intrinsic muscles occur more frequently in the ulnar digits and that these are the same digits that are involved with camptodactyly [11].

Evaluation

Differentiation of camptodactyly from other conditions is accomplished through careful history and physical examination. Camptodactyly is seen in the absence of trauma, inflammation, and palpable lesions. The deformity is slowly progressive and generally occurs in isolation.

As camptodactyly is a diagnosis of exclusion, other etiologies on the differential must be ruled out – trigger finger, palmar fibromatosis, Dupuytren's contracture, boutonniere deformity (central slip rupture), inflammatory arthritis, symphalangism, arthrogriposis or pterygium syndrome. A trigger finger may be associated with a palpable click on extension. Juvenile palmar fibromatosis or Dupuytren's disease is associated with palpable subcutaneous nodules. A boutonniere deformity should be associated with antecedent trauma and swelling. Inflammatory arthridities manifest with inflammation and more generalized involvement. Symphalangism is characterized by no active or passive joint motion and an absence of skin creases. Arthrogryposis involves generalized muscular and skeletal deficiencies. Pterygium syndrome is usually associated with involvement of multiple joints.

Following a thorough examination of the upper extremity, active and passive range of motion of the PIP joint should be evaluated and the influence of adjacent joint positions should be noted. FDS tightness can be determined by tenodesis, in which passive wrist and MCP extension places the FDS on stretch and results in further loss of passive PIP extension. Intrinsic motor deficiency can be assessed using the Bouvier maneuver, in which active PIP extension is tested with the MCP joint stabilized in flexion. Restoration of full PIP extension suggests that inadequate MCP flexion, via the intrinsic muscles, contributes to the deformity.

Extensor competence can be tested using an extensor tenodesis test in which full flexion of the wrist and MCP places the extensor system on stretch. This should result in full PIP extension. Long-standing flexion deformities can result in attenuation of the central slip, in which case PIP extension would not be seen. Volar skin deficiency can be determined by testing passive PIP extension with the MCP in flexion and in extension. Blanching and loss of passive PIP extension when the MCP is extended suggests deficiency.

Flexor digitorum profundus (FDP) and FDS function of each finger should be evaluated. Given that the FDP to each finger acts through a common muscle belly, in order to test isolated FDS function to an individual finger, all other digits must be held in extension while finger flexion of the digit of interest is evaluated. The ring and small finger FDS are conjoined in 30% of people. If PIP flexion is not possible for the small finger, release of the ring finger should result in PIP flexion of both digits if their FDS is conjoined. FDP is assessed by isolated distal interphalangeal joint flexion.

Plain radiographs of the affected finger should be obtained. Most valuable is a true lateral to

assess for any deformity of the proximal phalanx head. As described above, characteristic flexion and flattening of the phalangeal head creating a "bird beak" appearance may be associated with camptodactyly. Woo Hong et al. have proposed two radiographic parameters that may be followed – the head angle and the head triangle ratio – but note that the degree of bony abnormality does not correlate with degree of clinical PIP contracture [18]. Ultrasound will demonstrate an abnormal lumbrical insertion if it is present – the fourth lumbrical muscle belly is seen as superficial rather than deep, and passive PIP flexion will cause motion in the muscle that is not seen with passive DIP flexion [19]. Given the low cost, ultrasound may be a useful adjunct in diagnosis and for preoperative planning. The superficial muscle belly may be seen on MRI as well; however, the ability of ultrasound to allow a dynamic examination makes the utility greater.

Treatment

Nonsurgical Management

Conservative management should be the first line of treatment. PIP contractures of less than 30° rarely have any functional impact, and sometimes more significant contractures may be tolerated. Methods of nonsurgical treatment include passive stretching, static splinting, dynamic splinting, or any combination of these. Results often rely upon patient and family compliance, but can also vary with patient age and severity of the contracture.

Rhee et al. reported on the results of passive stretching alone for simple camptodactyly in children younger than 3 years of age. They included 61 digits in 22 patients. Their stretching protocol involved 5 min of passive stretching 20 times per day until the deformity was corrected or the improvement "stabilized," followed by maintenance stretching 5 to 10 times per day. Children were found to have significant corrections; the only correlation with degree of improvement was the initial flexion contracture [4]. Although they demonstrated good results in a homogenous group of Korean children with type I camptodactyly, their protocol is time intensive, requires considerable caregiver effort, and the long-term outcomes, especially regarding the risk of progression or recurrence as children move into adolescence, are unknown.

This protocol was used in a cohort radiographic study assessing bony remodeling, and found that passive stretching alone improved imaging parameters of the proximal phalanx head as well as contracture angle from 34° to 6°. Notably, however, no correlation between clinical contracture and radiographic parameters was found [18].

Benson et al. reported on the results of passive stretching combined with static splinting in patients with all types of camptodactyly. Their protocol used static splints worn 15–18 hours per day and daily passive stretching. In types I and III, the average correction was 23–1° with a mean follow-up of 36 months. Patient with type II camptodactyly experienced an overall worsening of the flexion contracture with this protocol [5].

Hori et al. used dynamic splints for 24 hours daily until near full correction was achieved (3–6 months), and then splinting was decreased to 8 hours a day. The average correction of the contractures was 40° to 10° with average follow-up of 56 months (minimum 10 months) [20]. Miura et al. also used dynamic splints and found that the results were better in children younger than 5 years than in children who were older than 5 years [21].

Yannascoli et al. recommends a multifaceted approach to nonoperative treatment. Their four components are passive stretching (four 5-minute sessions daily), extensor strengthening exercises using rubber band resistance, nocturnal static progressive splinting and dynamic extension splinting during waking hours [6]. While they do not present a series, they report good results.

More recently, botulinum toxin has been trialed in the treatment of camptodactyly with good results. Urban et al. reports a series of 12 patients who underwent injection of 10–25 units into each interosseous (dorsal and palmar) as well as the hypothenar muscles (if the small finger was involved). No splinting was used. Ten patients

stabilized or improved their degree of contracture with only one treatment, with an additional patient requiring two injections for improvement. The last patient failed conservative treatment and was treated with surgery [22]. This treatment avenue warrants further exploration.

Surgical Management

Surgical treatment of camptodactyly should be reserved for severe cases in which all efforts towards nonsurgical management have failed. The results of surgery are historically inconsistent; however, several recent protocols are more encouraging. The risk of PIP flexion loss needs to be weighed against the more limited gains in PIP extension. Typical surgical indications are flexion contracture more than 50°, impaired hand function, unacceptable aesthetic result, or a rapidly progressive contracture more than 30°. Netscher advocates for surgical intervention on any digit demonstrating skeletal changes of the proximal phalangeal head [7]. Postoperative rehabilitation is key to treatment success and patient compliance should be confirmed prior to surgery.

A Zancolli stepwise approach to surgical release has been the most successful in published literature. It takes into account all potentially involved structures and ensures the most complete release and reconstruction. Careful patient selection is key to optimizing outcomes – patients with severe subluxation of the middle phalanx, joint space narrowing, limited total motion preoperatively or questionable compliance are unlikely to have satisfactory surgical outcomes.

The skin incision assumes a potential volar soft tissue deficit following correction. A midline longitudinal approach with subsequent Z-plasties at closure can provide moderate length [10, 11] if the contracture is less than 60°. Contractures more than 60° need local tissue rearrangement. Wall et al. describe an axially based rotation flap off the dorsal branch of the digital artery on the side of tightest contracture. The base width should be 1–1.5 cm, and taper distally. This flap is raised to the mid-axial line and Cleland's ligament released to allow transposition 45° across the PIP flexion crease. The donor may be closed primarily or covered with a full thickness skin graft [23].

Once any volar skin flaps are raised and the PIP incision made, any subcutaneous tissues or tight fascial bands are released. Previous authors have suggested opening from the PIP joint to the transverse carpal ligament to inspect the entire length of the FDS and correct any abnormal anatomy, however recent case series with exposure limited to the PIP and proximal phalanx report good success [6, 7, 14, 23, 24]. These protocols all recommend complete FDS tenotomy if extrinsic tightness test is positive, thus any abnormal lumbrical origin or insertion on the FDS is negated without the need for an extensive exposure.

FDS tenotomy should be performed at the level of Camper's chiasm [6, 7]. The lumbrical is then identified and followed proximally to the MCP level to ensure there are no abnormal bands inserting onto the proximal phalanx; if these are found they are released [6].

Next in the stepwise approach, the PIP extension is assessed. If full extension is not yet achieved, sequential release of the volar plate and then accessory collateral ligaments is performed. Reassessment after each release is required. The last resort to regain full extension is release of the true collateral ligaments, and should be rarely performed [6, 23]. Any surgical release of the PIP joint results in considerable inflammation and scar and is likely an important factor in the loss of flexion noted in some series or case reports [8–11, 25], emphasizing the need for minimizing release to only what is needed.

Preoperative exam is key in the next step of the procedure. If the Bouvier maneuver demonstrates a severe lag (>70°) preoperatively, the FDS should be transferred directly into the extensor [6, 7, 14]. (Fig. 17.2b) Mild preoperative lag is treated with splinting in extension for 4 weeks. Several surgeons recommend pinning the PIP in extension for 3–4 weeks regardless of preoperative lag to prevent recurrent contracture [23]. Another alternative is a lasso procedure to produce MCP flexion (Fig. 17.2a), although this is becoming less commonly used [6].

If the FDS has been found to act independently, it can be transferred without further dissection. If it is not independent, the FDS needs to

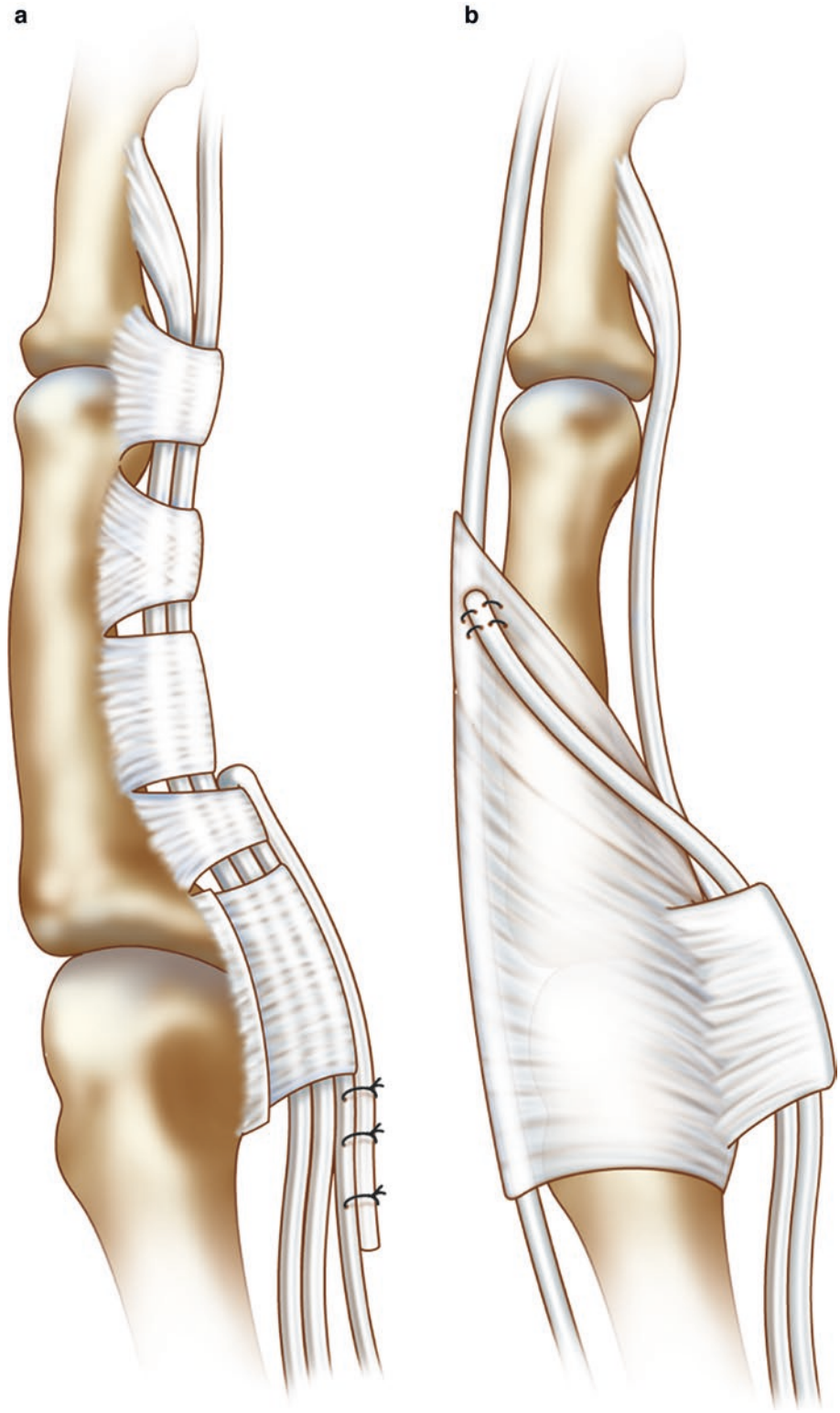

Fig. 17.2 (**a**) Zancolli lasso procedure. The FDS tendon is released from its insertion and sutured around the A2 pulley to act primarily as an MCP flexor. (**b**) Intrinsic transfer. The FDS tendon is re-routed to insert into the extensor apparatus to act as an MCP flexor and a PIP extensor

be dissected and freed from the adjacent FDS. Alternatives for tendon transfer include an adjacent FDS [12] tendon or the extensor indicis proprius (EIP) re-routed volar to the intermetacarpal ligament [2, 26]. Some authors caution that any immediate intrinsic transfers decrease postoperative flexion and should be avoided, so controversy continues [6, 23].

The last consideration in the surgical approach is addressing any pre-operative boutonniere deformity. If present, a Fowler tenotomy should be performed [7]. No joint recontouring attempts should be made, as addressing the soft tissues has demonstrated good remodeling of the PIP joint with soft tissue only procedures in skeletally immature patients. Historically, osteotomies have poor postoperative results and are not recommended.

Postoperative protocols have slight variation, but typically use 2–3 weeks of plaster immobilization followed by continual orthosis wear with a transition to nocturnal wear around 6 weeks postop for a total of 12 weeks [23]. If the PIP was pinned intraoperatively, it may be removed at 3 weeks [23, 24].

Overall, results of camptodactyly release have improved significantly: in 1990, Siegert et al. reported poor results of surgical treatment [25] and McFarlane reported an average flexion to distal crease of palm of 1.8 cm [11]. In the latter series only 33% of patients retained full flexion. In case series where the PIP joint was rarely released, the loss of flexion was minimal and often less than 10° [8, 9]. Smith reported an improvement of 57° with surgery [9] and Foucher reported 68% to 88% improvement depending upon the preoperative type [8].

Evan et al. performed a retrospective review of 31 digits where the total arc of motion pre-surgery and post-surgery was unchanged, however the position of the arc was significantly more extended [24]. While the authors report this position is more functional, there are no objective or patient reported outcomes to support this claim. Recently, Hamilton et al. reported an 18-patient series with a postoperative contracture of 3° with a total arc of motion of 88° [14], and Netscher et al., an 18-digit series with an improvement of flexion contracture from 62° to 4° with no loss of finger flexion [7]. It isn't clear why Evan reported losses in flexion, whereas Hamilton and Netscher didn't, in spite of what seem like similar surgical approaches. The use of a K-wire to fixate the PIP in extension may be one difference. Other differences may be related to more subtle surgical and rehabilitation nuances.

Difficulty in assessing the true results of this approach arises from the small study sizes and heterogenous population – type I, II and III camptodactyly were reported together to increase numbers. The results of surgery are additionally difficult to compare due to differences in methodology and incompatible formats of results reporting. There may be differences in surgeon skill, aggression of release and in the rehabilitation protocol or access to therapy. Recent attempts at meta-analysis have not provided additional data. All studies report one to three failures requiring salvage with PIP fusion [7, 14, 24]; this is always an option for severe cases.

In our experience, the flexion deformity tends not to produce functional impairment. When there are functional limitations and patients are informed of the potential losses of finger flexion, they often decline surgical treatment. If Netscher's results in which correction of the deformity without loss of finger flexion are reproducible, our thresholds to proceed with surgical treatment may change.

In summary, camptodactyly release has variable results, and nuances in surgical and rehabilitation techniques likely contribute to final motion. Patients undergoing operative release must be prepared for the possibility of flexion loss, however this may not affect satisfaction with outcome. Further study with standardized results and functional assessment is needed to better inform patients about the success of surgery.

Summary

Camptodactyly is a flexion contracture of the PIP joint of which the etiology camptodactyly remains hotly debated. The majority of patients rarely complain of functional loss, even with sig-

nificant contractures, and most prefer to avoid surgery. Nonsurgical treatment is the first line and mainstay of management, although recent surgical algorithms have demonstrated improved results and should be considered for functionally limiting deformities. Loss of flexion remains a significant concern with surgical treatment, and given that lack of full extension is better tolerated than loss of flexion, these risks must be considered when surgery is considered.

Clinodactyly

Clinodactyly (Greek; clino = incline/slope, daktylos = finger) refers to digital angulation in the radioulnar plane distal to the MCP joint. It is classified as a failure of hand-plane formation or differentiation in Manske and Oberg's modification of the International Federation of Societies for Surgery of the Hand classification of congenital hand anomalies [27]. The earliest report of the condition is attributed to Smith, who described its radiographic appearance in 1896 [28].

Incidence and Classification

Incidence of the condition is difficult to accurately assess, as the accepted parameters of normalcy vary. Minor angulation of the digits, especially the small finger, is very common and generally considered to be a normal variant. The stated upper limit of normal angulation varies between 10° and 15°; a considerable variation in incidence rates follows, with reports ranging from 1% [29] to 20% [30]. In North America incidence has been reported as 1%, compared to 3% to 5% in Japan [31].

Burke and Flatt grouped 50 patients with clinodactyly into three broad categories: familial/classic clinodactyly; clinodactyly associated with other congenital abnormalities; and clinodactyly due to epiphyseal injuries [32]. The third grouping refers to posttraumatic angular deformities resulting from various insults, not true congenital conditions.

Cooney proposed the most commonly utilized classification system of simple, complicated and complex, based upon tissue involvement and angulation. Simple forms involve bone only, while complex forms involve both bone and soft tissue. If the angulation is greater than 45° the designation of complicated is added. Complex clinodactyly is typically associated with syndactyly, whereas complex complicated clinodactyly is often associated with polydactyly or macrodactyly [33].

More recently, Ali and Rayan proposed a simple classification based on severity of angular deformity. Group 1 referred to physiologic angulation, which they defined as <5°; group 2 defined as mild angulation between 5° and 10°; group 3 was defined as moderate deformity between 15° and 30°, and group 4 was defined as severe deformity of greater than 30° [34].

Etiology

Clinodactyly is most commonly due to an abnormally triangular or trapezoidal shaped middle phalanx which is the result of an anomalous, longitudinally oriented epiphysis running along the short side of the involved phalanx (Fig. 17.3). The proximal physis is usually normal, whereas the distal physis may be aberrantly persistent [30]. Light and Ogden have further characterized this longitudinal epiphyseal bracket as c-shaped [35]. This abnormal tethering usually occurs on the radial aspect of the phalanx and results in progressive angulation of the digit towards the unbracketed side.

A very short, triangular "delta" phalanx is the result of early complete ossification of a C-shaped bracket and results in the most severe deformities [30]. Incomplete, or cartilaginous, brackets allow for longitudinal growth on one side – a trapezoidal phalanx develops as growth is prevented on the bracketed side, which causes progressive angulation [36]. The longitudinal epiphyseal bracket may not be visible radiographically until the age of 3–4 years because the physis is not yet ossified.

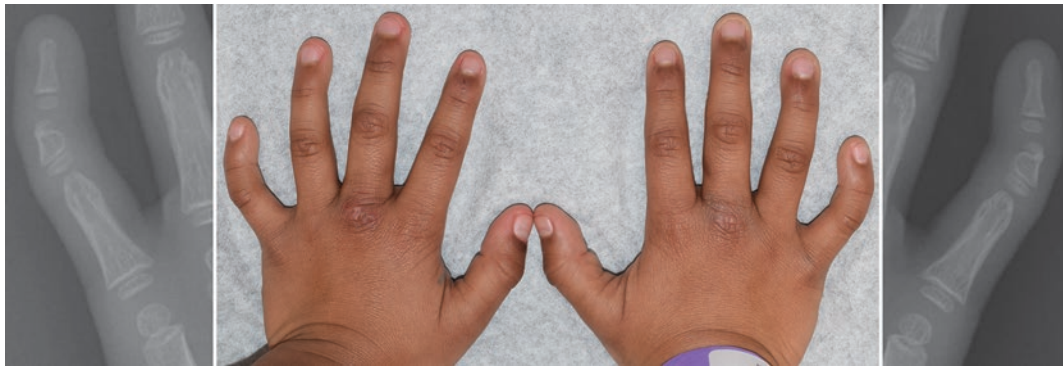

Fig. 17.3 Clinodactyly of small finger. Longitudinal bracketed epiphysis of middle phalanx results in radio-ulnar deviation. The difference has no functional consequence and is purely cosmetic. No treatment is indicated

Clinodactyly of the thumb associated with Apert's syndrome, while it shares a radially angulated presentation with classic clinodactyly, may be the result of a different etiology. There is continued debate regarding if the clinodactyly is the result of an anomalous insertion of the abductor pollicis brevis muscle onto the distal phalanx, or due to an abnormal bracketed physis [37, 38]. Clinodactyly can occur in association with a triphalangeal thumb with a delta phalanx as the extra phalanx; however, discussion of this entity is beyond the scope of this chapter.

Abnormal growth causing clinodactyly may also occur as a result of a growth plate insult that produces asymmetric growth and physeal closure. Trauma, fractures, thermal injury, frostbite, inflammatory arthritis, and tumors can be responsible for such growth plate abnormalities.

Clinodactyly typically presents as radial deviation of the small finger at the middle phalanx, is often bilateral, and is more common in males. The thumb and ring finger are the next most frequently affected digits, although it has been reported in all digits as well as the proximal and distal phalanges [39]. Work by Dutta and Hersh has confirmed the mode of genetic inheritance to be autosomal dominant with variable penetrance [29, 40]. It is usually an isolated finding, but can be associated with a number of other hand differences and syndromes including trisomy 21 and trisomy 18 (Table 17.2). Apert and Rubinstein–Taybi syndromes are associated with bilateral thumb clinodactyly [41, 42]. The "kissing delta

Table 17.2 Causes and associated conditions of clinodactyly

	Conditions
Trauma	Phalangeal shaft malunion
	Frostbite injuries
	Salter–Harris I–V fractures
Chromosomal disorders	Down's syndrome
	Klinefelter's syndrome
	Turner's syndrome
	Trisomy 18
	Trisomy 21
	Cri du chat
	XXXXY
	XXXXX
Limb anomalies	Symphalangism
	Familial brachydactyly
Craniofacial disorders	Apert's syndrome
	Orodigital facial
	Orodigital palatal
	Oculodentodigital
	Treacher Collins
Miscellaneous	Silver's syndrome
	Prader–Willi
	Cornelia de Lange
	Seckel dwarfism
	Marfan's syndrome
	Myositis ossificans progressive
	Mohr's syndrome
	Goltz
	Freeman–Sheldon
	Laurence–Moon–Biedl
	Poland
	Holt Oram
	Fanconi anemia
	Nail patella syndrome

Adapted from [32]

phalanx" deformity, Trevor disease, and Mohr–Wriedt brachydactyly are associated with index finger clinodactyly [39]. Clinodactyly can also be seen with polydactyly and macrodactyly.

A genetic work-up should be considered if any additional abnormalities are noted during physical examination of a child presenting with clinodactyly.

Evaluation

Most patients seek care due to cosmetic concerns or progressive deformity. A complete hand examination should be performed and assessment of any additional abnormalities noted. Measurements should be documented by goniometer.

Radiographs should be obtained to assess for early physeal closure or delta phalanx, and to measure the degree of skeletal angulation. As noted above, radiographs obtained too early will not demonstrate a bracketed epiphysis as there is insufficient ossification. Advanced imaging, such as MRI, may allow further characterization of the physis, but has little role in clinical management and is not routinely obtained.

Differential diagnosis is limited, but includes infection with osteomyelitis and Salter-Harris fracture with angular displacement. These diagnoses are typically ruled out by history, as clinodactyly is a slowly progressive deformity not associated with any trauma, erythema or swelling.

Treatment

Nonsurgical Management

Clinodactyly of the small finger (see Fig. 17.3) is rarely functionally limiting, as any flexion impairment can typically be compensated for with increased digital abduction. Observation alone is the appropriate course of action for such cases, as the possibility for significant scarring and loss of range of motion with surgical correction for the sole purpose of potentially improving the appearance of the finger represents an unacceptable risk. There is no role for splinting or stretching of the digit, as it is completely ineffective [32].

Clinodactyly of the thumb has more significant implications to opposition and pinch while that of central digits can affect flexion or digital cascade. Unless there is functional impairment, no treatment is needed.

Surgical Management

Angulation of 30° to 40° will often interfere with hand function and is usual threshold for surgical intervention. Correction requires either resection of the longitudinal epiphyseal bracket allowing the digital curvature to correct over time with longitudinal growth or osteotomy of the phalanx.

Physiolysis addresses the angular deformity by excising the abnormal longitudinal epiphyseal bracket and interposing fat. This allows the curved digit to straighten over time with longitudinal growth, as the concave side is no longer tethered. As this procedure requires growth potential to achieve angular correction, it is limited to patients with open growth plates and is best performed at an earlier age. Vickers initially described the results of physiolysis of 12 digits in six patients, with an average age of 9. He achieved good results, although one patient, aged 12 at the time of surgery, required an osteotomy to correct residual deformity. The ideal time for physiolysis is less than 6 years of age and should be avoided after the age of 9 [35, 39, 43–46].

The procedure is performed from a lateral approach on the short or concave side of the finger (Fig. 17.4g–i). The neurovascular bundle is identified and protected, and the bone exposed along the length of the affected phalanx. Care should be taken to ensure the PIP and DIP joints are not violated; a 25-gauge hypodermic needle inserted into these joints can serve as a visual reference to prevent injury to the normal proximal and distal physes. Once the normal physes are identified, the bracketed, longitudinal physis is excised from between them using a synovial rongeur. It is essential that the entire middle physis is removed – the resection should be taken to the level of cortical bone, which is noted visually by

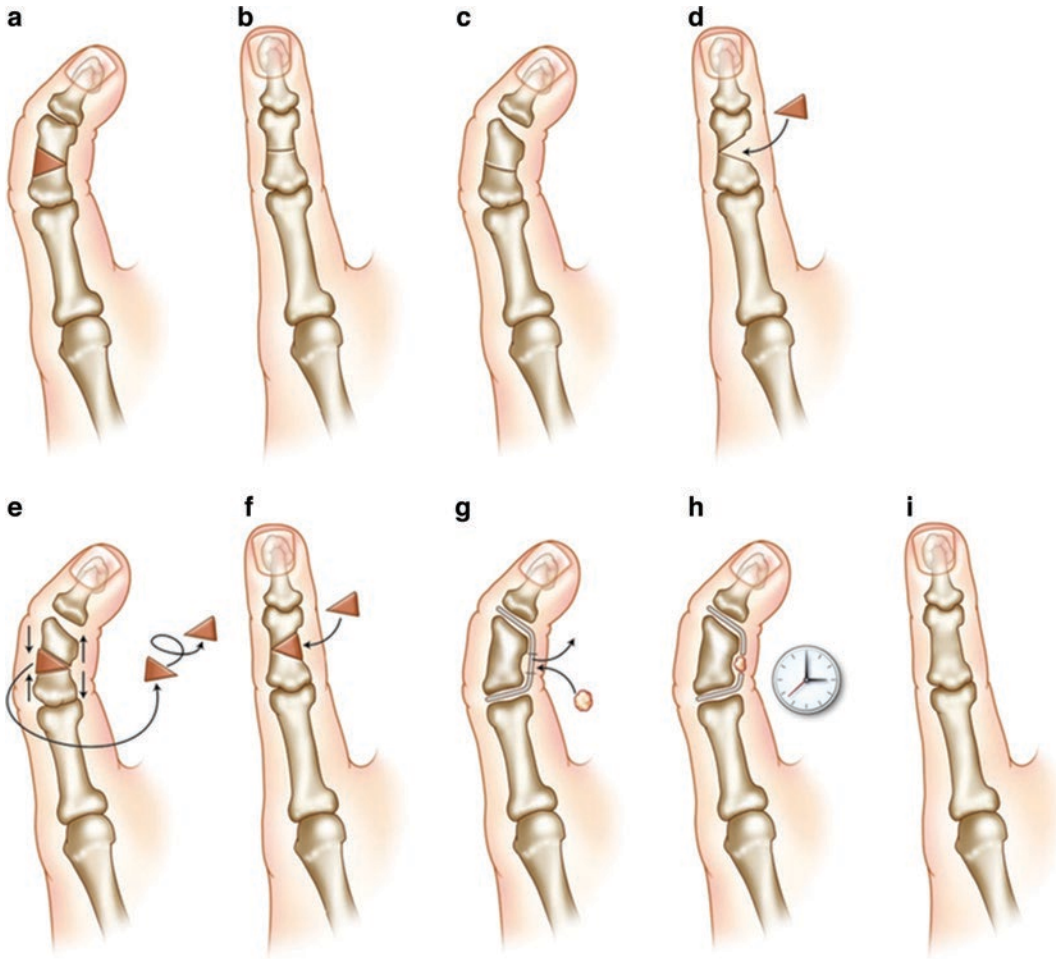

Fig. 17.4 Options for surgical treatment of clinodactyly when functional impairment occurs. (**a**, **b**) Closing wedge osteotomy. (**c**, **d**) Clinodactyly treatment. Opening wedge osteotomy with bone graft. (**e**, **f**) Clinodactyly treatment. Reverse wedge osteotomy with autograft. (**g**–**i**) Clinodactyly treatment. Physiolysis

a change from white to red tissue [44]. After complete resection, a 2- to 5-mm fat graft is placed into the defect from a donor of the surgeon's choice; hypothenar and antecubital fossa are common. Skin is closed in a single layer and the hand protected for 2–3 weeks before allowing full motion and weight bearing.

Patient and parents should be cautioned that results are not immediate. Maximal correction is typically seen around a year post-operatively, as the procedure relies on restoration of normal growth to correct the angulation. In cases of failed correct, a repeat physiolysis should not be attempted, and instead an osteotomy performed [44].

Several small series of physiolysis are reported in the literature. A review of 35 digits treated with physiolysis revealed an average correction of 11°; improved correction (20° ± 9.7°) was obtained in fingers with greater deformity (>40°) preoperatively [47]. A 30 finger series reported by Gillis et al. had good correction from an average of 43° to 24°, or a 46% correction of the initial deformity and no need for repeat surgery [45]. Medina reports the largest series of 27 digits with a minimum 6 year follow-up and average correction from 38° to 8°, an impressive 79% correction, with no patient requiring subsequent osteotomy [44]. None of the recent series report

early epiphyseal closure; in Vicker's original series he reported this complication once [43].

Multiple osteotomy options have been described: closing wedge osteotomy [34], opening wedge osteotomy [23, 32, 41], reverse wedge osteotomy [48], a partial excision greenstick, or "PEG" osteotomy [49], and distraction osteotomy [50]. The common theme amongst all osteotomies is correction of the angular deformity of the digit. Each technique presents unique advantages and disadvantages.

Opening wedge osteotomy (Fig. 17.4c–d) offers the advantage of maintaining length, but is a technically demanding procedure [35]. When the middle phalanx is to be corrected, a dorsal approach allows excellent visualization of the bone via a wedge-shaped incision. If a lateral approach is used, a z-plasty may need to be designed to allow adequate lengthening of soft tissues. The extensor is carefully protected by a subperiosteal dissection. Two K-wires should be inserted prior to the osteotomy – a 0.045-in wire retrograde through the DIP translated to the concave (osteotomy) side of the finger and a temporary 0.035 wire across the PIP to pin it in place. The DIP wire is based towards the concavity because it will be used as the final fixation across the osteotomy. This technique ensures that the correction occurs through the osteotomy site and not through the ligaments of the DIP or PIP joints [23].

As in a physioloysis, two 25-gauge hypodermic needles may be inserted into the DIP and PIP joints to allow visual confirmation of the phalangeal angulation. A transverse osteotomy is then created, which should be incomplete on the long (convex) side of the finger to allow this to act as a hinge. In young children, a scalpel may also be used to initiate the cut into bone; in older children an ostetotome may be needed. An oscillating saw is generally too big for accurate cuts in young children, however a piezoelectric saw is a good alternative if available, as it allows for accurate cuts with minimal risk to soft tissues.

The digit is then straightened until the needles in the DIP and PIP are parallel and then the retrograde wire is passed across the osteotomy site. A second wire is placed across the osteotomy for additional fixation and to prevent rotation. Bone grafting is not required [23]. The needles and PIP wire are then removed and skin closed. Wires are maintained for 6 weeks and then removed.

Tansley and Pickford described a modification of the opening wedge osteotomy in which they created a greenstick fracture, which required only interosseous wiring for fixation. They coined this partial excision greenstick (PEG) osteotomy, with the described advantages of minimizing the risk of soft tissue injury and improved rotational control [49].

Carstam and Theander described a reverse wedge osteotomy in which a wedge of bone was excised from the non-bracketed side of the digit, reversed, and transfixed into the site of an opening wedge osteotomy on the bracketed side of the digit with a wire. They achieved good results with this technique in three patients with an average age of 14 years, reporting deformity correction to 10° or less in all cases [48]. Given the small size of this bone wedge however, it is rarely a viable option in small children and should be reserved for older patients – typically teenagers who are skeletally mature. It is a technically demanding procedure, requiring either an extended approach or multiple approaches for access, increasing the risk of injury to the soft tissues, scarring, and stiffness.

Closing wedge osteotomy (Fig. 17.4a, b) is simple, technically straightforward, and reliable; however, it further shortens an already short digit and may slacken the extensor mechanism. It is performed in a similar manner; however, two osteotomies are required and a wedge of bone is removed to allow straightening of the digit.

Outcomes are again only available with small series of heterogenous patients. Gillis et al. shared a series of 11 digits with opening wedge osteotomies with a 37.5% correction – from an average of 39° to 22° – however, 3 patients required revision osteotomy [45]. Rayan reported on a series of 25 fingers treated with a closing wedge; average angulation improved from 33° preoperatively to 9° postoperatively and fingers achieved an average of 79% correction; they noted less than 4° loss of total active motion which was not discernible by the patients [34].

Burke and Flatt in their review of 50 patients with clinodactyly advised waiting until skeletal maturity before performing a closing wedge osteotomy in order to achieve maximum length of the finger, thereby minimizing the risks of shortening and range of motion compromise [32].

Our approach to clinodactyly involves evaluation and potential treatment of each tissue type involved. A z-plasty is used to address the deficient soft tissue on the contracted side (Fig. 17.5). Abnormal muscle insertion is then assessed. In the case of Rubinstein-Taybi or Apert syndrome, the abductor pollicis brevis tendon may have an abnormally distal insertion. Release and reinsertion more proximally may help to address a primary deforming force. Although improvements in clinodactyly have been reported with these soft tissue procedures or with physiologysis alone, we prefer to be more definitive in correction. An incision through the epiphyseal bracket is continued across the phalanx as an opening wedge osteotomy. Bone allograft is then used as a spacer to disrupt the bracketed ephiphysis and stabilize the correction. This adds no further surgical morbidity and if the allograft takes, the treatment can be definitive (see Fig. 17.5). We prefer opening wedge osteotomies given that digits requiring surgical treatment are generally hypoplastic and afforded more function with additional length.

In the case of thumb clinodactyly associated with Apert syndrome, there tends not to be a longitudinal bracketed epiphysis. Generalized hypoplasia and pre-existing joint stiffness can make osteotomy technically challenging (Fig. 17.6). Even though a proximal phalanx may not be visualized on x-ray, it is generally present, though sometimes severely hypoplastic with lack of ossification. Families generally report improved function even if stiffness and hypoplasia limit the degree of correction that is possible.

In the case of triphalangeal thumbs with a delta phalanx, excision of the phalanx often allows correction of the deformity.

Summary

Clinodactyly is the congenital curvature of a digit in the radioulnar plane. Clinically significant clinodactyly is rare – curvature of the small finger up to 10 to 15° is common and considered a normal variant. Nonoperative management is the appropriate treatment for the majority of cases; surgery should not be undertaken for cosmetic concerns alone. For the rare case where the cur-

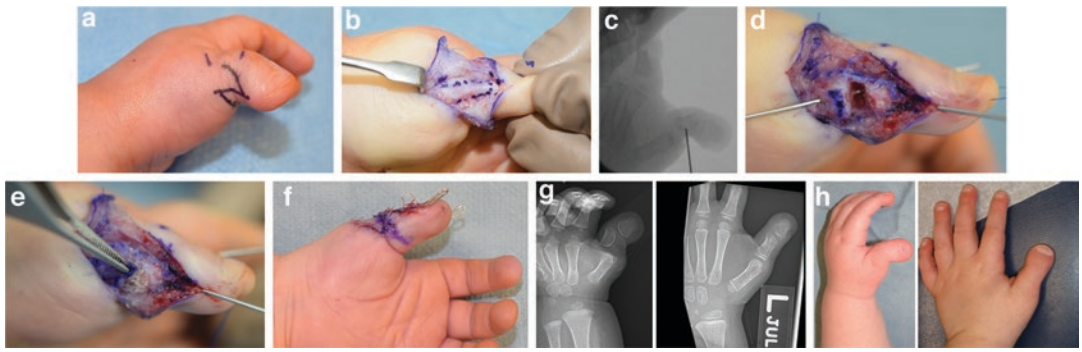

Fig. 17.5 Case example of bilateral thumb clinodactyly in a child with Rubenstein–Taybi syndrome. (**a**) Z-plasty incision for exposure and to allow soft tissue lengthening on radial side of thumb. (**b**) Abductor pollicis brevis insertion elevated with short periosteal sleave. (**c**) Osteotomy at waist of proximal phalanx, through the longitudinal bracketed ephiphysis. (**d**) Opening wedge osteotomy to lengthen thumb for opposition and pinch. (**e**) Defect bridged with allograft and abductor pollicis brevis reinserted at base of proximal phalanx. (**f**) Z-plasty flaps transposed and bone fixed with K-wires. (**g**) Radiographs pre-op and 3 years post-op. The correction has been maintained and the proximal phalanx has assumed more normal morphology. (**h**) Clinical appearance pre-op and 3 years post-op. Family reports greater ease for opposition and pinch. The scar is well hidden and the thumb has a natural appearance

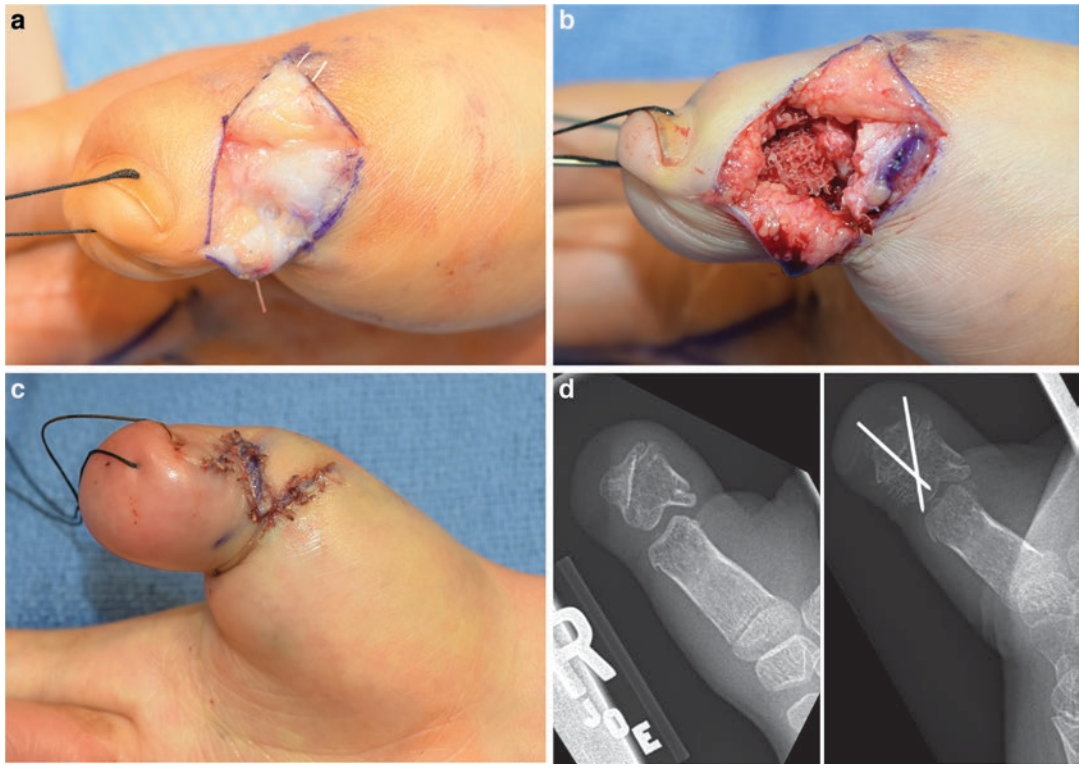

Fig. 17.6 Case example of bilateral thumb clinodactyly in a child with Apert syndrome. (**a**–**d**) As opposed to congenital clinodactyly due to a longitudinal bracketed ephiphysis, clinodactyly seen with Apert syndrome is associated with soft tissue and bone dysplasia. (**a**) The abductor pollicis brevis inserts abnormally into the radial base of the distal phalanx. (**b**) Opening wedge osteotomy is performed to maximize digit length. (**c**) Z-plasty is needed to lengthen the soft tissues on the affected side. (**d**) The osteotomy can be challenging due to the very short radial border of proximal phalanx, generalized dysplasia, and pre-existing joint stiffness. Allograft was used in this case but autograft can also be used. Correction is limited by generalized dysplasia, however, families report improvements in opposition and pinch

vature is severe enough to present functional limitations, surgical options include physiolysis in younger patients and osteotomy in older patients with good results and few complications.

References

1. Smith RJ, Kaplan EB. Camptodactyly and similar atraumatic flexion deformities of the proximal interphalangeal joints of the fingers. A study of thirty-one cases. J Bone Joint Surg Am. 1968;50(6):1187–203.
2. Burke FD. In: Gupta A, Kay SP, editors. The growing hand. London: Mosby; 2000. 4 p.
3. Kozin SH, Kay SP, Griffin JR, Ezaki M. Congenital contracture. In: Green DP, Hotchkiss RN, Pederson WC, Wolfe SW, editors. Green's operative hand surgery. 6th ed. Philadelphia: Elsevier; 2013. 20 p.
4. Rhee SH, Oh WS, Lee HJ, Roh YH, Lee JO, Baek GH. Effect of passive stretching on simple camptodactyly in children younger than three years of age. J Hand Surg. 2010;35(11):1768–73.
5. Benson LS, Waters PM, Kamil NI, Simmons BP, Upton J. Camptodactyly: classification and results of nonoperative treatment. J Pediatr Orthop. 1994;14(6):814–9.
6. Yannascoli SM, Goldfarb CA. Treating congenital proximal interphalangeal joint contracture. Hand Clin. 2018;34(2):237–49.
7. Netscher DT, Hamilton KL, Paz L. Soft-tissue surgery for camptodactyly corrects skeletal changes. Plast Reconstr Surg. 2015;136(5):1028–35.
8. Foucher G, Lorea P, Khouri RK, Medina J, Pivato G. Camptodactyly as a spectrum of congenital deficiencies: a treatment algorithm based on clinical examination. Plast Reconstr Surg. 2006;117(6):1897–905.

9. Smith PJ, Grobbelaar AO. Camptodactyly: a unifying theory and approach to surgical treatment. J Hand Surg. 1998;23(1):14–9.
10. McFarlane RM, Curry GI, Evans HB. Anomalies of the intrinsic muscles in camptodactyly. J Hand Surg. 1983;8(5 Pt 1):531–44.
11. McFarlane RM, Classen DA, Porte AM, Botz JS. The anatomy and treatment of camptodactyly of the small finger. J Hand Surg. 1992;17(1):35–44.
12. Courtemanche AD. Camptodactyly: etiology and management. Plast Reconstr Surg. 1969;44(5):451–4.
13. Ogino T, Kato H. Operative findings in camptodactyly of the little finger. J Hand Surg Br. 1992;17(6):661–4.
14. Hamilton KL, Netscher DT. Evaluation of a stepwise surgical approach to camptodactyly. Plast Reconstr Surg. 2015;135(3):568e–76e.
15. Maeda M, Matsui T. Camptodactyly caused by an abnormal lumbrical muscle. J Hand Surg Br. 1985;10(1):95–6.
16. Inoue G, Tamura Y. Camptodactyly resulting from paradoxical action of an anomalous lumbrical muscle. Scand J Plast Reconstr Surg Hand Surg. 1994;28(4):309–11.
17. Minami A, Sakai T. Camptodactyly caused by abnormal insertion and origin of lumbrical muscle. J Hand Surg Br. 1993;18(3):310–1.
18. Hong SW, Kim J, Kwon OS, Lee MH, Gong HS, Baek GH. Radiographic remodeling of the proximal phalangeal head using a stretching exercise in patients with camptodactyly. J Hand Surg. 2020;45(5):e1–e10.
19. Favril A, Vanhoenacker F, Goubau Y, Jager T. Camptodactyly resulting from anatomical variation of lumbrical muscles: imaging findings. Skelet Radiol. 6 ed. 2019;48(12):2009–14.
20. Hori M, Nakamura R, Inoue G, Imamura T, Horii E, Tanaka Y, et al. Nonoperative treatment of camptodactyly. J Hand Surg. 1987;12(6):1061–5.
21. Miura T. Non-traumatic flexion deformity of the proximal interphalangeal joint-its pathogenesis and treatment. Hand. 1983;15(1):25–34.
22. Urban M, Rutowski R, Urban J, Mazurek P, Kuliński S, Gosk J. Treatment of camptodactyly using injection of botulinum neurotoxin. Adv Clin Exp Med. 2014;23(3):399–402.
23. Wall LB, Ezaki M, Goldfarb CA. Camptodactyly treatment for the lesser digits. J Hand Surg. 2018;43(9):874.e1–4.
24. Evans BT, Waters PM, Bae DS. Early results of surgical management of camptodactyly. J Pediatr Orthop. 2017;37(5):e317–20.
25. Siegert JJ, Cooney WP, Dobyns JH. Management of simple camptodactyly. J Hand Surg Br. 1990;15(2):181–9.
26. Gupta A, Burke FD. Correction of camptodactyly. Preliminary results of extensor indicis transfer. J Hand Surg Br. 1990;15(2):168–70.
27. Manske PR, Oberg KC. Classification and developmental biology of congenital anomalies of the hand and upper extremity. J Bone Joint Surg Am. 2009;91(Suppl 4):3–18.
28. Smith TT. Peculiarity in the shape of the hand in idiots of the mongol type. Paediatrics. 1896;2:315–20.
29. Dutta P. The inheritance of the radially curved little finger. Acta Genet Stat Med. 1965;15(1):70–6.
30. Jones GB. Delta phalanx. J Bone Joint Surg Br. 1964;46:226–8.
31. Fujita H, Iio K, Yamamoto K. Brachymesophalangia and clinodactyly of the fifth finger in japanese children. Acta Paediatr Jpn. 1964;31(1):26–30.
32. Burke F, Flatt A. Clinodactyly. A review of a series of cases. Hand. 1979;11(3):269–80.
33. Cooney WP. Camptodactyly and clinodactyly. In: Carter P, editor. Reconstruction of the child hand. Philadelphia: Lea & Febiger; 1991.
34. Ali M, Jackson T, Rayan GM. Closing wedge osteotomy of abnormal middle phalanx for clinodactyly. J Hand Surg. 2009;34(5):914–8.
35. Light TR, Ogden JA. The longitudinal epiphyseal bracket: implications for surgical correction. J Pediatr Orthop. 1981;1(3):299–305.
36. Ty JM, James MA. Failure of differentiation: Part II (arthrogryposis, camptodactyly, clinodactyly, madelung deformity, trigger finger, and trigger thumb). Hand Clin. 2009;25(2):195–213.
37. Dao KD, Shin AY, Kelley S, Wood VE. Thumb radial angulation correction without phalangeal osteotomy in Apert's syndrome. J Hand Surg. 2002;27(1):125–32.
38. Oishi SN, Ezaki M. Reconstruction of the thumb in Apert syndrome. Tech Hand Up Extrem Surg. 2010;14(2):100–3.
39. Qattan Al MM. Congenital sporadic clinodactyly of the index finger. Ann Plast Surg. 2007;59(6):682–7.
40. Hersh AH, Demarinis F, Stecher RM. On the inheritance and development of clinodactyly. Am J Hum Genet. 1953;5(3):257–68.
41. Wood VE, Flatt AE. Congenital triangular bones in the hand. J Hand Surg. 1977;2(3):179–93.
42. Jain A, Rehman S, Smith G. Long-term results following osteotomy of the thumb delta phalanx in Rubinstein-Taybi Syndrome. J Hand Surg Eur Vol. 2010;35(4):296–301.
43. Vickers D. Clinodactyly of the little finger: a simple operative technique for reversal of the growth abnormality. J Hand Surg Br. 1987;12(3):335–42.
44. Medina JA, Lorea P, Elliot D, Foucher G. Correction of clinodactyly by early physiolysis: 6-year results. J Hand Surg. 2016;41(6):e123–7.
45. Gillis JA, Nicoson MC, Floccari L, Khouri JS, Moran SL. Comparison of Vickers' physiolysis with osteotomy for primary correction of clinodactyly. Hand (N Y). 2019;95:1558944719827999.
46. Bednar MS, Bindra RR, Light TR. Epiphyseal bar resection and fat interposition for clinodactyly. J Hand Surg. 2010;35(5):834–7.

47. Caouette-Laberge L, Laberge C, Egerszegi EP, Stanciu C. Physiolysis for correction of clinodactyly in children. J Hand Surg. 2002;27(4):659–65.
48. Carstam N, Theander G. Surgical treatment of clinodactyly caused by longitudinally bracketed diaphysis ("delta phalanx"). Scand J Plast Reconstr Surg. 1975;9(3):199–202.
49. Tansley PDT, Pickford MA. The partial excision greenstick (PEG) osteotomy: a novel approach to the correction of clinodactyly in children's fingers. J Hand Surg Eur. Vol. 7 ed. 2009;34(4):516–8.
50. Ravishanker R, Bath AS. Distraction – a minimally invasive technique for treating camptodactyly and clinodactyly. Med J Armed Forces India. 2004;60(3):227–30.

18 Synostosis and Coalitions of the Hand and Wrist

Hilton P. Gottschalk and Terry R. Light

Carpal Coalition

Congenital carpal coalitions are uncommon. The incidence is variable; for example, the condition is more common in African Americans. Carpal coalitions can be either isolated or associated with a syndrome. Isolated carpal coalitions most frequently occur between the lunate and triquetrum; however, coalitions have been described between almost all adjacent carpal bones. When carpal coalitions are associated with a syndrome, multiple carpal bones can be involved. Most inter-carpal coalitions are asymptomatic. The condition is usually discovered as an incidental finding during radiographic evaluation following trauma. Patients with symptomatic carpal coalitions tend to have incomplete coalitions.

Embryology

Carpal coalitions are anatomic variations which are the result of failure of separation of the cartilaginous interzone of adjacent bones. Three distinct layers in the interzone have been described: a central loose layer, which gives rise to the synovium and intracapsular structures, and two denser zones, which form the articular cartilage of the two bones [1–3]. If the central layer does not develop appropriately or at all, then either a partial or complete coalition will result. For this reason, many authors prefer the term "incomplete coalition" when describing the lack of bony continuity across the carpal bones [3–5]. Thus, the term "fusion" should be avoided because the mechanism is a failure of segmentation of the cartilaginous precursors rather than the joining of two distinct structures [2].

The theory of failure of segmentation applies well to coalitions between adjacent bones in the same row, specifically the lunate and triquetrum. With respect to pisiform hamate coalitions, this theory is not well supported. O'Rahilly examined carpal anomalies in embryos, looking at articular interzones of future contiguous bone structures, and observed that the pisiform and hamate are not united in cartilage during development [6, 7]. The coalition between the pisiform and hamate is hypothesized to occur as a consequence of ossification of the distal portion of the flexor carpi ulnaris or because the pisohamate ligament undergoes metaplasia, transforming into bone [6–11].

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Incidence

Congenital coalitions occur in less than 1% of the population [12]. The most frequent carpal coalition is between the lunate and triquetrum. The incidence varies by race, with a rate of 0.1% in a Caucasian population compared to 1.6% in African Americans and greater than 8% in certain West African tribes [2, 8, 13, 14]. Lunotriquetral coalitions are twice as common in females as in males. There appears to be a multifactorial inheritance pattern [13].

Classification

Carpal coalition was first described by Sandifort in 1779 with the first documented case report in 1908 by Corson [15]. Subsequent publications have been published describing many variations in carpal coalitions. In 1952, A. B. DeVilliers Minnaar [16] described 12 cases of congenital coalition of the lunate and triquetral bones in the South African Bantu and divided them into 4 types (Table 18.1). The four Minnaar subtypes of these coalitions are (1) incomplete fusion resembling a pseudarthrosis, (2) proximal osseous bridge with a distal notch of varying depth, (3) complete fusion of lunate and triquetrum alone, and (4) complete fusion with other carpal anomalies [16]. Though this scheme has been used to describe other carpal coalitions, it has limitations. First, associated anomalies can be seen in Minnaar types I and II [17, 18]. Second, associated anomalies are not restricted to the hands alone, and many may involve the feet or other parts of the skeleton as well. The Minnaar classification may be too narrow in scope [10, 17, 19]. Lastly, the Minnaar classification scheme does not adequately address the substantial variation in non-osseous coalitions. It has been observed that incomplete coalitions tend to be more symptomatic than their complete counterparts [2, 7, 10, 14, 20, 21]. In light of these limitations, Burnett [10] proposed a simplified classification scheme with two main types, non-osseous or osseous. He states that this "simplified terminology captures the two main variations in coalition appearance, which are likely to be associated with differences in clinical significance" [10].

Table 18.1 Minnaar [16] classification of lunate triquetrum coalitions

Type I	Incomplete fusion resembling a pseudarthrosis
Type II	Fusion with a notch of varying depth
Type III	Complete fusion of lunate and triquetrum alone
Type IV	Complete fusion associated with other carpal anomalies

Carpal coalitions can occur in isolation or associated with syndromes. Isolated coalitions have been described between all adjacent carpal bones [3, 7, 8, 13, 21–28]. More commonly, the non-syndromic coalitions involve only two bones (Fig. 18.1a, b), usually within the same carpal row, while syndrome-associated coalitions often include multiple bones (see Fig. 18.1c).

Isolated Carpal Coalitions

The most common isolated carpal coalition is between the lunate and triquetrum [14, 29]. The majority of these coalitions are bilateral, asymptomatic, and incidental findings; most require no treatment. However, there is growing evidence that incomplete coalitions are more susceptible to injury and hence can become symptomatic [2, 5, 7, 14, 20]. Incomplete coalition is likely the result of a failure of separation during early fetal development, with the degree of cellular death dictating the type of coalition which will develop [5, 8, 13, 16]. Ritt et al. [14] believe that the incomplete coalitions are covered by a thin layer of articular cartilage that in time can wear down and lead to localized degenerative arthritis or be unusually susceptible to fracture. In patients who have symptomatic incomplete coalitions between the lunate and triquetrum, lunate-triquetrum (LT) fusion is recommended. LT fusion provides predictable improvement of symptoms, with little loss of motion [5, 12, 14, 20].

Less common is a coalition between the hamate and pisiform. The first case in the

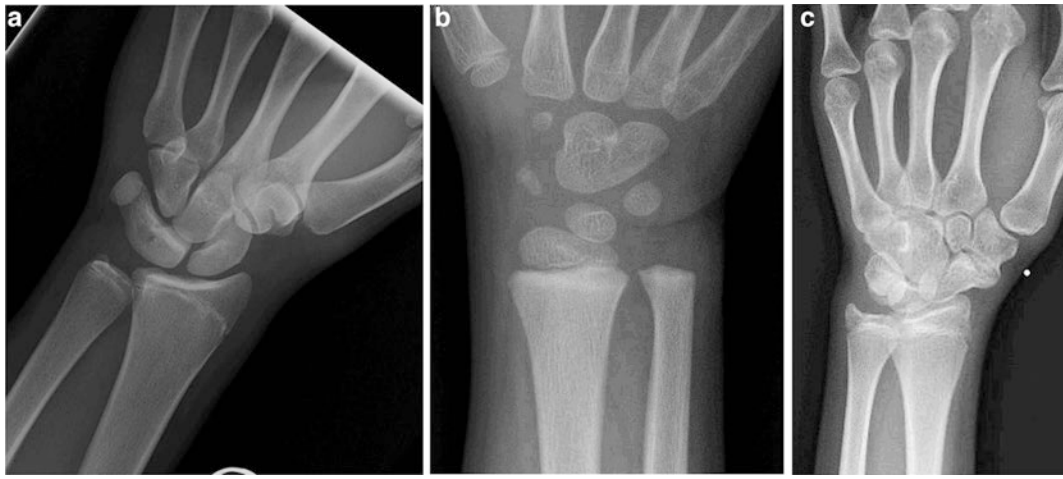

Fig. 18.1 (**a**) Incomplete coalition between lunate and triquetrum (Minnaar type II). (**b**) Incomplete coalition between capitate and hamate. (c) Multiple coalitions—capitate and hamate; scaphoid and trapezium

English literature was described by Cockshott as an isolated asymptomatic entity [9]. However, subsequent authors have reported ulnar side symptoms, including pain and/or paresthesias [7, 10, 11, 30, 31]. According to Burnett, ulnar neuropathy was more frequent in non-osseous hamate-pisiform coalitions compared to those displaying an osseous coalition [10, 31]. In addition, non-osseous coalitions may be more susceptible to degenerative arthritis given the abnormal joint mechanics and the thin cartilage surfaces between the affected carpals [10, 30]. The literature suggests that patients with an osseous hamate-pisiform coalition are predisposed to fracture [7, 10, 30]. An acute symptomatic hamate-pisiform coalition should be initially treated by conservative therapy (typically immobilization). If immobilization does not resolve the pain, then treatment should consist of excision of the pisiform and accompanying coalition [7, 10, 11].

Syndromes Associated with Coalitions

Carpal coalitions are seen in patients with a variety of syndromes:

1. Arthrogryposis
2. Diastrophic dwarfism
3. Dyschondrosteosis
4. Nievergelt syndrome
5. Ellis-van Creveld syndrome
6. Hand-foot-genital syndrome
7. Fetal alcohol syndrome
8. Oto-palato-digital syndrome
9. Turner syndrome

Typically, the syndrome-associated coalitions involve multiple carpal bones and cross-carpal rows and are often associated with other anomalies in the involved extremity as well as anomalies of other organ systems [5, 22, 29].

Diastrophic Dwarfism and Dyschondrosteosis

Diastrophic dwarfism is a form of short-limbed dwarfism and is autosomal recessive. It is more common in patients of Finnish descent and contains a mutation in the sulfate transporter protein on chromosome 5 [22.] Much like patients with arthrogryposis, it is believed that these coalitions are more acquired than congenital, secondary to higher incidence as patients get older.

Dyschondrosteosis is another form of dwarfism. It is a rare inherited mesomelic type associated with bilateral Madelung deformities, and patients may have different types of carpal coalitions. Treatment is tailored toward the wrist deformity if symptomatic [32].

Nievergelt Syndrome

First reported by Nievergelt in 1944 [33], Nievergelt's syndrome is a very rare type of mesomelic dysplasia. It is typically an autosomal dominant inheritance. It is associated with specific deformities of the radius, ulna, tibia, and fibula. As described by Nievergelt, there is radioulnar synostosis and a typical rhomboid shape of the tibia and fibula. Some reports have described associated carpal coalitions as well as involvement of the feet [32, 34].

Ellis-van Creveld Syndrome

Also known as chondro-ectodermal dysplasia, Ellis-van Creveld syndrome is an autosomal recessive disorder with characteristics of disproportionate dwarfism, congenital heart disease, dysplastic nails and teeth, polydactyly, and other hand anomalies [22, 35–38]. The disorder has variable expression with genetic defects in the EVC1 and EVC2 genes, which are located on chromosome 4p16 [36, 38].

The incidence of Ellis-van Creveld syndrome is estimated to be 1 in 60,000 live births, with boys and girls equally affected. The radiographic findings include delayed bone maturation and particularly involve the lateral tibial condyle, leading to genu valgum [38, 39]. Additional radiographic findings include shortened ribs, a trident acetabular roof, and premature ossification of the femoral heads. Although not specific for Ellis-van Creveld syndrome, findings on hand radiographs include coalition of the hamate and capitate, postaxial polydactyly, fusion of metacarpals, and clinodactyly of the small finger.

Treatment focuses on the congenital heart disease and respiratory changes secondary to the thoracic insufficiency. These children typically require early removal of neonatal teeth to help with feeding. The postaxial polydactyly is treated based on the physical findings [38]. No treatment is required for the carpal coalition.

Syndromes with Carpal and Tarsal Coalitions

The combination of carpal and tarsal coalitions can occur in several conditions, including hand-foot-genital syndrome, symphalangism, and arthrogryposis.

Hand-Foot-Genital Syndrome

Hand-foot-genital syndrome (formerly hand-foot-uterus syndrome) was first described in 1970 in four generations of a single family [40]. Hand-foot-genital syndrome is an autosomal dominant disorder caused by a nonsense mutation in HOXA13 [41]. Both males and females can be affected. In females, there may be duplication of the genital tract and other abnormalities involving the ureters and urethra. Males may present with hypospadias of variable severity [42, 43]. Abnormalities in the lower limb consist of small feet with short great toes and tarsal coalitions. The upper extremity includes shortened, somewhat stiff thumbs. Clinically the thumb is proximally placed with a hypoplastic thenar eminence; the index finger is ulnarly deviated, while the small finger often demonstrates clinodactyly and brachydactyly. Delayed ossification and coalition of the carpal bones, specifically the scaphoid and trapezium, may be noted. Surgical intervention for the limb deformities is usually not necessary, but these patients do need urologic evaluation [43].

Symphalangism

Symphalangism is an uncommon condition characterized by fusion of the interphalangeal joints of the hands and feet [44, 45]. The term was first used by Harvey Cushing in 1916 to describe a family with ankylosis of the interphalangeal joints of the hand [46, 47]. Two types of symphalangism are recognized: proximal and distal. This refers to the proximal interphalangeal joint (most common) or the distal interphalangeal joint; either form is inherited in an autosomal dominant pattern [44, 45, 48]. Clinically, patients will have limited or no motion across the interphalangeal joint without flexion creases. Radiographs prior to skeletal maturity may suggest a joint space, but as the cartilaginous bridge between phalanges ossifies as the skeleton matures, bony continuity across the joint will be apparent [45].

Flatt and Wood described three forms of symphalangism [48]:

1. True symphalangism without additional skeletal abnormalities
2. Symphalangism associated with symbrachydactyly
3. Symphalangism with syndactyly

The small finger is most commonly affected, followed by the ring, long, and index fingers [44, 48, 49].

Multiple additional skeletal abnormalities have been reported in association with symphalangism, including brachydactyly, camptodactyly, clinodactyly, syndactyly, radiohumeral fusion, carpal coalitions, pes planus, bilateral hip dislocation, tarsal coalitions, and cervical and thoracic spinal fusions [44, 45]. The most common carpal coalition occurring in association with symphalangism is triquetrum-hamate; capitate-hamate and capitate-trapezium, triquetrum-lunate, and scaphoid-trapezium coalitions have also been reported [22, 47, 50]. Despite the radiographic appearance, fusion of the phalanges in symphalangism rarely impairs hand function.

Arthrogryposis Multiplex Congenita

Arthrogryposis multiplex congenita encompasses several conditions of differing etiology and mixed clinical features. Common to each type are multiple congenital contractures in multiple body areas [51, 52]. The term "arthrogryposis" is more of a description of clinical findings than a specific diagnosis, with the overall prevalence being one in 3000 live births [52, 53]. The etiology of arthrogrypotic syndromes is presumed to be multifactorial resulting in limitation of fetal movement. The resultant effect is loss of muscle mass with imbalance of muscle power across joints, which provokes a collagen response. This in turn leads to partial replacement of muscle volume and collagenous thickening of joint capsules and finally joint fixation [54].

Although tarsal coalitions can occur in arthrogryposis, carpal coalitions are more common [22]. The coalitions can be variable, with the proximal carpals involved first and then more extensive involvement between rows [22]. Newcombe et al. [55] reported that these carpal coalitions seen in arthrogryposis are likely acquired rather than congenital. They dissected specimens and found evidence of some remnants of joint space. Another theory is that the continued stretching and splinting in these patients causes fractures which lead to eventual coalitions.

The typical patient with arthrogryposis will have a flexed and ulnarly deviated wrist. Most of these patients will have a rigid flexion deformity and are resistant to nonoperative treatment [56]. As these patients mature, the midcarpal joint can become obliterated from the multiple carpal coalitions. Coalition between the scaphoid and capitate is frequently observed. The presence of this coalition makes proximal row carpectomy impossible in these children [56]. Ezaki and Carter [56] describe a biplanar wedge resection of the carpus designed to extend the wrist and correct the ulnar deviation. Timing of surgery is recommended before the child reaches preschool age.

Isolated carpal coalitions are usually asymptomatic; however, when they form partial coalitions, they are more susceptible to injury. Partial coalitions, refractory to conservative treatment, can be either excised or fused (depending on their location) with good success. Syndrome-associated carpal coalitions tend to involve both carpal rows, though few require surgical intervention.

Oto-Palato-Digital Syndrome

Oto-palato-digital (OPD) syndrome has characteristic findings affecting ears, palate, and skeleton. The hands and feet are affected predominantly, with carpal bones deformed in appearance. It has been described that the trapezoid may be more "comma"-shaped along with an associated transverse-oriented capitate [22, 32, 57].

Metacarpal Synostosis

Metacarpal synostosis is an uncommon congenital hand malformation characterized by the coalescence of adjacent metacarpals [58]. It most often involves the ring and little finger metacarpals. The condition can be found in isolation or in

association with other hand abnormalities, including polydactyly, radial and ulnar deficiencies, cleft hand, and Apert syndrome [58–61]. Isolated metacarpal synostosis is most often sporadic, though cases have been described that suggest familial inheritance in either X-linked recessive [59, 62] or autosomal dominant patterns [63]. In patients with X-linked recessive inheritance, recent exome sequencing detected a nonsense mutation in exon 3 of FGF16, which is part of the Xq21.1 chromosome [62]. Jamsheer et al. [62] also concluded that FGF16 may play a role in fine-tuning the human skeleton of the hand.

Physical Findings

The condition most commonly occurs between the ring and little finger metacarpals (Fig. 18.2). Typically the little finger is short, hypoplastic, with limited range of motion, and held in an abducted position. This awkward abducted position limits digital dexterity and may disturb hand function, for example: getting the digit caught in pockets and other enclosed spaces [58, 59, 64]. In addition, some patients have noticed that small objects may fall through their hands, more commonly seen in middle-ring finger metacarpal synostosis [58].

Classification

Metacarpal synostosis may be partial or complete. Both forms represent a failure of differentiation. Two classification schemes have been described. Buck-Gramcko and Wood [59] identified three types of anatomic deformity based on the extent of the synostosis (Table 18.2). This type of classification is helpful in defining the extent of metacarpal involvement but may not be

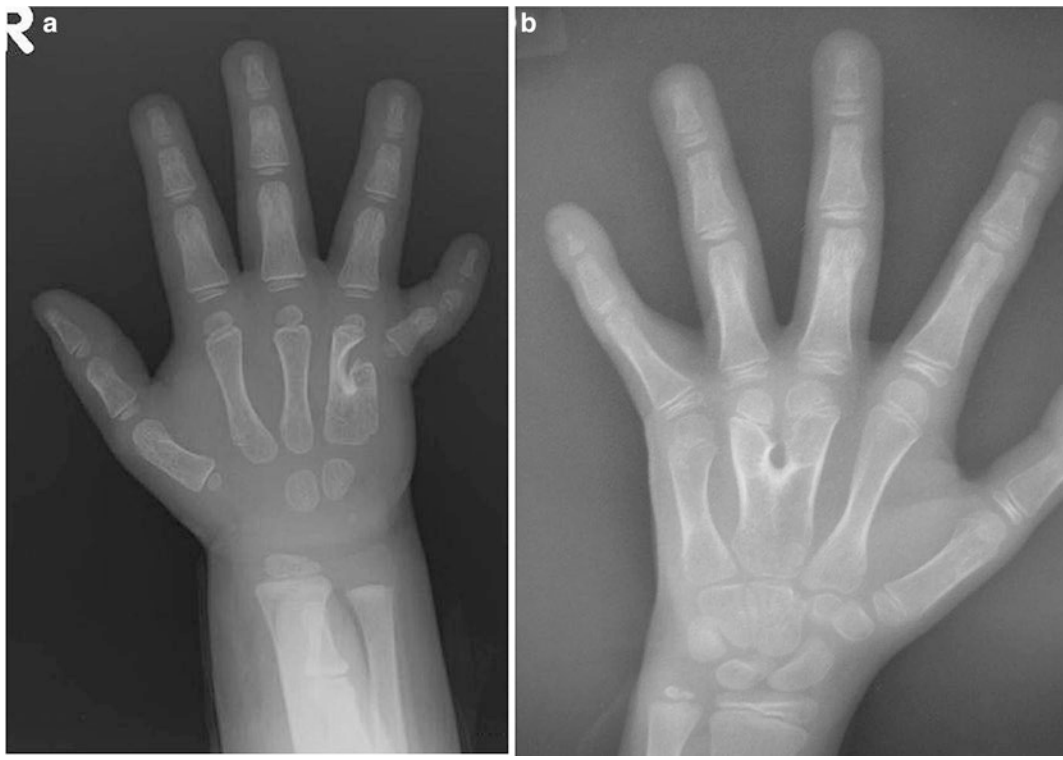

Fig. 18.2 (**a**) Radiograph of a ring-little metacarpal synostosis with abduction of the little finger. (**b**) Radiograph of a middle-ring metacarpal synostosis

Table 18.2 Buck-Gramcko and Wood [59] classification of metacarpal synostosis

Type I	Coalition only at the base of the metacarpal
Type II	Synostosis extends up to half the length of the metacarpal
Type III	Synostosis extends more than half the length of the metacarpal

as helpful in providing guidelines for treatment [58, 59].

Foucher et al. [60] described a system using letters of the alphabet (I, U, Y, k) and based the system on the shape of the synostosis, the degree of hypoplasia, direction of epiphyseal growth, and deformity of the finger distal to the synostosis.

Gottschalk et al. [58] attempted to quantify the extent of abduction deformity in patients with metacarpal synostosis. A posteroanterior radiograph should be taken with the patient's digits adducted as much as possible. For ring-small finger metacarpal synostosis, the middle metacarpal is used as a reference point. The angle between the abducted small digit and the axis of the middle metacarpal are measured. In contrast, when the middle finger metacarpal is involved, the angle formed by the proximal phalanges is documented (Fig. 18.3). We recommend having the patient adduct the fingers as much as possible during the posteroanterior radiograph to give a uniform measurement of deformity.

Treatment

Not all metacarpal synostoses are the same, and treatment will vary. Most surgical techniques involve splitting the metacarpal synostosis and placing a spacer to hold the bones apart [58–61, 64, 65]. Our preferred spacer is a bone graft substitute, coralline hydroxyapatite (Interpore, Biomet, Parsippany, NJ), which mimics the porosity of cancellous bone. This limits donor site morbidity.

The technique is as follows: under tourniquet control, a longitudinal incision is made on the dorsum of the hand over the synostosis. The

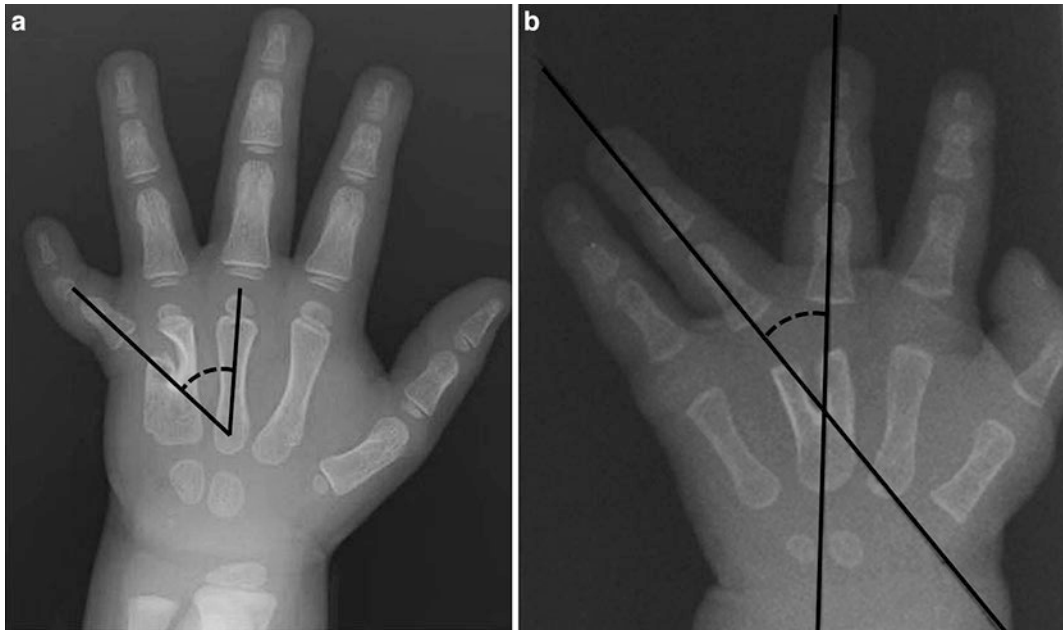

Fig. 18.3 (**a**) The angle between the abducted small digit and the axis of the middle metacarpal are measured in a ring-little metacarpal synostosis. (**b**) In a middle-ring metacarpal synostosis, the angle between the affected digits is calculated by using the longitudinal axes of both proximal phalanges

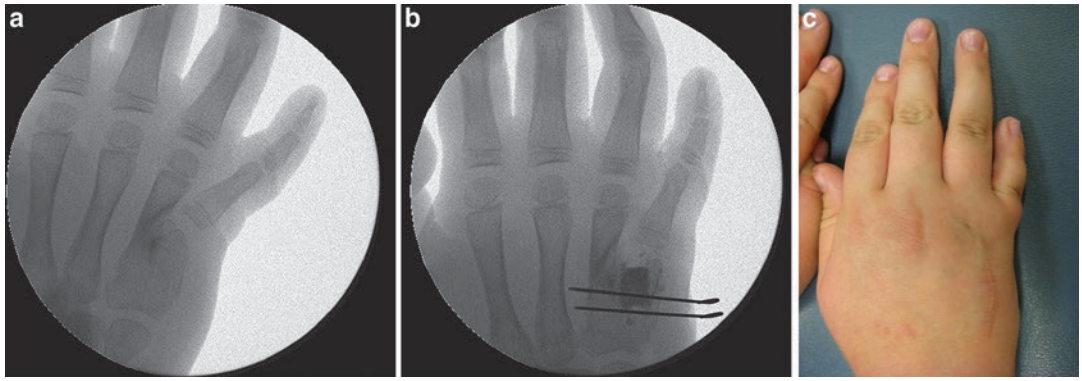

Fig. 18.4 (**a**) Fluoroscopic image of a ring-little metacarpal synostosis before correction. (**b**) Intraoperative image after placement of the bone graft substitute and pinning, with the graft well proximal to the growth plate of the ring metacarpal. (**c**) Clinical appearance 1 year after surgery. Note the improved adduction posture of the little finger; however, the finger remains hypoplastic

extensor tendons are retracted, and a Keith needle is used to identify the midpoint of the coalition under fluoroscopy. The synostosis is split longitudinally, and a lamina spreader is placed between the bones to assess the size of the spacer needed. As the lamina spreader is opened, the finger alignment begins to normalize. The graft is cut to size and placed at the osteotomy site. Care is taken to make sure that the graft is proximal to the growth plates (Fig. 18.4), to avoid creating a growth arrest. Transverse pins are placed through both metacarpals to secure the graft. We bury the pins under the skin, and a cast or splint is worn for at least 4 weeks. The pins remain buried until symptomatic.

Although the abduction deformity has been corrected, this specific procedure does not address the hypoplastic nature of the small finger. The decreased motion at the little finger metacarpophalangeal joint will persist [58, 59]. In addition, certain metacarpal synostoses are not amenable to this technique. Each case should be evaluated.

References

1. Sledge CB. Some morphologic and experimental aspects of limb development. Clin Orthop Relat Res. 1966;44:241–64.
2. Resnick CS, Grizzard JD, Simmons BP, Yaghmai I. Incomplete carpal coalition. AJR Am J Roentgenol. 1986;147:301–4.
3. Kennedy K, Waller CJ, Hartley RH. Congenital lunotriquetral and capitotrapezoid coalitions. J Hand Surg Eur Vol. 2010;35B:79–80.
4. Garn SM, Burdi AR, Babler WJ. Prenatal origins of carpal fusions. Am J Phys Anthropol. 1976;45:203–8.
5. Simmons BP, Mckenzie WD. Symptomatic carpal coalition. J Hand Surg Am. 1985;10A:190–3.
6. O'Rahilly R. A survey of carpal and tarsal anomalies. J Bone Joint Surg. 1953;35A:626–42.
7. Richterman IE, Kozin SH. Symptomatic pisiform hamate synchondrosis: a case report and review of the literature. J Hand Surg Am. 1996;21A:311–3.
8. Cockshott WP. Carpal fusions. Am J Roentgenol Radium Therapy, Nucl Med. 1963;89:1260–71.
9. Cockshott WP. Pisiform hamate fusion. J Bone Joint Surg. 1969;51A:778–80.
10. Burnett SE. Hamate-pisiform coalition: morphology, clinical significance, and a simplified classification scheme for carpal coalition. Clin Anat. 2011;24:188–96.
11. Kawamura K, Yajima H, Takakura Y. Pisiform and hamate coalition: case report and review of literature. Hand Surg. 2005;10:101–4.
12. Gross SC, Watson HK, Strickland JW, Palmer AK, Brenner LH. Triquetral-lunate arthritis secondary to synostosis. J Hand Surg Am. 1989;14A:95–102.
13. Garn SM, Frisancho AR, Poznanski AK, Schweitzer J, McCann MB. Analysis of tiquetral-lunate fusion. Am J Phys Anthropol. 1971;34:431–3.
14. Ritt MJ, Maas M, Bos KE. Minnaar type 1 symptomatic lunotriquetral coalition: a report of nine patients. J Hand Surg Am. 2001;26A:261–70.
15. Szaboky GT. Anomalous fusion between the lunate and triquetrum. J Bone Joint Surg. 1969;51A:1001–3.
16. DeVilliers Minnaar AB. Congenital fusion of the lunate and triquetral bones in the South African Bantu. J Bone Joint Surg. 1952;34B:45–8.
17. Hughes PC, Tanner JM. The development of carpal bone fusion as seen in serial radiographs. Br J Radiol. 1966;39:943–9.

18. Carlson DH. Coalition of the carpal bones. Skelet Radiol. 1981;7:125–7.
19. Burnett SE, Case DT. Naviculo-cuneiform I coalition: evidence of significant differences in tarsal coalition frequency. Foot. 2005;15:80–5.
20. Van Schoonhoven J, Prommersberger KJ, Schmitt R. Traumatic disruption of a fibrocartilage lunate-triquetral coalition—a case report and review of the literature. Hand Surg. 2001;6:103–8.
21. Peters S, Colaris JW. Carpal coalitions: symptomatic incomplete bony coalition of the capitate and trapezoid—case report. J Hand Surg Am. 2011;36A:1313–5.
22. Poznanski AK, Holt JF. The carpals in congenital malformation syndromes. Am J Roentgenol Radium Therapy, Nucl Med. 1971;112:443–6.
23. Samir N, Al-Mahrezi A. Congenital fusion of the trapezium and trapezoid. Sultan Qaboos Univ Med J. 2010;10:405–6.
24. Wilson SM, Moreel P, Roulot E. Symptomatic congenital fusion of the scaphoid and the trapezium. J Hand Surg Am. 2006;31B:581.
25. Moreel P, Wilson SM, Descamps S, Roulot E. Bilateral congenital fusion of the scaphoid and the trapezium. A case report. Rev Chir Orthop Reparatrice Appar Mot. 2008;94:84–6.
26. Weinzweig J, Watson HK, Herbert TJ, Shaer JA. Congenital synchondrosis of the scaphotrapezio-trapezoidal joint. J Hand Surg Am. 1997;22A:74–7.
27. Ingram C, Hall RF, Gonzalez M. Congenital fusion of the scaphoid, trapezium, trapezoid and capitate. J Hand Surg Am. 1997;22B:167–8.
28. Kahane S, Isaac SM, Wildin C. A new type of carpal coalition. J Hand Surg Eur Vol. 2012;37:581–2.
29. Delaney TJ, Eswar S. Carpal coalitions. J Hand Surg Am. 1992;17A:28–31.
30. Ganos DL, Imbriglia JE. Symptomatic congenital coalition of the pisiform and hamate. J Hand Surg Am. 1991;16A:646–50.
31. Berkowitz AR, Melone CP, Belsky MR. Pisiform-hamate coalition with ulnar neuropathy. J Hand Surg Am. 1992;17A:657–62.
32. Gottschalk MB, Danilevich M, Gottschalk HP. Carpal coalitions and metacarpal synostoses: a review. J Hand. 2016;11(3):271–7.
33. Nievergelt K. Positiver Vaterschaftsnachweis auf grund erblicher Missbildungen der Extremitaeten. Arch Klaus Stift Vererbunsforsch. 1944;19:157.
34. Pearlman HS, Edkin RE, Warren RF. Familial tarsal and carpal synostosis with radial-head subluxation (Nievergelt's syndrome). J Bone Joint Surg. 1964;46:585–92.
35. Ellis RW, Van Creveld S. Syndrome characterized by ectodermal dysplasia, polydactyly, chondro-dysplasia and congenital morbus cordis; report of three cases. Arch Dis Child. 1940;15:65–84.
36. Polymeropoulos MH, Ide SE, Wright M, Goodship J, Weissenbach J, Pyeritz RE, et al. The gene for the Ellis-van Creveld Syndrome is located on chromosome 4p16. Genomics. 1996;35:1–5.
37. Galdzicka M, Patnala S, Hirshman MG, Cai JF, Nitowsky H, Egeland JA, et al. A new gene, EVC2, is mutated in Ellis-van Creveld syndrome. Mol Genet Metab. 2002;77:291–5.
38. Muensterer OJ, Berdon W, McManus C, Oestreich A, Lachman RS, Cohen MM Jr, et al. Ellis-van Creveld syndrome: its history. Pediatr Radiol. 2013;43(8):1030–6.
39. Caffey J. Chondroectodermal dysplasia (Ellis-Van Creveld disease); report on three cases. Am J Roentgenol. 1952;68:875–86.
40. Stern AM, Gall JC Jr, Perry BL, Stimson CW, Weitkamp LR, Poznanski AK. The hand-foot-uterus syndrome. A new hereditary disorder characterized by hand and foot dysplasia, dermatoglyphic abnormalities, and partial duplication of female genital tract. J Pediatr. 1970;77:109–16.
41. Goodman FR, Bacchelli C, Brady AF, Brueton LA, Fryns JP, Mortlock DP. Novel HOXA13 mutations and the phenotypic spectrum of hand-foot-genital syndrome. Am J Hum Genet. 2000;67:197–202.
42. Halal F. The hand-foot-genital (hand-foot-uterus) syndrome: family report and update. Am J Med Genet. 1988;30:793–803.
43. Innis JW. Hand-foot-genital syndrome. In: Pagon RA, Adam MP, Bird TD, editors. Gene reviews [internet]. Seattle: University of Washington; 1993–2013.
44. Letts M, Davidson D, Beaule P. Symphalangism in children: case report and review of the literature. Clin Orthop Relat Res. 1999;366:178–85.
45. Tuncay I, Akpinar F, Tosun N. Congenital true complete symphalangism of all proximal interphalangeal joints of hands with carpal anomalies: a case report. Hand Surg. 2001;6:223–6.
46. Cushing H. Hereditary anchylosis of the proximal phalangeal joints (Symphalangism). J Nerv Ment Dis. 1916;43:445.
47. Geelhoed GW, Neel JV, Davidson RT. Symphalangism and tarsal coalitions: a hereditary syndrome. J Bone Joint Surg. 1969;51B:278–89.
48. Flatt AE, Wood VE. Rigid digits or symphalangism. Hand. 1975;7:197–213.
49. Dellon AL, Gaylor R. Bilateral symphalangism of the index finger. J Bone Joint Surg. 1976;58A:270–1.
50. Harle TS, Stevenson JR. Hereditary symphalangism associated with carpal and tarsal fusions. Radiology. 1967;89:91–4.
51. Kalampokas E, Kalampokas T, Sofoudis C, Deligeoroglou E, Botsis D. Diagnosing arthrogryposis multiplex congenital: a review. ISRN Obstet Gynecol. 2012;2012:264918.
52. Bamshad M, Van Heest AE, Pleasure D. Arthrogryposis: a review and update. J Bone Joint Surg. 2009;91(Suppl 4):40–6.
53. Bevan WP, Hall JG, Bamshad M, Staheli LT, Jaffe KM, Song K. Arthrogryposis multiplex congenital (Amyoplasia) an orthopaedic perspective. J Pediatr Orthop. 2007;27:594–600.

54. Swinyard CA, Bleck EE. The etiology of arthrogryposis (multiple congenital contracture). Clin Orthop Relat Res. 1985;194:15–29.
55. Newcombe DS, Abbott JL, Munsie WJ, Keats TE. Arthrogryposis multiplex congenital and spontaneous carpal fusion. Arthritis Rheum. 1969;12:345–54.
56. Ezaki MB, Carter PR. Carpal wedge osteotomy for the arthrogrypotic wrist. Tech Hand Up Extrem Surg. 2004;8:224–8.
57. Langer LO Jr. The roentgenographic features of the oto-palato-digital (OPD) syndrome. Am J Roentgenol Radium Therapy, Nucl Med. 1967;100(1):90–106.
58. Gottschalk HP, Bednar MS, Moor M, Light TR. Metacarpal synostosis: treatment with a longitudinal osteotomy and bone graft substitute interposition. J Hand Surg Am. 2012;37A:2074–81.
59. Buck-Gramcko D, Wood VE. The treatment of metacarpal synostosis. J Hand Surg Am. 1993;18A:565–81.
60. Foucher G, Navaro R, Medina J, Khouri RK. Metacarpal synostosis: a simple classification and a new treatment technique. Plast Reconstr Surg. 2001;108:1225–31.
61. Miura T. Congenital synostosis between the fourth and the fifth metacarpal bones. J Hand Surg Am. 1988;13A:83–8.
62. Jamsheer A, Zemojtel T, Kolanczyk M, Stricker S, Hecht J, Krawitz P, et al. Whole exome sequencing identifies FGF16 nonsense mutations as the cause of X-linked recessive metacarpal 4/5 fusion. J Med Genet. 2013;50(9):579–84. https://doi.org/10.1136/jmedgenet-2013-101659.
63. Temtamy D, McKusick V. The genetics of hand malformations (Chapter 8). In: Birth defects, Original article series. Vol. 14, No. 3. New York: Alan R. Liss; 1978.
64. Horii E, Miura T, Nakamura R, Nakao E, Kato H. Surgical treatment of congenital metacarpal synostosis of the ring and little fingers. J Hand Surg Am. 1998;23B:691–4.
65. Iwasawa M, Hayashi R, Matsuo K, Hirose T. The use of costal cartilage as a spacer in the treatment of congenital metacarpal fusion. Eur J Plast Surg. 1988;11:138–40.

Congenital Clasped Thumb

19

Hisham Abdel-Ghani and Mostafa Mahmoud

Definition

A persistent flexion of the thumb with lack of active extension after the age of 3 months of life has been variously termed congenital clasped thumb [1], pollex varus [2], infant's persistent thumb-clutched hand [3], thumb in palm deformity [4], and flexion adduction deformity of the thumb [5] (Fig. 19.1). This definition applies to simple form or isolated forms of clasped thumbs but complex cases with evident contractures, syndromes, or windblown deformity could be diagnosed at birth. It should be differentiated from the developmental spastic adduction deformity of the thumb associated with brain insults, including cerebral palsy, that are usually not congenital in nature.

Clinical Picture

Congenital clasped thumb has heterogeneous presentations. The main finding is lack of active extension of the metacarpophalangeal (MCP) joint of the thumb. Anderson and Breed suggested that the Moro reflex might be a useful way to detect congenital clasped thumb early. The thumb normally extends during the Moro reflex [6].

Lack of active extension may involve also the interphalangeal (IP) joint of the thumb (Fig. 19.2). There may be callosities on the dorsum of the IP joint secondary to grasping objects against that side of the thumb (see Fig. 19.2). The carpometacarpal (CMC) articulation may be mobile and show active extension or may be stiff, especially in cases of severe deformity or generalized disorders. Full passive range of movement of the thumb indicates absence of soft tissue contractures. Limitation of passive extension of the thumb with full wrist extension reveals hidden shortening of the flexor pollicis longus (FPL) muscle. Limitation of passive extension of the thumb with the wrist in neutral position indicates the presence of palmar soft tissue contractures that may be associated with skin webbing at the level of MCP joint (see Fig. 19.1b). The first web space may show variable degrees of narrowing and skin deficiency (Fig. 19.3). The MCP joint may show variable degrees of instability that may become evident only after surgical release of flexion contracture. In severe cases, the thumb may appear very short, stumpy, adducted, flexed, and externally rotated (see Fig. 19.3). The thenar muscles may show some degree of mild hypoplasia. Severe thenar muscle hypoplasia or aplasia points to the diagnosis of congenital hypoplastic thumb type III [7, 8] with predominant deficiency of extrinsic extensor tendons rather than clasped thumb. Meticulous examination and analysis of

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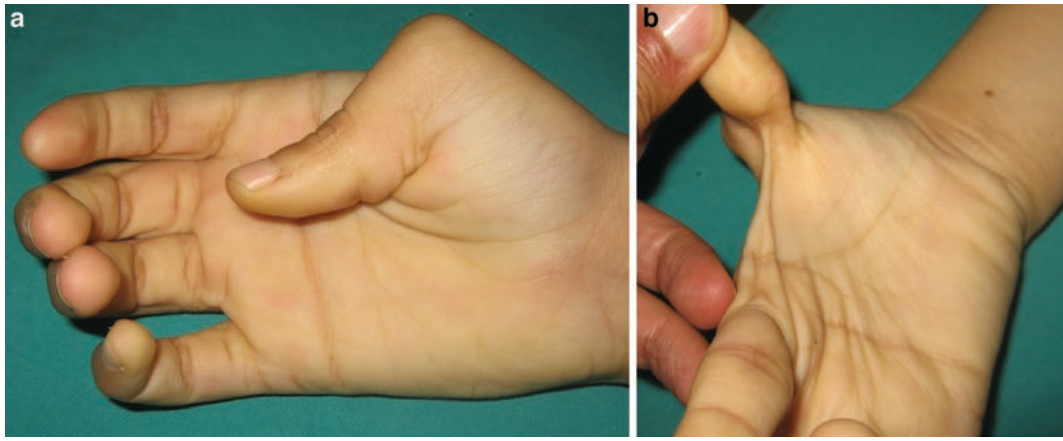

Fig. 19.1 (**a**) Congenital clasped thumb with lack of extension of MCP joint only and active extension of the IP joint. (**b**) Palmar contracture of the thumb

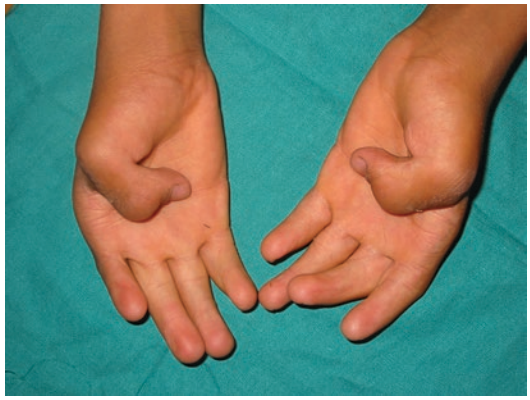

Fig. 19.2 Congenital clasped thumb with flexed IP joint indicating combined deficiency of both EPL and EPB. Callosities are evident on the dorsum of IP joint

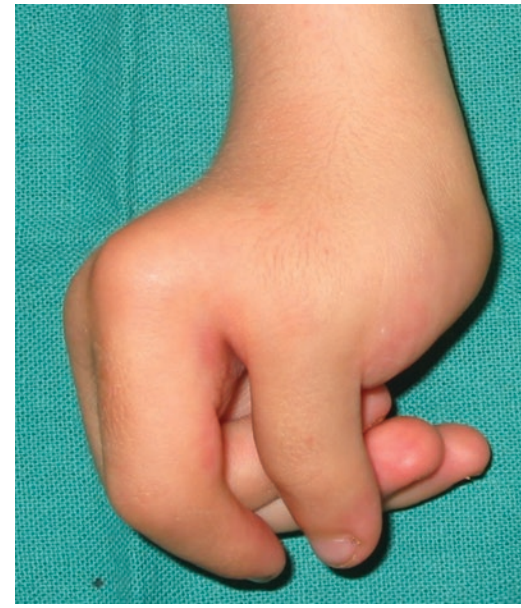

Fig. 19.3 Clasped thumb with severe narrowing of the web space and extension contracture of the wrist

deformities are mandatory to plan treatment accordingly.

Associated deformities of the hands with clasped thumb include abnormal skin creases (see Fig. 19.2), stiffness of the fingers with incomplete flexion (see Fig. 19.2), wrist extension deformity (see Fig. 19.3), camptodactyly (Fig. 19.4), radial deviation of index finger (Fig. 19.5), lack of extension of the index finger (Fig. 19.6), and ulnar drift hand (Fig. 19.7) [8].

Ulnar drift hand is characterized by ulnar deviation of the fingers at the level of the MCP joints with or without flexion contracture of the MCP joints. Although ulnar deviation of the fingers is the most common feature of ulnar drift hand, webbing of the thumb to the palm is the most limiting disability [9].

Clasped thumb could be diagnosed in radial club hand in the presence of well-developed thenar muscles and flexed thumb (Fig. 19.8) [8].

Some cases show lack of extension or severe hypoplasia of index finger or index and middle fingers and the only active functioning fingers are the ring and little ones (see Fig. 19.6). After cor-

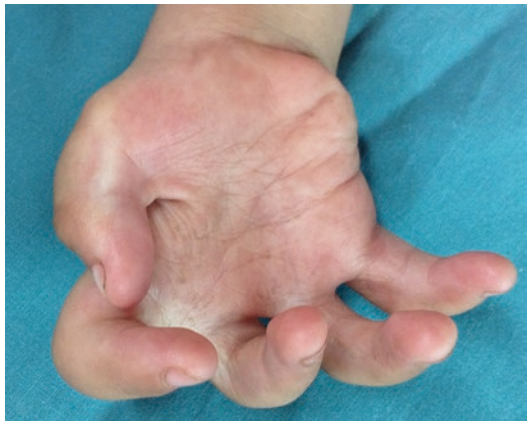

Fig. 19.4 Clasped thumb with palmar thumb webbing and camptodactyly of the four fingers

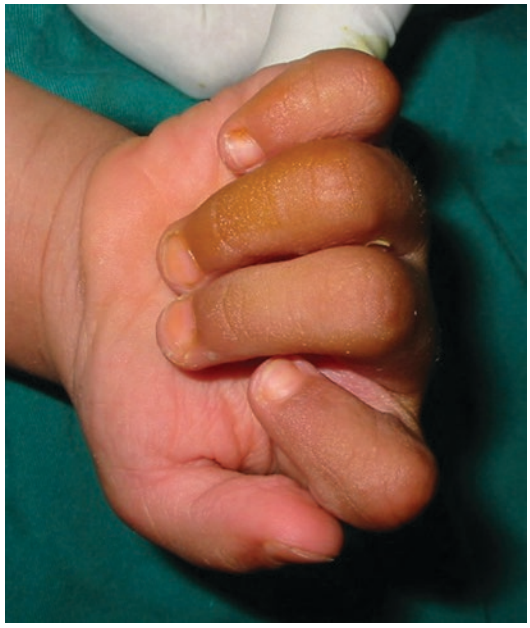

Fig. 19.5 Radial deviation of the index finger at the level of the MCP joint in association with clasped thumb

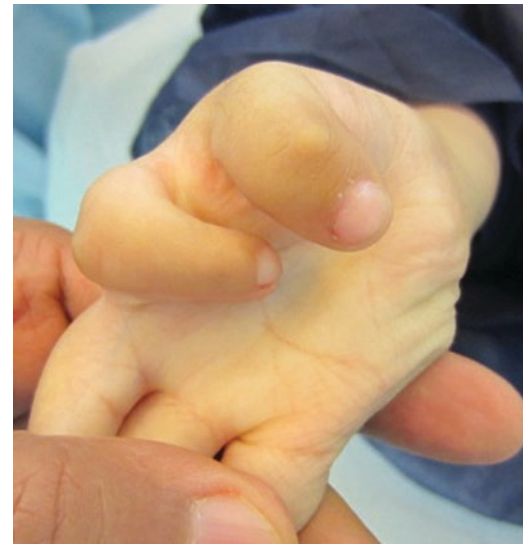

Fig. 19.6 Clasped thumb associated with deficient extensors of the index finger

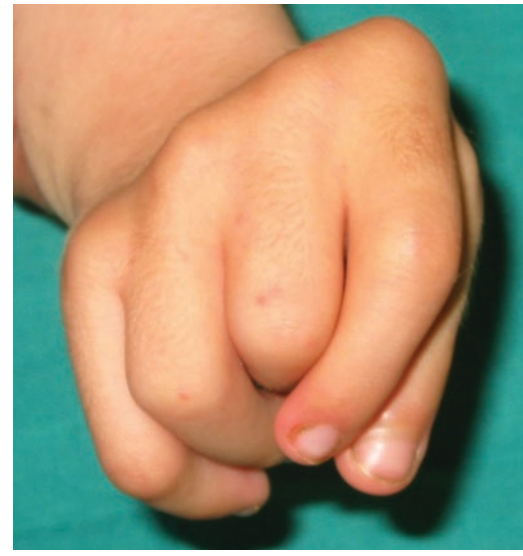

Fig. 19.7 Ulnar drift hand

rection of thumb deformity, the patients continue to grasp with the reconstructed thumb against the ulnar most fingers. Congenital clasped thumb commonly manifests as part of generalized disorder especially multiple joint contractures syndromes collectively called arthrogryposis [2, 8, 10–12]. Arthrogryposis is a purely descriptive term. It is defined as the presence of two or more joint contractures in multiple body areas [2]. Wood considered ulnar drift hand representing a conglomerate of syndromes and different anatomical causes. Probably all of these cases represent a forme fruste of arthrogryposis [9].

Arthrogryposis with CNS involvement includes chromosomal abnormalities and other syndromes [13].

Congenital clasped thumb should be differentiated from trigger thumb, where a palpable nod-

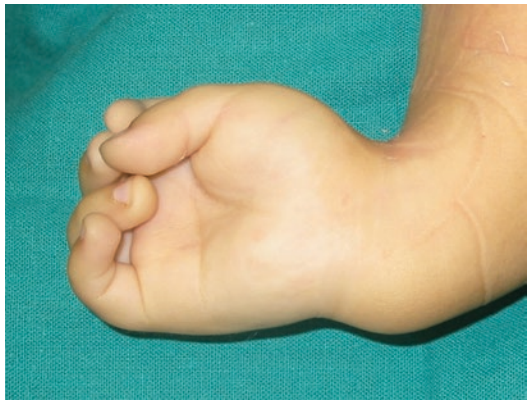

Fig. 19.8 Radial dysplasia with congenital clasped thumb, evident by presence of well-developed thenar muscles and flexed thumb

ule of the flexor pollicis tendon is present at the level of the MCP joint. When locked, the IP joint is flexed with extension of the MCP joint and a palpable clunk is felt on unlocking the trigger thumb and extending the IP joint [14].

Pathoanatomy and Classification

Many authors have suggested that flexor extensor imbalance is central to the development of clasped thumb. The long extensor tendons are not totally absent, but vestigial strands or hypoplastic extensor tendons are always present [8, 10, 15, 16]. Flatt [17] found that in the course of tendon transfer, the vestigial tendon narrows proximally and eventually ends in fibro fatty tissues rather than muscular tissue. Crawford et al. [16] found that on releasing the flexion contractures, all tissues were involved, including skin, subcutaneous fascia, and periarticular structures. They also found an increase in fibrous tissue present in the form of numerous subcutaneous strands in the digits, palm, and forearm, making dissection, mobilization, and transfer of the tendons more difficult than anticipated [16, 17, 19].

Weckesser et al. [20] classified congenital clasped thumbs into four groups. Group I consisted of isolated clasped thumb. The extensor pollicis brevis (EPB) or extensor pollicis longus (EPL) muscles and tendons are either weak or attenuated. In addition to the deformities seen in group I, group II patients have associated flexion contractures of the fingers. These deformities are believed to be the result of mild to moderate arthrogrtyposis. Group III deformity is related to radial ray hypoplasia with findings of hypoplasia of extensor, flexor, and thenar muscles as well as associated osseous elements. Group IV patients are a miscellaneous category that include polydactyly. We believe that this classification includes cases that should not be considered as clasped thumbs.

McCarroll [10] classified congenital clasped thumbs into supple and complex types. The former is characterized by lack of active thumb extension with ability to fully reverse the deformity passively. The latter group may demonstrate soft tissue contractures, lax ligaments, and tight skin in addition to the lack of active thumb extension.

Tsuyuguchi et al. [11] designed a classification consisting of three groups: Group I: The supple clasped thumb, where the thumb is passively abductable and extendable against the resistance of thumb flexors, without other digital anomalies. Group II: The clasped thumb with hand contractures, where the thumb is not passively extendable and abductable, with or without other digital anomalies. Group III: The clasped thumb, which is associated with arthrogryposis or windblown hand.

We have not found any anatomical differences or different outcome between Tsuyguchi's types II and III, so we prefer using the McCarroll subtypes [10].

In complex cases, abnormal articular surface of the first MCP joint was described with hypoplasia of the volar aspect of the first metacarpal head. The dorsal capsule of the MCP joint may be adherent to the cartilage of the metacarpal head and sharp dissection was needed to separate it [8, 16]. The flexion contracture of the MCP joint is secondary to skin deficiency, abnormal subcutaneous fibrous tissue and contracted periarticular structures including volar plate, collateral ligaments, and capsule [8, 10]. Shortening of the FPL may add to the flexion contracture. Narrowing of the web space is secondary to con-

tracture of one or more of the following structures: palmar fascia, adductor pollicis, first dorsal interosseous muscles and contracture of the capsule of CMC joint [8, 21]. The pathology of complex clasped thumb could be summarized as hypoplastic or attenuated thumb extensors, flexion contracture of MCP joint, ulnar collateral laxity or global instability of the MCP joint, adduction contracture of the CMC joint, and contracture of the first web space. We noted that the severity of these pathological findings is variable, and dependent on the age of the patient at the time of surgery [8, 17, 21].

Prevalence and Etiology

Congenital clasped thumb occurs twice as often in males as in females and it is bilateral in more than 80% [8, 17, 20, 22]. Positive family history of 32–36% was reported [8, 20]. Positive consanguinity was reported as high as 60% [8]. The high incidence of bilateral deformity implies that a defect is present in the zygote before the first cell division. In supple deformity, the very limited and specific nature of the defect also suggests that the cause is a genetic defect rather than some environmental influence on the zygote, which would be much more likely to produce widespread defects. The familial occurrence of this anomaly in a number of cases adds to the evidence for genetic defect [8, 20].

The high incidence of defect in the EPB may have a phylogenetic basis in that this phylogenetically new muscle is found only in the gorilla and in man [20].

Most of the cases of congenital clasped thumbs are part of generalized disorders. Abdel-Ghani et al. [8] reported associated congenital malformation in 77.5% of cases, incidence of 15% of associated malformations of the hand [8, 23], and 68% incidence of associated syndromes [8]. The most common associated anomalies are manifestations of congenital contractures: congenital hip dislocation, congenital knee dislocation, knee stiffness, congenital clubfeet, congenital vertical talus, scoliosis, elbow stiffness, and limited shoulder movement. Rarely reported associated anomalies were ventricular septal defect and congenital blindness [8]. There were no reported abdominal anomalies in association with clasped thumbs [8, 23, 24].

In the majority of cases, congenital clasped thumb is part of congenital multiple contractures loosely termed arthrogryposis. Arthrogryposis, as defined before, describes the multiple congenital contractures that are part of more than 200 different disorders. Arthrogryposis could be classified into three major categories: amyoplasia, distal arthrogryposis, and syndromic arthrogryposis [13].

Amyoplasia is also called arthrogryposis multiplex congenital (AMC) or classic arthrogryposis. It is the most common form, seen in approximately 1/3000 live births, and has sporadic incidence with no genetic or hereditary predisposition [24]. AMC is associated with thumb deformities but not clasped thumb.

The second group is distal arthrogryposis syndromes, which are a group of autosomal dominant syndromes with congenital contractures primarily involving the hands and feet, which often are associated with abnormal facies without primary neurological and/or muscle disease affecting limb function [13]. Many affected individuals present in an orthopedic setting. Although they are termed distal, they are associated with other deformities that are not localized to the hands and feet. There are at least 10 different types of distal arthrogryposis that include a large number of syndromes [13, 25]. The most common distal arthrogryposis syndromes that are linked to clasped thumbs are Freeman–Sheldon syndrome, multiple pterygia syndrome, digitotalar dysmorphism, clasped thumb clubfoot syndrome, and congenital contractural arachnodactyly [25]. In amyoplasia and distal arthrogryposis, central neurological examination is normal.

The third group of congenital multiple contractures include a great number of genetic syndromes and chromosomal anomalies. This group is characterized by abnormal neurological examination secondary to central nervous system or peripheral neuromuscular disorders. This group is a common cause of arthrogryposis and responsible for the most severe forms. Central nervous system disor-

ders can be suspected on clinical examination if hyperreflexia, unilateral arthrogryposis, or cognitive deficits are present and can be anatomically localized by magnetic resonance imaging of the brain or spinal cord [13]. This group includes a great number of genetic syndromes and chromosomal anomalies. Examples from this group are COFS (cerebro-oculo-facio-skeletal) syndrome, congenital muscular dystrophy, Miller–Dieker (lissencephaly), lethal multiple pterygium syndrome, Pena-Shokeir phenotype, Potter syndrome, Zellweger syndrome, trisomy 8/mosaicism, trisomy, and many others. This group includes lethal syndromes and syndromes with severe disabilities due to central nervous system malfunction. Mental retardation/CNS involvement is found in approximately 25% of individuals with arthrogryposis [13, 26].

The features of these syndromes are described to allow diagnosis, establish prognosis, provide family counseling, and treatment. Increased recognition will lead to improved knowledge of the natural history [25].

Arthrogryposis appears to occur secondary to fetal akinesia (lack of movement), which is the common endpoint of several different in utero processes. The causes of arthrogryposis include conditions that are intrinsic to the fetus, such as neuromuscular disorders, skeletal dysplasias, or aneuploidy, as well as those resulting from influences extrinsic to the fetus [27].

While the pathoanatomy and pathophysiology vary and continue to be investigated, it appears that the joints initially have full developmental potential but fail to form mobile articulations secondary to the absence of active movement in utero. This theory has been supported by a number of chick embryo studies, in which paralytic agent were administrated during development, resulting in abnormal joint morphology and stiffness [28]. The lack of joint motion results in articular cartilage abnormalities, failure of joint cavitation, and secondary fusions.

Amyoplasia has an increased prevalence in twins and in extrinsic conditions that would lead to decreased limb movement, such as a bicornuate uterus, oligohydramnios, or intrauterine crowding [29]. Also it may be secondary to major vascular insult to the fetus [26].

Most of the cases of distal arthrogryposis are due to mutations in genes responsible for myofiber function, including TNNI2, TNNT3, TPM2, MYH3, AND MYH8 [30–35].

Treatment

Supple Clasped Thumb

Most of these cases respond to non-operative treatment. In young infants, especially those with shortening of FPL muscle, they respond well to manipulation by the mother. Manipulation entails bringing the thumb out of the palm and holding it in an extended position. Stretching exercises should be done while the wrist is in extension to effectively stretch the short FPL muscle. Mothers are instructed to do exercises with every feeding and diaper change.

Splinting is used if there is no active thumb extension after trial of manipulation. We find difficulty in applying splints in very young infants or small hands. Different forms of splints were used. We use a rigid splint that keeps the wrist in full extension and the thumb in full abduction with extension of the MCP joint. There is no solid protocol for splinting; almost similar protocols were followed by Weckesser [1], McCarroll [10], Lipskeir and Weizenbluth [36], and Abdel-Ghani et al. [8]. Currently, we start exercises at the time of presentation if splinting cannot be applied. Once we can use splints, full-time splinting is adopted until observing active thumb extension. This is followed by daily exercises and night splinting for further 6 months. Flatt [17] mentioned that if there is no improvement of the posture of the thumb or absolute lack of any active extension after 3 months of splinting, then it is reasonable to assume that the EPB is non-functional. He assumed that there is no harm in continuing splinting for further 3 months, but it is unlikely to have active thumb extension after this extra time of splinting [17].

Lin et al. [22] reported successful treatment of supple form with splinting in patients below 1 year of age. Tsuyuguchi et al. [11] and Abdel-Ghani et al. [8] reported excellent results of splinting in all patients with supple clasped

thumbs in all their patients with an average time of splinting more than 3 months. In our practice, most of the patients presented early, before age of 6 months, with shortening of FPL respond well and restore full active thumb extension with proper stretching exercises and splinting.

The long-term results of treatment with corrective splinting have been shown to be good if the response to primary treatment was good. No adverse effects on growth of the hand have been noted [17].

Splinting was not as successful in treating those with volar side contracture, but it was superior to employing passive range of motion alone in these cases [8, 11].

Kozin mentioned that the goal of splinting is to prevent additional attenuation of the hypoplastic extensor mechanism and allow hypertrophy over time [37]. We hypothesize that keeping the thumb in a splint allows growth of the child while the attenuated extensor tendons are kept unstretched. This allows differential growth of the bones and the extensor tendons, allowing stretching of the long thumb flexors and shortening of extensor tendons. This is why splinting is effective in young infants with rapid rate of growth and less effective in older children with slower rate of growth.

Complex Clasped Thumb

Early manipulation could be tried in all patients during the first few months of life. This may improve the deformity and contractures but will usually fail to correct it completely. A trial of night splinting may be used in selected cases but in severe deformities and marked laxity of the MCP joint, splints could not be applied or effective. Most of these cases will require surgical intervention.

Surgical Treatment

Surgery for clasped thumbs is a la carte; surgery is tailored according to the present deformities (Fig. 19.9). Reconstruction of clasped thumbs entails different combinations of surgical procedures [21]:

- Restoration of active thumb extension
- Web space reconstruction
  - Release of thumb web space and palmar thumb contracture
  - Widening of the skin of web space and skin augmentation of the volar aspect of the thumb
- Stabilization of MCP joint
- Lengthening of FPL

Timing of surgery is variable; Senrui recommended surgery between the ages of 3 and 5 years [38]. In our experience, surgery is feasible after the age of 1.5–2 years without maximum limits. We postpone surgery until the radiological appearance of ossification of the proximal phalangeal epiphysis of the thumb to allow successful chondrodesis or arthrodesis of MCP joint [21]. All surgeries are done under tourniquet control, and magnifying loupes are mandatory.

Restoration of Active Thumb Extension

Tendon transfer to restore active thumb extension is indicated in the presence of mobile and stable MCP joint. This is done in cases of supple deformities failing to respond to non-operative treatment or in complex cases after ligament reconstruction of the MCP joint and widening the web space. The most commonly used transfers are extensor indicis (EI) [5] or the ring finger flexor digitorum superficialis (FDS) [38]. The extensor digitorum communis (EDC) tendon to the index can also be used as a transfer, but only after demonstrating an effective EI [17]. Less commonly, the extensor carpi radialis longus transfer may be used [39]. In cases of absent EPL, the EI is usually absent [17]. Transfer is done to attenuated EPB or EPL tendons. Using either EI or ring finger FDS provides enough length for transfer, but if using any of the wrist extensors, tendon graft is mandatory.

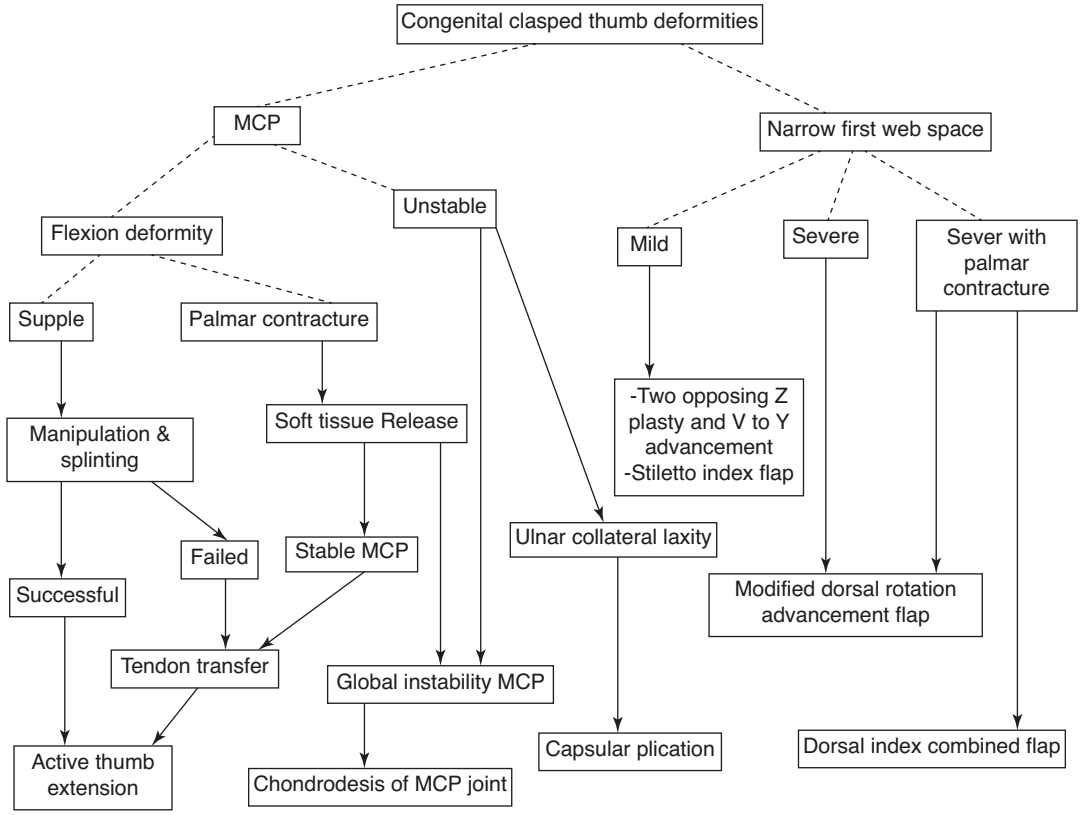

Fig. 19.9 Algorithm for management of congenital clasped thumb

Technique of EI Transfer [37]

Make a short transverse incision at the head of the index metacarpal and locate the EI tendon deeper and ulnar to the EDC tendon to index finger. Divide the tendon at its confluence with the extensor hood. Next make a short transverse incision over the dorsum of the wrist in line with the EI tendon and withdraw the tendon into this wound. Make a bayonet-shaped incision over the dorsoulnar aspect of the thumb centered over the MCP joint. Identify the attenuated thumb extensor tendons. Reroute the tendon of the EI. We do not use an osseous tunnel in the proximal phalanx for the EI tendon as originally described [37], and instead we suture it to the attenuated extensor tendons [17, 40].

Technique of FDS of the Ring Finger Transfer [38]

The tendon is divided proximal to the vincula longa through an oblique incision over the palmar aspect of the proximal interphalangeal joint and drawn into the forearm. It is drawn back under the abductor pollicis longus tendon into another small incision, which has been made at the radial side of the wrist and then attached to the vestigial tendons of the EPB or EPL.

We retrieve the tendon by a transverse incision at the level of A1 pulley; this provides enough length for the transfer without the need to go distal at the level of the proximal phalanx.

In the patients with arthrogryposis, this transfer may not be possible because of the lack of

demonstrable FDS or flexor digitorum profundus function. Once it has been determined that a profundus tendon is present, the superficialis tendon may be harvested.

Web Space Reconstruction

This entails release of contracted tissues and skin reconstruction and augmentation of the web and palmar aspect of the thumb.

Release of Contracted Tissues

Release of contracted tissues entails release of contractures of deeper tissues of the thumb web space and the palmar aspect of the thumb. This is usually done through the skin incisions used to reconstruct the skin of the web space and skin deficiency of the palmar aspect of the thumb.

Release of Thumb Web Space

Dissection is deepened through the skin incisions designed to widen the web to the underlying fascia over the intrinsic muscles, protecting the distal branches of the superficial radial nerve, the flexor tendon, and neurovascular bundles to the index finger. The tight structures to be released are identified; the fascia of the first web space is the most common structure to require release. The origin of adductor pollicis muscle is the second most common structure to need release from the third metacarpus [21]. If necessary, the first dorsal interosseus muscle is elevated from the first metacarpus. The thumb is then manipulated into extension and abduction. If necessary, the CMC joint capsule is released. After achieving full release, the first metacarpus is maintained in full abduction with two crossed K-wires across the first web space [8, 21, 41, 42]. Abdel-Ghani et al., [21] reported surgery on 69 complex clasped thumbs. Release of the first web space involved release of the intermetacarpal fascia in all 69 thumbs, adductor pollicis in 41 thumbs, first dorsal interosseous in 35 thumbs, and CMC joint in 30 thumbs.

Ezaki and Oishi prefer to release the thenar muscles from their origins at the base of the palm even through a separate incision. Also, they release both heads of the adductor pollicis through this palmar incision. If necessary, they leave the palmar incision to heal by secondary intention [43]. We did not find this release necessary, as we manipulate the thumb and stabilize it in full abduction and not just full extension, which does not necessitate this form of release of the thenar muscles.

Release of Palmar Contracture of the Thumb

Treatment of the MCP joint flexion contracture requires release of all thick subcutaneous fascial adhesions with preservation of the digital bundles. The flexor tendon sheath also may contribute to flexion contracture and may require release to allow full extension of the thumb. Extensive release of the volar plate or of the MCP joint capsule to achieve full extension may destabilize the joint and make it unsuitable for transfer. Sharp dissection is required to release the adherent capsule to the head of the metacarpus. After full release, the joint is manipulated to full extension. Transarticular pinning using one or two crossing Kirschner wires is used to hold the joint in full extension [8, 21, 44].

Skin Reconstruction and Augmentation of the Web and Palmar Aspect of the Thumb

Different techniques of skin reconstruction of the web space are used according to the degrees of narrowing of the web. The aim of skin reconstruction is to provide wide web with rounded edge and without scarring along its edge. Random-based skin flaps are the most common techniques used. The flaps should extend beyond the edge of the web to avoid consequent recurrence of contracture after healing and with follow-up. We found that simple Z-plasty is not useful because it deepens the web, transforming

it into a slit with apparent lengthening of the thumb and poor cosmetic appearance [45]. For mild cases, four flap Z-plasty or double opposing Z-plasty with Y to V advancement [46] gives a natural appearance of the widened web space [45]. Ezaki and Oishi [43] described an index rotation (stiletto) flap that could be used either for widening the web space or for skin augmentation of palmar thumb contracture. This flap cannot address both deformities; however, they are commonly encountered together. It is useful in moderate cases of narrowing of the first web space.

We currently use the modified dorsal rotation advancement flap described by the first author [21, 41, 42, 47]. This flap provides a wide-tipped long flap that extends long enough beyond the edge of the web to the mid-palm. In addition to widening of the web, it provides skin augmentation for the thumb palmar contracture.

In severe palmar thumb contracture, we use the dorsal index-combined flap described by Mahmoud et al. [19]. This technique combines a dorsal index flap with a dorsal triangular flap and a palmar rectangular one to widen the web. These two flaps provide good skin augmentation and release of severe palmar contracture [19].

Modified Dorsal Rotation Advancement Flap Technique (Fig. 19.10) [21, 42, 47]

The flap is begun on the dorsum of the hand with a straight incision over the first metacarpal bone. The second, ulnar incision curves from the second to the fifth metacarpal bones, extending to the wrist level. The two lines are extended in rectangular shape to the edge of a narrow first web (see Fig. 19.10c).

On the palmar aspect, either an inverted T-shaped incision or a Z-shaped incision is made extending into the mid-palm to end along the axis of the middle finger (see Fig. 19.10d) [21, 42]. Meticulous technique of raising the flap is very important to the preservation of a good blood supply to its elongated apex, which has a relatively narrow base. Many arteries and veins are taken with the flap, as described by Buck-Gramcko [44]. The distal, rectangular part of the flap is fully released from its bed, but the more proximal dissection is carried out at the epifascial level, with careful preservation of the perforating vessels and the branches of the dorsal carpal arch and the radial artery (the first and second dorsal

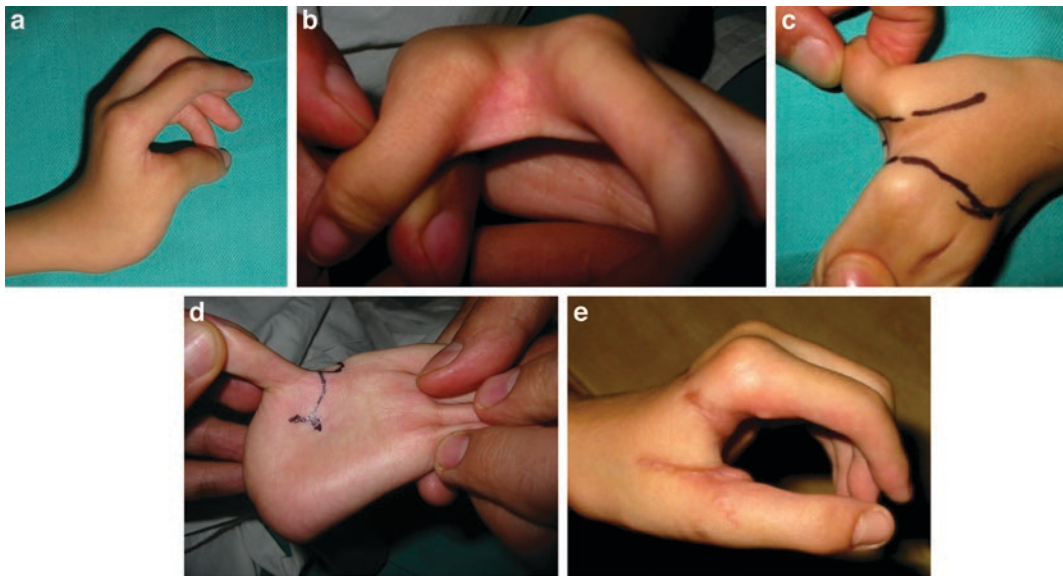

Fig. 19.10 (**a**) Clasped thumb. (**b**) Severe narrowing of the web space and marked instability of the MCP joint. (**c**, **d**) Drawing of the dorsal rotation advancement flap on the dorsum of the hand. (**e**) Result of surgery after widening of the web and chondrodesis of the MCP joint

metacarpal arteries). Some of the terminal branches of these vessels may be ligated at the edge of the flap to allow greater arc of rotation. The tourniquet should be released intraoperatively to check good perfusion of the apex of the flap. All fibrous bands and contracted fascia between the first and second metacarpal bones are released in the conventional manner to allow full thumb abduction. The released web is maintained by two K-wires crossing between the first and second metacarpal bones. The flap is then advanced along the radial incision and rotated along the ulnar incision to occupy the first web space. It can then be sutured to its recipient incision in the mid-palm far beyond the edge of the first web space.

In most of cases the donor site is closed with direct sutures. Sometimes, it is necessary to use skin grafts the ulnar side of the thumb. A small Burrow's triangle on the larger wound margin on the ulnar side of the flap could be excised and used as skin graft [47].

Dorsal Index-Combined Flap (Fig. 19.11) [19]

This technique was designed by the authors to overcome the limitation of the index stiletto flap for releasing a severely contracted web combined with severe palmar contracture of the thumb. They added two incisions to the stiletto flap to

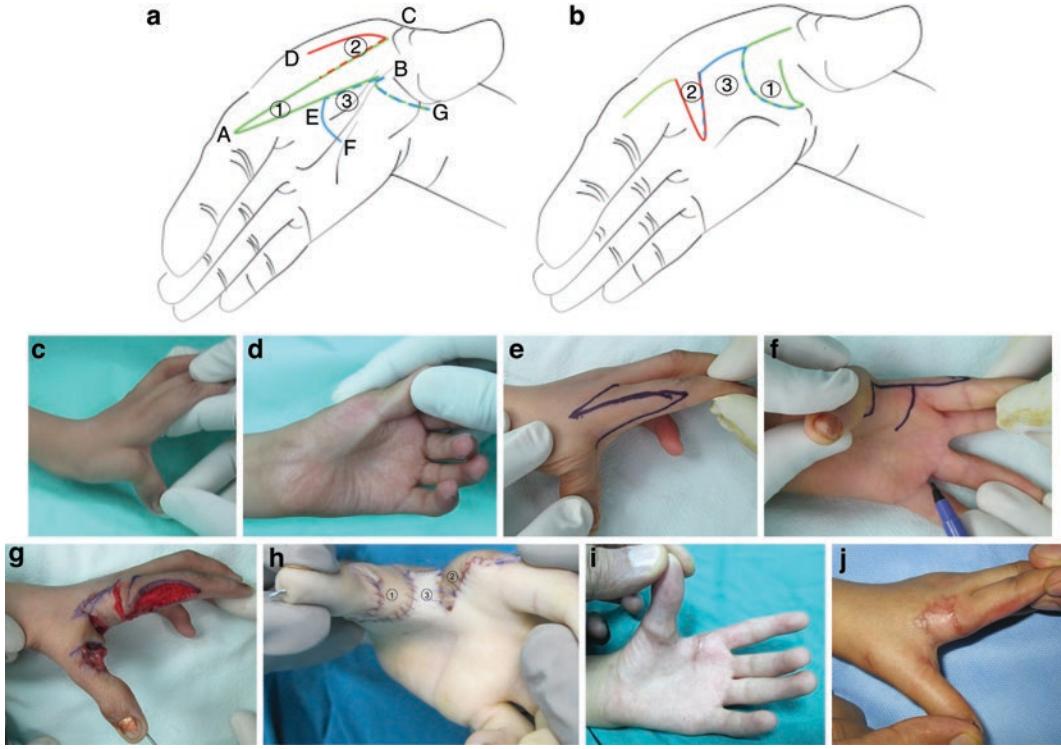

Fig. 19.11 (**a**) Diagram of the dorsal index combined flap. The classic index stiletto flap (bordered by green line) with the two-step modification. First, a dorsal incision (red line) half the length of the index flap creating a distally based triangular flap from the dorsum of the hand. Second, palmar incisions (blue line) of the same length to receive the dorsal flap and raise a palmar rectangular flap to be sutured across the web to the dorsal incision. The green bordered angle joining the points C-A-B represents the dorsal index (stiletto) flap (1). The red-bordered angle created by line C-D represents the dorsal triangular rotation flap (2). The palmar flap is bordered by lines joining points F-E-B-G (3). (**b**) Drawing of the flap after transposition. (**c**) A case of congenital clasped thumb with unstable MCP joint and severe narrowing of the web space. (**d**) Very evident palmar thumb contracture. (**e**, **f**) Drawing of the dorsal index-combined flap. (**g**, **h**) Transposition of the flaps. (**i**, **j**) Clinical appearance after healing of the flap with widening of the web and release of palmar thumb contracture

utilize skin from the dorsal and palmar aspect of the web to add to the width of the web and the stiletto flap is reserved for augmentation of the contracted skin on the palmar aspect of the thumb (see Fig. 19.11).

Technique

The first incision starts at the radial aspect of the index proximal interphalangeal (PIP) joint at point A, extending proximally in the plane between the dorsal and palmar skin to the level of the thumb MCP joint (point B) (see Fig. 19.11a). The second incision passes proximally and dorsally from point A to point C to create an isosceles triangle with the apex not less than 20°. This creates the proximally based index flap (flap 1) (see Fig. 19.11a). Point B is the pivot point of this flap located on the dorsal aspect of the thumb index web commissure. A more proximal starting point is recommended for tight index finger digital skin. Ezaki and Oishi [43] recommended a ratio of 3:1 to keep the viability of this flap. This index flap (see Fig. 19.11a, b) encloses the excess radial skin at the index base, and continues over the dorsal aspect of the first web space. The third incision starts from point C at a 30–45° angle, directing distally half the length of the index flap to point D, resulting in a dorsal triangle that comprise the dorsal triangular rotational flap (flap 2) (see Fig. 19.11a). The palmar rectangular flap (flap 3) is enclosed between two incisions; the first starts at point E (midway between points A and B) to point F at an angle of 60° and equal in length to line CD (see Fig. 19.11a). This incision releases the thumb web space and provides bed for the dorsal triangular rotational flap (see Fig. 19.11b). The release of the palmar skin contracture starts from point B as a curved incision across the palmar aspect of the thumb MCP joint crease, reaching the radial mid axial aspect of the thumb MCP joint at point G. This second incision completes the palmar rectangular flap and provides a bed that receives the dorsal index flap (see Fig. 19.11). The index flap is rotated into the palmar aspect, curving around the base of the thumb at the level of the MCP joint (point A to point G) and the palmar rectangular flap dorsally to suture its proximal border to the distal border of the index flap and its advancing border BE to the line CD. The web width increases by the breadth of the two triangular flaps collectively. The palmer rectangular flap increases the web depth by suturing it proximally (see Fig. 19.11).

Stabilization of the MCP Joint

In the presence of ulnar collateral ligament instability, stability of the MCP joint is achieved by tightening the ulnar capsule of the MCP joint in a "double breasted" manner. If global instability or severe palmar contracture necessitates excessive capsular release, we prefer doing chondrodesis of the MCP joint. Therefore, we postpone surgery until the appearance of the ossific nucleus of the proximal phalanx epiphysis to achieve bone-to-bone fusion rather than cartilage-to-cartilage fusion.

Technique

After exposing the articular surfaces of the MCP joint, the articular cartilage of the articular surfaces is shaved until one reaches the ossific nucleus of the epiphysis of the proximal phalanx and the subchondral bone of the head of the metacarpus. Care should be taken to avoid injury of the growth plate of the proximal phalynx. We can excise more bone from the metacarpal head to shorten it as needed to achieve extension of the MCP joint. Chondrodesis with shortening of the first metacarpal usually alleviates the need for palmar release of the thumb. One or two K-wires are used to stabilize the MCP joint in 10–20° of flexion [21, 41, 42]. It is really arthrodesis rather than chondrodesis.

Lengthening of the FPL

It should be released after release of the palmar contracture of the thumb. Arthrodesis of the MCP joint with shortening of the proximal metacarpus usually relatively lengthens the flexor pollicis longus (FPL) and alleviates the need for its lengthening. When required, lengthening is done at the level of distal forearm by Z-lengthening or intramuscular tenotomy [19].

Rehabilitation After Surgery

The operative splint and K-wires are removed after 6 weeks of surgery. Skin care and gentle massage and stretching are done at home. Children start to move the thumb spontaneously. We do not ask for professional physiotherapy. The position is maintained in a night splint with the thumb extended for at least 6 months postoperatively, and daytime active use of the thumb is encouraged.

Evaluation of Results of Treatment

There are no universal criteria for the evaluation of the results of management of clasped thumb, due to the difficulty in assessing the thumb function at that young age, and different systems used by authors for evaluation of their results. Some authors used the degree of active extension of first MCP joint as the reference for evaluation [20, 22]. Tsuyuguchi et al. [11] added the degree of active radial abduction of the CMC joint to their system of evaluation. Lipskeir and Weizenbluth [36] added the width of the first web space to their scoring system, and they mentioned that active extension of first MCP joint is the most important factor for the prehension of large objects.

Because it is of no value to achieve active thumb extension without having stable MCP joint or without widening of the web, it is very important to consider these parameters in evaluation. Using the active extension as the sole criterion for assessment is possible in type I cases, where this is the only deficient function. We used a combination of criteria to evaluate results of surgery and thumb function [8]:

- Parents' satisfaction: regarding cosmetic appearance and function
- Thumb position and appearance: degree of abduction and rotation
- Stability of MCP joint
- Thumb function: degree of opposition and the ability to grasp different objects

The degree of abduction, rotation, stability, and opposition were graded into four grades according to Gilbert (personal communication) (Table 19.1).

Using this system of evaluation, Abdel-Ghani et al. assessed postoperative results in 28 hands [8]. Parents of all the patients were satisfied with the results. Cosmetic appearance was not satisfactory with simple Z-plasty. The appearance of the first web space was better with the other techniques. The modified dorsal rotational advancement flap allowed a maximum degree of widening more than the other techniques used. In the case of ulnar collateral ligament instability of the MCP joint, ligamentous stabilization is a prerequisite for tendon transfer. Although the ligament reconstruction did not give excellent stability, the residual instability did not interfere with thumb function. In the case of global instability of the MCP joint, chondrodesis is the best way to achieve stability, and usually obviates the need for tendon transfer [8]. Our results of chondrodesis [8, 21] are better than that reported by Tsuyuguchi et al. [11] and Lipskeir and Weizenbluth [36]. There was improvement of the grasp pattern in all the operated thumbs.

Properly planned treatment according to the type of the deformity improves the cosmetic appearance and functional capabilities of the hand (see Fig. 19.9).

Table 19.1 Gilbert's method of assessment of thumb function (personal communication)

Abduction	Rotation	Stability	Opposition	Results
40°–45°	110°–120°	Very stable (normal stability in all planes)	With little	Excellent
30°–40°	90°–100°	Stable (stable at the ulnar side)	With ring	Good
10°–30°	80°–90°	Mild instability (no problem at pinch)	With middle	Fair
0°–10°	<80°	Unstable	None	Poor

References

1. Weckesser E. Congenital flexion-adduction deformity at the thumb (congenital clasped thumb). J Bone Joint Surg. 1955;37A:977–84.
2. Miller JM. Pollex varus. report of two cases. Univ Hosp Bull Ann Arbor. 1944;10:10–1.
3. White JW, Jensen WE. The infant's persistent thumb-clutched hand. J Bone Joint Surg. 1952;34A:680–8.
4. Matev I. Surgical treatment of spastic thumb-in-palm. J Bone Jt Surg Br. 1963;45B:703–8.
5. Broadbent TR, Woolf RM. Flexion-adduction deformity of the thumb–congenital-clasped thumb. Plast Reconstr Surg. 1964;34:612–6.
6. Anderson TE, Breed AL. Congenital clasped thumb and the Moro reflex. J Pediatr. 1981;99:664–5.
7. Manske PR. Longitudinal failure of upper limb formation. An Instructional Course Lecture, The American Academy of Orthopaedic Surgeons. J Bone Joint Surg Am. 1996;78A:1600–23.
8. Abdel-Ghani H, El-Naggar A, Hegazy M, Hanna A, Tarraf Y, Temtamy S. Characteristics of patients with congenital clasped thumb: a prospective study of 40 patients with the results of treatment. J Child Orthop. 2007;1:313–22.
9. Wood VE. Another look at the causes of the windblown hand. J Hand Surg Br. 1994;19:679–82.
10. McCarroll HR Jr. Congenital flexion deformities of the thumb. Hand Clin. 1985;1:567–75.
11. Tsuyuguchi Y, Masada K, Kawabata H, Kawai H, Ono K. Congenital clasped thumb: a review of forty-three cases. J Hand Surg Am. 1985;10:613–8.
12. Hall JG, Aldinger KA, Tanaka KI. Amyoplasia revisited. Am J Med Genet Part A. 2014;164:700–30.
13. Bamshad M, Van Heest AE, Pleasure DM. Arthrogryposis: a review and update. J Bone Joint Surg. 2009;91:40.
14. Ruland RT, Slakey JB. Acquired trigger thumb vs. congenital clasped thumb: recognize the difference: a case report. Hand. 2012;7:191–3.
15. Hall JG. Arthrogryposis (multiple congenital contractures): diagnostic approach to etiology, classification, genetics, and general principles. Eur J Med Genet. 2014;57:464–72.
16. Crawford HH, Horton CE, Adamson JE. Congenital aplasia or hypoplasia of the thumb and finger extensor tendons. J Bone Joint Surg. 1966;48:82–91.
17. Flatt AE. The care of congenital hand anomalies. 2nd ed. St. Louis: Quality Medical Publishing; 1994.
18. Crawford HH, Horton CE, Adamson JE. Congenital aplasia or hypoplasia of thumb and fingers extensor tendons. J Bone Joint Surg. 1966;48-A:82–91.
19. Mahmoud M, Abdel-Ghani H, Elfar JC. New flap for widening of the web space and correction of palmar contracture in complex clasped thumb. J Hand Surg Am. 2013;38:2251–6.
20. Weckesser EC, Reed JR, Heiple KG. Congenital clasped thumb (congenital flexion-adduction deformity of the thumb). A syndrome, not a specific entity. J Bone Joint Surg. 1968;50:1417–28.
21. Abdel-Ghani H, Mahmoud M, Shaheen A, Abdel-Wahed M. Treatment of congenital clasped thumb in arthrogryposis. J Hand Surg Eur. 2017;42(8):794–8.
22. Lin SC, Hung TH, Hsu HY, CH LCG. A Simple Splinting Method for Correction of supple congenital clasped thumbs in infants. J Hand Surg Br. 1999;24:612–4.
23. Temtamy SMV. The genetics of hand malformation. New York: Alan R. Liss; 1987.
24. McCarroll HR, Manske PR. The windswept hand. In: Buck-Gramcko D, editor. Congenital malformations of the hand and forearm. Philadelphia: Churchill Livingstone; 1998. p. 313–25.
25. Beals RK. The distal arthrogryposes: a new classification of peripheral contractures. Clin Orthop Relat Res. 2005:203–10.
26. Hall JG. Arthrogryposis multiplex congenita: Etiology, genetics, classification, diagnostic approach, and general aspects. J Pediatr Orthop Part B. 1997;6:159–66.
27. Rink BD. Arthrogryposis: a review and approach to prenatal diagnosis. Obstet Gynecol Surv. 2011;66:369–77.
28. Mitrovic D. Development of the articular cavity in paralyzed chick embryos and in chick embryo limb buds cultured on chorioallantoic membranes. Acta Anat (Basel). 1982;113:313–24.
29. Hall JG, Reed SD, Driscoll EP. Part 1. Amyoplasia: a common, sporadic condition with congenital contractures. Am J Med Genet. 1983;15(4):571–90.
30. Sung SS, Brassington AM, Krakowiak PA, Carey JC, Jorde LB, Bamshad M. Mutations in TNNT3 cause multiple congenital contractures: a second locus for distal arthrogryposis type 2B. Am J Hum Genet. 2003;73:212–4.
31. Toydemir RM, Rutherford A, Whitby FG, Jorde LB, Carey JC, Bamshad MJ. Mutations in embryonic myosin heavy chain (MYH3) cause Freeman-Sheldon syndrome and Sheldon-Hall syndrome. Am J Hum Genet A. 2006;38:561–5.
32. Toydemir RM, Chen H, Proud VK, Martin R, Van Bokhoven H, Hamel BCJ, et al. Trismus-pseudocamptodactyly syndrome is caused by recurrent mutation of MYH8. Am J Hum Genet A. 2006;140:2387–93.
33. Alvarado DM, Buchan JG, Gurnett CA, Dobbs MB. Exome sequencing identifies an MYH3 mutation in a family with distal arthrogryposis type 1. J Bone Joint Surg. 2011;93:1045–50.
34. Kimber E, Tajsharghi H, Kroksmark K, Oldfors ATM. A mutation in the fast skeletal muscle troponin I gene causes myopathy and distal arthrogryposis. Neurology. 2006;67:597–601.
35. Tajsharghi H, Kimber E, Kroksmark AK, Jerre R, Tulinius MOA. Embryonic myosin heavy-chain

mutations cause distal arthrogryposis and developmental myosin myopathy that persists postnatally. Arch Neurol. 2008;65:1083–91.
36. Lipskeir E, Weizenbluth M. Surgical treatment of the clasped thump. J Hand Surg Am. 1989;14:72–9.
37. Kozin S. Clasped thumb. In: Green DP, Hotchkiss RN, Pederson WC, Wolfe SW, editors. Green's operative hand surgery. 6th ed. Philadelphia: Churchill Livingston; 2011. p. 1399–401.
38. Senrui H. Congenital contractures. In: Buck-Gramcko D, editor. Congenital malformations of the hand and forearm. Philadelphia: Churchill Livingstone; 1998. p. 295–309.
39. Zadek I. Congenital absence of extensor pollicis longus of both thumbs. Operation and cure. J Bone Joint Surg. 1934;16:432–4.
40. Mih AD. Congenital clasped thumb. Hand Clin. 1998;14:77–84.
41. Oishi SN, Agranovich O, Pajardi GE, Novelli C, Baindurashvili AG, Trofimova SI, et al. Treatment of the upper extremity contracture/deformities. J Pediatr Orthop. 2017;37:S9–15.
42. Oishi S, Agranovich O, Zlotolow D, Wall L, Stutz C, Pajardi G, et al. Treatment and outcomes of arthrogryposis in the upper extremity. Am J Med Genet Part C. 2019;181:363–71.
43. Ezaki M, Oishi SN. Index rotation flap for palmar thumb release in arthrogryposis. Tech Hand Up Extrem Surg. 2010;14:38–40.
44. Buck-Gramcko D. Syndactyly between the thumb and index finger. In: Buck-Gramcko D, editor. Congenital malformations of the hand and forearm. Philadelphia: Churchill Livingstone; 1998. p. 141–7.
45. Abdel-Ghani H, Amro S. Characteristics of patients with hypoplastic thumb: a prospective study of 51 patients with the results of surgical treatment. J Pediatr Orthop Part B. 2004;13
46. Hirshowiz BAKRM. Combined double Z-plasty and Y-V 725 advancement for thumb web contracture. Hand. 1975:291–2.
47. Abdel GH. Modified dorsal rotation advancement flap for release of the thumb web space. J Hand Surg Am. 2006;31:226–9.
48. Nazir Baba A, Bhat YJ, Mushtaq Ahmed S, Nazir A. Unilateral cleft hand with cleft foot. Int J Health Sci (Qassim). 2009;3(2):243–6.

Part IV

Duplication

Radial Polydactyly

20

Goo Hyun Baek and Jihyeung Kim

Introduction

Radial polydactyly is sometimes called polydactyly of the thumb, preaxial polydactyly, thumb duplication, bifid thumb, or split thumb. Radial polydactyly was originally classified as a "duplication" by the International Federation of Societies for the Surgery of the Hand (IFSSH) rather than as a "failure of formation" or "failure of differentiation" [1]. Now, it is classified as a "malformation", a failure of axis formation, and/or differentiation of the radioulnar hand plate according to the Oberg, Manske, and Tonkin classification [2].

Epidemiology and Genetics

Radial polydactyly is a common congenital difference of the upper extremity in all races, and about 20 percent of them occur bilaterally. Its incidence had been reported at 0.08 to 1.4 per 1000 live births [3, 4]. Radial polydactyly was the most common specific anomaly (15%) among the anomalies affecting only the hand plate at three Midwestern referral centers of United States [5]. Syndactyly was more common than polydactyly in the study from University of Iowa [6]. However, in Asian countries such as Japan, Korea, and Hong Kong, polydactyly is more common than syndactyly [7, 8]. Most radial polydactyly occur sporadically. However, when associated with triphalangeal thumb, higher hereditary predisposition has been identified. Among 21 patients of radial polydactyly with triphalangeal thumb, ten patients had a family history of the same abnormality in close relatives [9]. Radial polydactyly can occur in rare syndromic diseases such as Fanconi's anemia, Holt-Oram syndrome, and Rubinstein-Taybi syndrome.

During limb development, the patter of the anterior-posterior (AP) axis is determined by the expression of sonic Hedgehog (SHH) in a region called the zone of polarizing activity (ZPA) [10]. Radial polydactyly is caused by sequence variants in the sonic hedgehog (SHH) enhancer, called zone of polarizing activity (ZPA) regulatory sequence (ZRS). The ZRS is almost 750–800 bp highly conserved functional element from humans to fish, located within intron 5 of the LMBR1 gene. Several point mutations in the ZRS have been described in humans, and caused variable phenotype of radial polydactyly and triphalangeal thumb [11]. Bone morphogenetic protein 7 (BMP-7) is expressed strongly in the interdigital mesenchyme of the vertebrate limb, which normally undergoes programmed cell death. Loss of BMP-7 likely allows for survival of programmed cell death, and can give rise to an

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extra digit [12]. GLI3 gene is crucial since all GLI3-associated human congenital diseases comprise limb malformations [13]. Mutations in this gene have been associated with several diseases including preaxial polydactyly and postaxial polydactyly.

Classification

The Wassel classification for polydactyly of the thumb was published in 1969 [6] and has been most widely used. This classification is a radiographic description based on the level of skeletal duplication (Table 20.1). Wassel type IV is the most common type, representing 29–43% of all polydactyly of the thumb, while type I is the least common [6, 14]. Type VII designates a triphalangeal thumb.

The Wassel classification is based on the radiographic assessment of the skeleton. In young children whose skeleton is immature, the true nature of the thumbs may not be apparent.

Table 20.1 Wassel classification for polydactyly of the thumb

Type I: A bifid distal phalanx with a common epiphysis that articulates with a normal proximal phalanx. There may be one common nail, but usually there are two distinct nails with a groove between them.
Type II: A completely duplicated distal phalanx. Each distal phalanx usually has its own epiphysis which articulates with the normal proximal phalanx.
Type III: A duplicated distal phalanx with a bifurcated proximal phalanx. The distal phalanges usually diverge from the longitudinal axis, or they may be parallel.
Type IV: A complete duplication of the proximal phalanx. Each proximal phalanx has its own epiphysis or a common epiphysis which articulates with a normal metacarpal or a metacarpal slightly widened to accommodate both proximal phalanges.
Type V: A bifurcated first metacarpal. Each head of the bifurcation articulates with a duplicated proximal phalanx which has its own epiphysis.
Type VI: Complete duplication of the entire first digit. One side may be more rudimentary than the other.
Type VII: A triphalangeal thumb or elements of a triphalangeal thumb accompanied by a normal thumb.

For instance, Wassel type I polydactyly can be classified as a type II until ossification of the distal phalangeal epiphysis becomes apparent [15]. The inclusion of the triphalangeal thumb has always been controversial [16]. Flatt's 1977 modification of the Wassel classification system excluded the triphalangeal thumb, considering this presentation a distinct type of thumb deformity [17]. Gramko and Behrens [18] modified Wassel's classification to include bifid trapezium and fully duplicated trapezium as type VII and VIII, respectively, and considered triphalangism separately. Wood [9] subdivided type IV polydactyly into type IV-A and IV-B. Both duplicated thumbs are triphalangeal thumb in type IV-A, and triphalangeal thumb is on the radial side in type IV-B. Miura [19] presented a case in which the triphalangeal thumb was on the ulnar side, which was added as type IV-C.

Wassel classification has several limitations. It does not include all presentations of radial polydactyly. Pedunculated type, triplicated thumb, and extra thumb which do not have bony connection with the main thumb, cannot be classified. And, it is insufficient to guide surgical intervention [16].

Temtamy and McKusick classified radial polydactyly into four types –thumb polydactyly (type I), polydactyly of a triphalangeal thumb, or opposable triphalangeal thumb (type II), polydactyly of an index finger, or nonopposable triphalangeal thumb (type III), and polysyndactyly (type IV) [4].

Chung et al. proposed a new classification system based on the anatomic morphology at the origin of the extra digit [20]. Type I was defined as the joint type, where the extra digit has its own joint at its origin. In type II, the single epiphyseal type, the extra digit originates from the epiphysis directly. Type III or the osteochondroma-like type originates from the metacarpal or phalangeal shaft of the main digit. Type IV is a hypoplastic type in which there is no bony connection between two thumbs. This classification system is easy to use and can guide practitioners in their discussions with patients regarding surgical outcomes and possible need for revision surgery [21].

Preoperative Evaluation

Sufficient discussion and explanation to the parents who have a baby with radial polydactyly on its clinical features and surgical outcome, is necessary to maintain good rapport after the surgery. It is very important to inspect both hands of the patient, when a baby with radial polydactyly and his/her parents visit the outpatient department (OPD). Most of the babies with unilateral involvement show smaller sizes of affected thumbs than that of contralateral normal thumbs. Thus, the parents should understand that even if the more dominant one is preserved in the affected thumb, it will be smaller in length and girth when compared to the unaffected side.

In babies with bilateral involvement, the nail size of index finger can be a reference to judge the size of the affected thumbs. The width of the index fingernail is about two-thirds of that of the thumb in normal babies.

Active motion of each joint is hard to observe because the babies usually clench their hands. Passive motion and varus and valgus stress tests of the joints, palpation of tendons (especially flexor tendons), and observation of skin crease may be helpful to evaluate the polydactylic thumbs. Little or absent passive motion at bifurcation site of minor thumb (mostly radial one) may suggest odd-numbered Wassel type I, III, or V. It is much easier to reconstruct a thumb which has stable joints in radioulnar plane. If the flexor tendon is palpable while moving the joint passively, good active motion can be expected postoperatively. When the skin crease is faint or absent, there is a strong possibility that the affected joint does not have effective motor power or the joint is fused, as in symphalangism.

Simple radiographs are very helpful for Wassel typing and surgical planning. Although it is not easy to obtain a true PA and lateral view of the affected thumbs, it is absolutely necessary for surgical planning. Radiographs of normal side in unilateral cases are also very important in assessing the size and shape of bones and joints of the affected thumbs comparatively. Medical photos are also needed for documentation and later evaluation of surgical outcome.

Before surgery, the parents should be informed that even if the thumb is reconstructed successfully, it will not be the same as the contralateral normal thumb in terms of function and cosmesis. The patients and their parents sometimes complain of applying a long-arm cast postoperatively. However, a short-arm cast can be easily removed spontaneously especially in young children.

In a study of 66 years of experiences for surgery of the duplicated thumb [22], there were 27.94% of patients with serious complications, 7.35% of them unsalvageable by secondary surgery, and 20.59% salvageable by secondary surgery. Recently, the complication rates are getting lower. When initial surgery was planned to restore all anatomic elements, the need for secondary surgery was quite unusual [23]. The primary issues affecting appearance after surgery for radial polydactyly were reduced nail width and angulation at interphalangeal joint. Reconstructed Wassel type VII thumbs had lower satisfaction score than other types [24].

Timing of Surgery

There has been no general agreement on proper timing of operation for radial polydactyly. It is recommended to perform surgery at about 1 year of age before the development of thumb-index finger pinch in the textbook of Green's operative hand surgery [25]. In the textbook *Campbell's Operative Orthopaedics*, it is recommended to perform surgical reconstruction when the child is about 18 months old, but no later than 5 years old if possible [26]. Indebted to recent advancement in pediatric anesthesia, most surgeries can be performed safely if the patient does not have serious-associated problems such as severe cardiac anomaly or pancytopenia. In certain cases, Wassel type VII, for example, bony shape of the delta bone is sometimes very important for surgical planning in which the surgical timing is better to be postponed until it is clearly visible in radiographs. Thus, timing of surgery depends on general condition of the patients, priority of surgery in patients with multiple-associated anomalies, types of radial polydactyly, and, most importantly,

surgeon's preference. There is no gold standard for surgical timing of radial polydactyly. However, earlier surgery is recommended when surgical planning is completed and the structures of the thumb are large enough to manipulate surgically.

Assessment of Surgical Outcome

A comprehensive scoring system was first introduced by Tada et al. in 1983 [27]. In their scoring system, the criteria for postoperative evaluation include range of motion, instability, and malalignment. However, they described that the cosmetic results based on the size of the preserved thumb and satisfaction of the patient were very difficult to assess objectively. Cheng el al. devised both subjective and objective assessment [28]. The subjective assessment is composed of functional and cosmetic results, and they were assessed by the patients and their parents. The criteria of the objective scoring system include segmental alignment, joint stability, joint mobility, thumb web, pulp condition, nail condition, residual prominence at excision site, and opposition and chunk pinch. The objective grading was classified "good" when the score was 20 to 30, "fair" when the score was 15–19, and "poor" when the score was less than 15. Japanese Society for Surgery of the Hand (JSSH) also suggested scoring system for the evaluation of the surgical outcome in radial polydactyly [29]. The scoring system composes of functional, aesthetic, and subjective scores (Table 20.2). Dijkman et al. performed a study to determine which of the assessment systems can be considered for the most common types of radial polydactyly (type II and IV) [30]. In the study, interobserver reliability was the highest for the JSSH scoring system, which also showed superior correlations with both examiner-rated and patient-rated visual analog scale (VAS) scores for functional and aesthetic outcome compared with the other nine assessment systems.

Surgical Technique

The surgical goal for reconstruction of the radial polydactyly is to make a straight, mobile, and stable thumb with good appearance in size and shape. However, even after a successful reconstruction, the reconstructed thumb is not perfect in terms of function and cosmesis. We are trying to make a better thumb in a given situation, not the best or perfect thumb.

The patients with radial polydactyly show very diverse manifestations, from a rudimentary

Table 20.2 Japanese Society for Surgery of the Hand (JSSH) evaluation form for radial polydactyly

Functional score			2 points	1 point	0 point
Abnormal alignment IP joint			5°	6–19°	≥20°
Abnormal alignment MP joint			≤5°	6–19°	≥20°
Instability IP joint			≤10°	11–19°	20°
Instability MP joint			≤40°	41–59°	≥60°
Active flexion IP joint + MP joint			≥90°	≥60°	<60°
Extension lag IP joint + MP joint			0°	<30°	≥30°
Palmar abduction MP joint + CMC joint			≥60°	31–59°	≤30°
Aesthetic score			**1 point**		**0 point**
Size			Acceptable		Unacceptable
Finger pulp/nail			Acceptable		Unacceptable
Surgical scar			Acceptable		Unacceptable
Bulging			None		Prominent
Subjective score			**1 point**		**0 point**
Pain			None		Pain
Satisfaction			Yes		No
Total score	**Excellent**	**Good**	**Fair**		**Poor**
	20	17–19	14–16		0–13

IP joint, interphalangeal joint; MP joint, metacarpophalangeal joint; CMC joint, carpometacarpal joint

floating type to a complex one. Ligation or simple excision may be enough for floating types of radial polydactyly. However, simple ablation of one digit has not produced satisfactory outcomes in most cases of radial polydactyly and it has resulted in retained deviation, stiffness, and/or ligamentous instability of the thumb. Although surgical concepts and techniques are still evolving, there are several reconstructive strategies to achieve a functionally and cosmetically acceptable thumb.

Surgical techniques to reconstruct radial polydactyly can be classified into five types – ligation, simple excision, excision and reconstruction, combination procedures (Bilhaut-Cloquet operation), and on-top plasty.

The surgical wound is usually closed with absorbable 5–0 or 6–0 sutures. If the wound is closed with nonabsorbable sutures, sedation of the patients may be needed for stitch out. A long-arm thumb spica cast with more than 90 degrees of elbow flexion is recommended postoperatively, because a short-arm thumb spica cast or a long-arm cast in a position of less flexed elbow can be easily taken off. Duration of immobilization for patients undergoing corrective osteotomy and/or reconstruction of collateral ligament should be 4–6 weeks depending on the patient age. Postoperative physical therapy is not necessary in most patients.

Ligation

In a pedunculated type of radial polydactyly (Fig. 20.1), ligation at the base as close as possible to its root with 5–0 or 6–0 nylon with or without local anesthesia can be performed at OPD or nursery. Ligated hypoplastic thumb is mummified and usually falls off within 2 weeks. A nubbin usually remains after fall-off. In case of postnatal torsion of pedunculated polydactyly, prompt surgical excision is necessary (Fig. 20.2). When the skin bridge measures more than 4 mm, excision under general anesthesia is recommended [15]. Even in pedunculated type of polydactyly, painful neuroma may develop after the ligation, which is an indication for surgical exploration [31].

Fig. 20.1 A pedunculated type of radial polydactyly

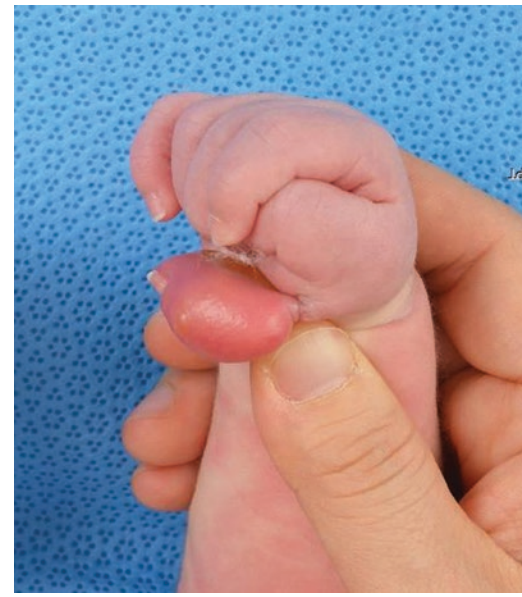

Fig. 20.2 Because of the torsion of the pedicle, swelling and discoloration progressed in the pedunculated polydactyly

Simple Excision

Simple excision under general anesthesia is indicated, when there is no bony connection between two polydactyly thumbs, and a dominant thumb shows good stability, motion, and alignment (Fig. 20.3).

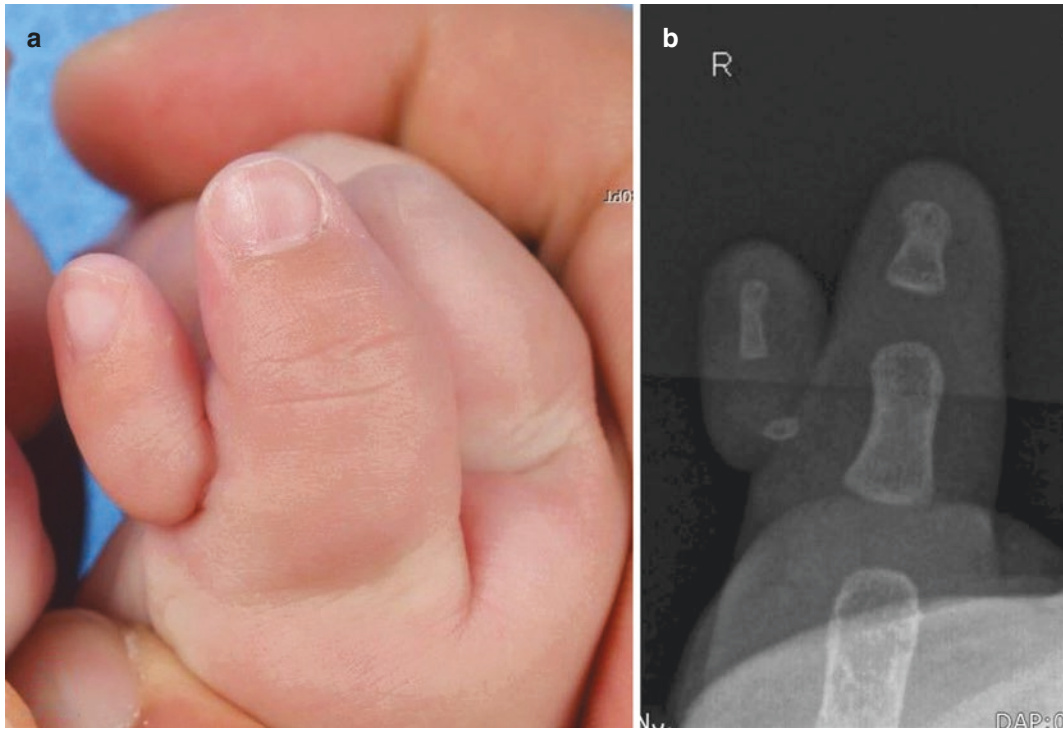

Fig. 20.3 (**a**, **b**) When there is no bony connection between two thumbs, simple excision is indicated

An elliptical incision is made around the minor thumb. The soft-tissue pedicle usually contains neurovascular structures. To avoid bleeding, the vessels should be ligated or cauterized. To prevent painful neuroma, the nerve should be identified, sharply transected, and imbedded in the soft tissue.

Excision and Reconstruction

More than half of the patients with radial polydactyly can be successfully treated by the "excision and reconstruction" technique (Fig. 20.4). Main components of this technique are arthroplasty, corrective osteotomy, and tendon realignment. When one of the two polydactylic thumbs is well developed, and the other one less developed, this technique is indicated. However, when both polydactylic thumbs are hypoplastic, this technique results in a small thumb which is sometimes smaller than the index finger. Surgical technique for Wassel types I and II is similar. Also, similar surgical technique can be applied to Wassel types III, IV, V, and VI. For the diversity of clinical features, surgical technique for Wassel type VII should be individualized case by case.

Arthroplasty

Arthroplasty consists of two components that are joint stabilization by ligamentoperiosteal flap [32], and partial excision of excessive portion of phalangeal or metacarpal head on which two thumbs sit.

Two thumbs sit on a single proximal phalangeal head in Wassel type I or II radial polydactyly, and on a single metacarpal in type III or IV. During dissection of minor thumb, distal insertion of collateral ligament should be preserved with adjacent periosteal tissue for later reconstruction. This ligamentoperiosteal flap will be reattached to base of phalangeal bone of the remained main thumb after removal of the minor thumb. The phalangeal or metacarpal head, when minor thumb is removed, is relatively large for the remained dominant thumb. This size mis-

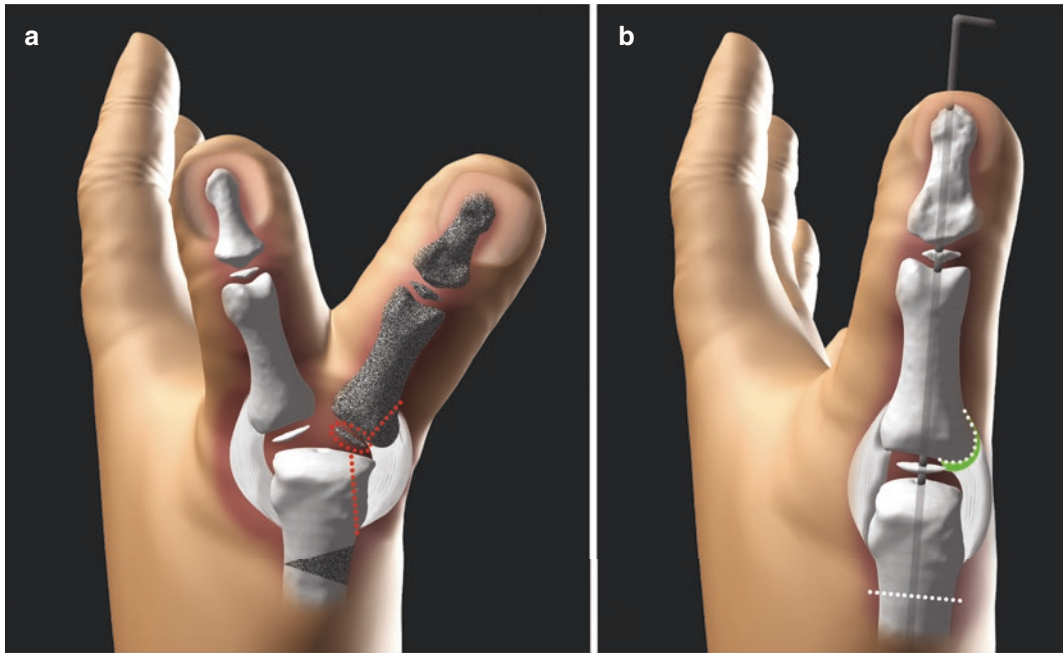

Fig. 20.4 (**a**, **b**) A ligamentoperiosteal flap is raised to reconstruct radial collateral ligament of MP joint. Metacarpal head is excised partially to fit base of dominant proximal phalanx. If necessary, corrective osteotomy was added to make a straight thumb

matching between two bones may cause angular deformity and/or bony prominence if it is not corrected. Thus, excessive portion of the head needs to be shaved or removed. Sometimes, a separate facet that articulates with the radial thumb to be deleted is observed. This facet can be used as a guideline to cut excessive portion. Conventional oscillating saw or osteotomes cannot be used for very small phalangeal bones of young children. Their phalangeal bones are soft enough that shaving of articular cartilage and partial ostectomy can be performed by a small rongeur or a surgical blade, no. 15 blade for example. Excessive tension of the reconstructed collateral ligament to correct angular deformity at the joint level is not recommended because the deformity is likely to recur and stiffness of the joint may occur. However, angular deformity of less than 10 degrees at the joint level can be corrected by this arthroplasty procedure. A longitudinal Kirschner wire (K-wire) is inserted to protect the reconstructed collateral ligament.

Corrective Osteotomy

Angulation at interphalangeal joint as well as reduced nail width is a primary issue affecting appearance after the surgery [24]. More than 20 degrees of angular deformity is not acceptable to most patients and parents. It can be corrected by closed-wedge osteotomy. Double level osteotomy at proximal phalangeal and metacarpal levels can be indicated to align severe divergent-convergent Wassel type IV.

Tendon Realignment

Abnormal insertions of flexor pollicis longus (FPL) and/or extensor pollicis longus (EPL) are not uncommon in radial polydactyly, especially in Wassel type IV. The FPL tendon attaches not only at its customary insertion, but also into the extensor by a tendon that passes around the radial aspect of the thumb. This anomalous muscle abducts the thumb instead of flexion, and is called as "pollex abductus" [33, 34]. The abnormal insertion of FPL and/or EPL may cause gradual

angular deformity even after successful bony alignment has been achieved by corrective osteotomy. When there are abnormal insertions of FPL and/or EPL tendons, the insertion sites should be corrected to achieve good flexion-extension arc. The abnormal insertion can be completely detached and reattached into the correct position. The phalangeal bones of young children are not so tough that the tendon can be sutured into the distal phalanx using 4–0 or 5–0 nylon. When the phalangeal bone is too hard to be sutured by nylon suture, a pull-out suture technique can be used. When the distal portion of the tendon is bifid and inserted into both polydactylic thumbs, it usually inserts at ulnar side of the radial thumb, and radial side of the ulnar thumb. If the radial thumb is to be removed, the tendon is detached from the insertion of the radial thumb and reattached into the ulnar side of the dominant ulnar thumb like a Y-shape to balance the vector forces (Figs. 20.5 and 20.6). During this procedure, the portion of tendinous insertion into the radial side of the remaining radial thumb needs to be detached to avoid abnormal abduction force.

In Wassel type IV, V, VI, or VII polydactyly of the thumb, some of the thenar muscles insert into the radial-sided polydactylic thumb. In most cases, the radial thumb is removed and the ulnar thumb is reconstructed. The insertion site of thenar muscles on radial thumb should be identified and dissected carefully for later reattachment to the main ulnar thumb.

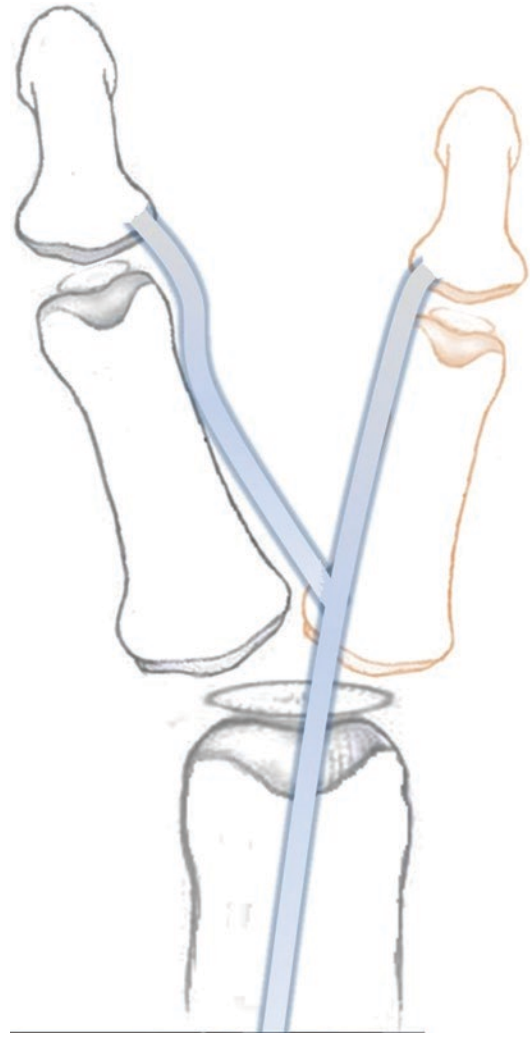

Fig. 20.5 The tendons frequently bifurcated distal to the MP joint, and insert to the side of each distal phalanx

Surgical Technique (Wassel Type I)

A 7-month-old girl showed radial polydactyly on right thumb (Fig. 20.7). The nail size, length, and girth of ulnar side thumb of left hand were good enough to perform the "excision of radial thumb and reconstruction" procedure. As the epiphyses of phalanges and metacarpal were not observed in simple radiograph (Fig. 20.8), it was hard to assess Wassel typing but easy to decide the surgical plan as "arthroplasty" with or without "tendon realignment". Corrective osteotomy will not be necessary because angular deformity at the IP joint is minimal. A racquet-shaped incision was designed. A zigzag incision has an advantage to prevent possible scar contracture, but this technique is not easy to be applied to a small-sized thumb less than an inch in length in infant age. During dissection, it was confirmed that base of two distal phalanges was fused to be Wassel type I. The dissection was deepened to expose distal phalangeal bone of the radial thumb, and a ligamentoperiosteal flap was raised. Distal phalanx of the radial thumb was cut to be removed, and articular surface of this radial thumb was seen. Articular surface for the radial thumb was cut using no. 15 blade (Fig. 20.9). The consistency of phalangeal bone in infant age is soft enough to be cut by surgical blade. There was no malalignment

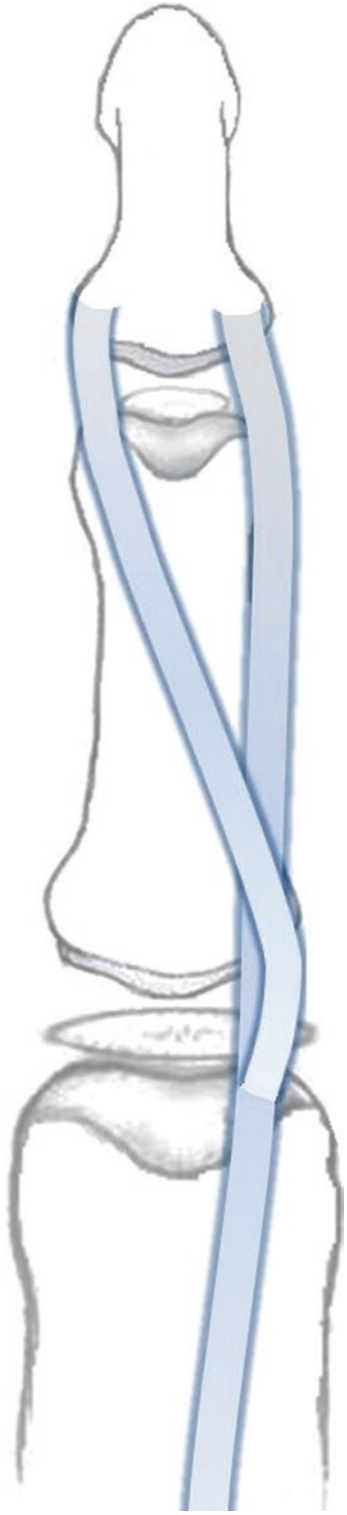

Fig. 20.6 The tendon insertion of minor thumb is detached and reattached to the main thumb in Y shape to balance the vector force

Fig. 20.7 Wassel type I polydactyly of right thumb. Ulnar thumb showed better configuration

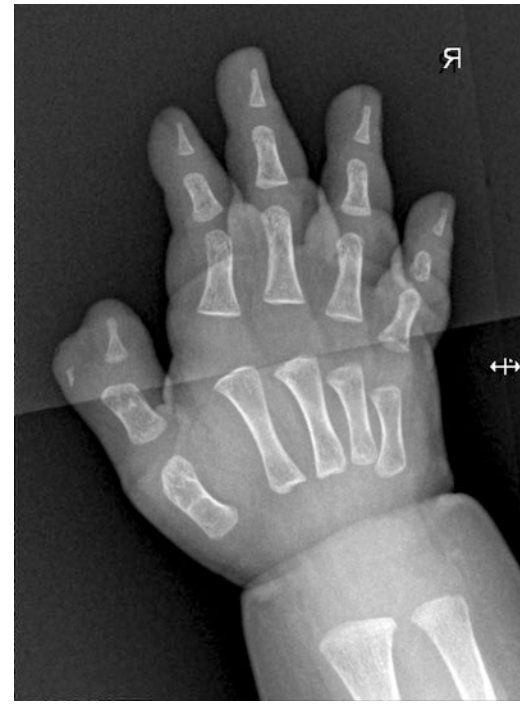

Fig. 20.8 Two thumbs sit on the proximal phalangeal head, and the head showed enlargement

of tendon found. After the arthroplasty procedure, the articular surface of the proximal phalanx fits that of ulnar thumb. Before reconstruction of the collateral ligament, a 0.7 mm K-wire was inserted longitudinally to protect it. The ligamentoperiosteal flap for reconstruction of the collateral ligament was attached to the new insertion site by 5–0 absorbable suture (Fig. 20.10). The reconstructed thumb looked straight (Fig. 20.11).

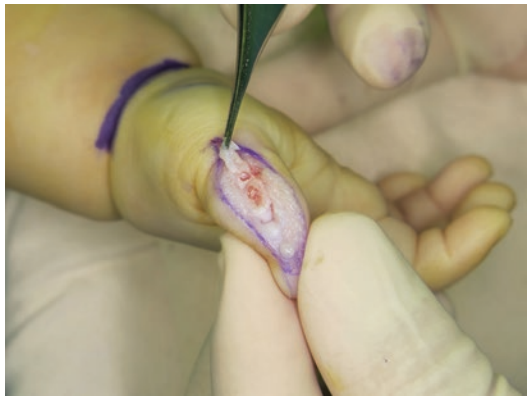

Fig. 20.9 A ligamentoperiosteal flap was raised (forcep), and excessive portion of the proximal phalangeal head was removed

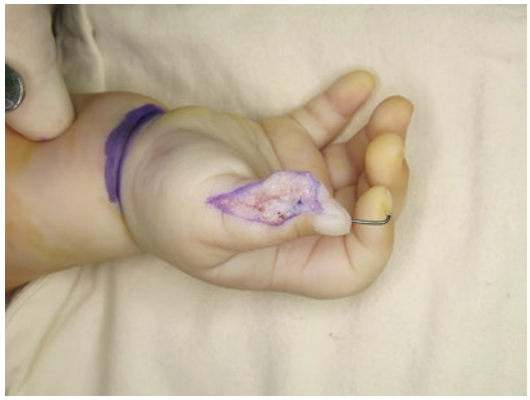

Fig. 20.10 A K-wire was inserted longitudinally, and the flap was reattached to the new insertion site

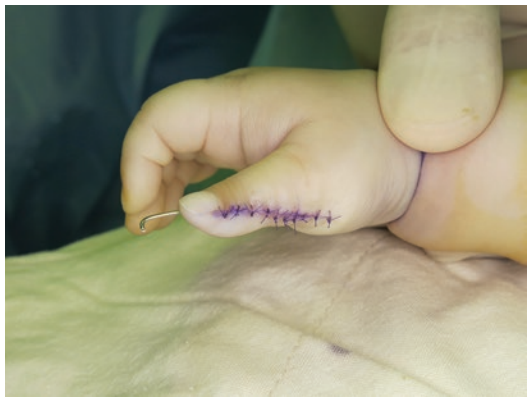

Fig. 20.11 Immediate postoperative finding

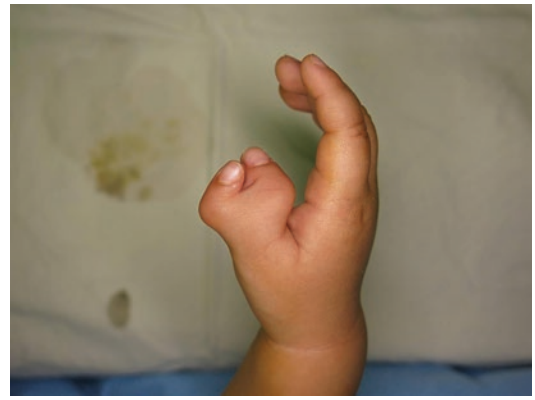

Fig. 20.12 A divergent-convergent Wassel type IV radial polydactyly of a 14-months-old boy

Surgical Technique (Wassel Type IV)

A 14-month-old boy showed a divergent-convergent Wassel type IV radial polydactyly on right side. The radial thumb was hypoplastic, but the ulnar thumb showed good size and shape (Fig. 20.12). There was 35 degrees of angular deformity at the IP joint of ulnar thumb which needed corrective osteotomy at proximal phalangeal neck level (Fig. 20.13). Medical photos and simple radiographs suggested strong possibility that arthroplasty of MP joint, and tendon realignment of EPL, FPL, and thenar muscles were necessary for proper reconstruction. Proximal phalangeal head of the ulnar thumb was underdeveloped, suggesting a potential recurrence of angular deformity postoperatively. A racquet-shaped incision was designed (Fig. 20.14). The EPL tendon was bifurcated at MP joint level, and inserted into both thumbs (Fig. 20.15). The insertion site of radial EPL slip was detached, and sutured to the ulnar side of dominant thumb to balance the extension force. The FPL tendon showed the same pattern (Fig. 20.16). The insertion site of radial FPL slip was detached and tagged with suture for later reattachment into the ulnar side of dominant thumb (Fig. 20.17). The abductor pollicis brevis muscle insertion into the radial thumb was detached from the proximal phalangeal base for later reattachment into the reconstructed thumb. The radial thumb was removed leaving ligamentoperiosteal flap for later reconstruction of the MP joint. The portion of metacarpal head to be resected was lined (Fig. 20.18), and a ligamentoperiosteal flap was raised and preserved. Excessive portion of articular cartilage and bone

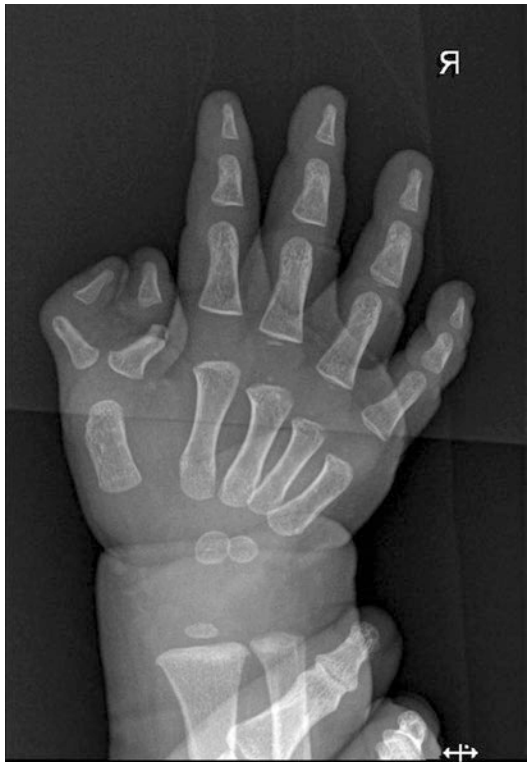

Fig. 20.13 The ulnar side thumb showed better bony development, although there was 35° of angular deformity at the IP joint

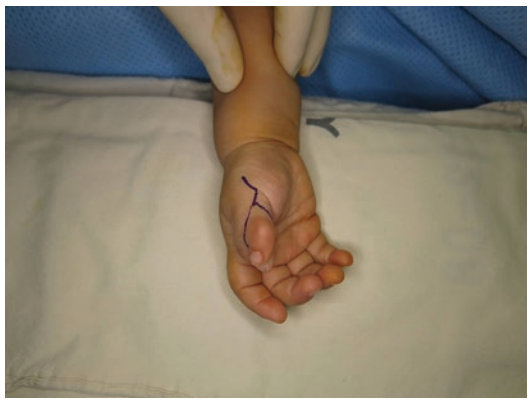

Fig. 20.14 Skin incision

was resected by a no. 15 blade and small osteotomes. With power instruments like an oscillating saw, it is very difficult to do fine osteotomy. The ligamentoperiosteal flap and detached abductor pollicis brevis tendon were preserved for later reattachment (Fig. 20.19). Then, proximal pha-

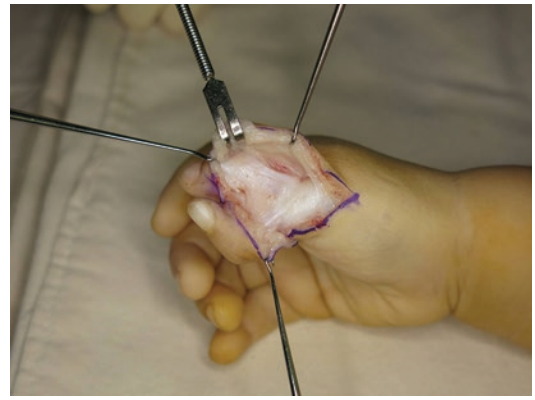

Fig. 20.15 The EPL tendon showed bifurcation at the MP joint level

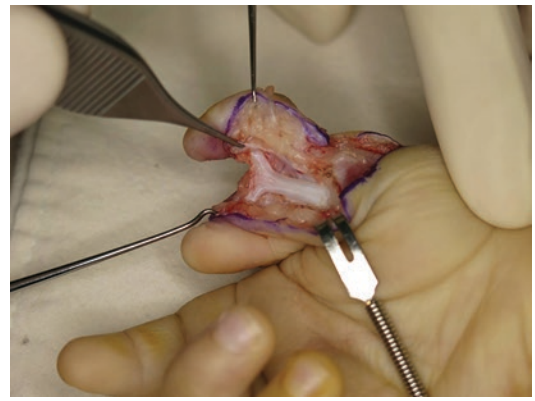

Fig. 20.16 The FPL tendon was bifurcated at the IP joint level

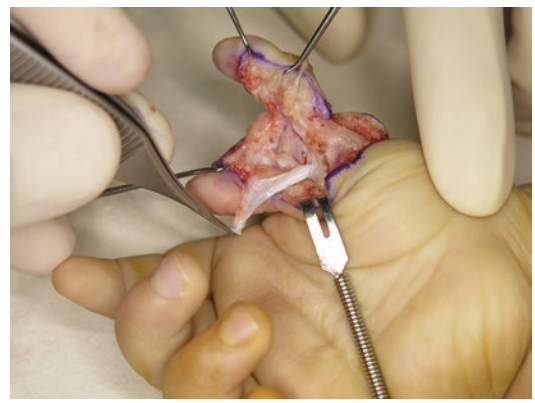

Fig. 20.17 The FPL insertion to the radial thumb was identified and preserved for later reattachment

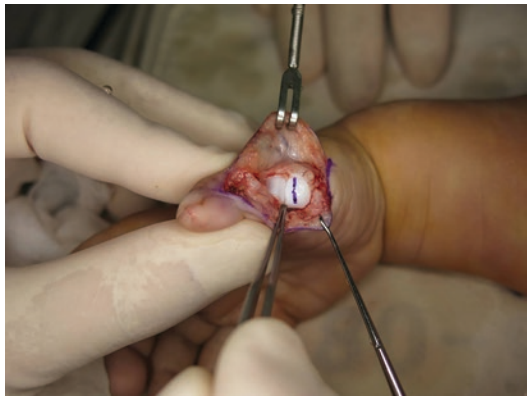

Fig. 20.18 Excessive portion of metacarpal head on which the removed radial thumb had sat was marked

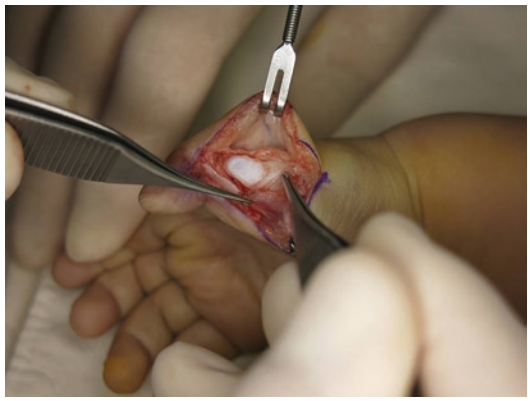

Fig. 20.19 After excision of excessive portion of the metacarpal head, the detached tendon of APB (left forcep) and a ligamentoperiosteal flap (right forcep) were preserved

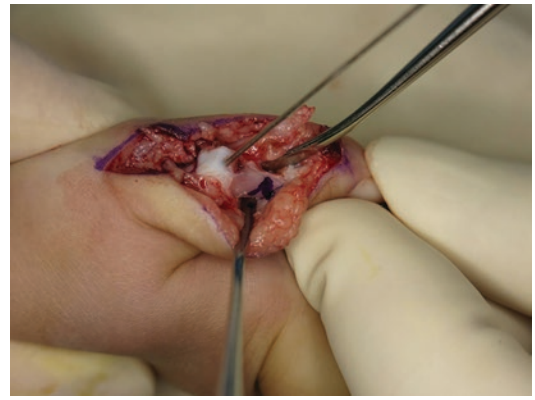

Fig. 20.20 The MP joint was fixed with a K-wire. Proximal phalanx was exposed subperiosteally for corrective osteotomy

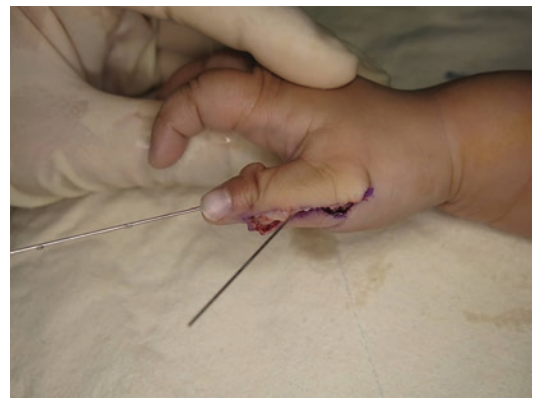

Fig. 20.21 The osteotomy site was fixed with a K-wire

lanx was dissected subperiosteally for ulnar-based closed- wedge osteotomy to correct angular deformity at the IP joint (Fig. 20.20). It is convenient to perform ulnar-based closed-wedge osteotomy from separate ulnar side incision. However, simultaneous medial and lateral incision on the same thumb may jeopardize blood circulation. The MP joint was fixed in a reduced position with a K-wire, and also osteotomy site of proximal phalanx was fixed with an additional K-wire (Fig. 20.21). Finally, the FPL tendon detached from the radial thumb was reattached into the ulnar side of reconstructed distal phalanx. The abductor pollicis brevis tendon detached from radial thumb as well as the previously raised ligamentoperiosteal flap for collateral ligament reconstruction was also reinserted into the base of proximal phalanx (Fig. 20.22). Alignment and appearance of the reconstructed thumb (Fig. 20.23), and the immediate postoperative radiograph (Fig. 20.24) showed good result.

Surgical Technique (Wassel Type VII)

Clinical features of Wassel type VII radial polydactyly are so diverse that there is no standard surgical technique. In certain cases, simple excision is enough to correct deformity (Fig. 20.25). On the other hand, very complex reconstruction procedure is needed in certain cases (Fig. 20.26).

A 12-month-old girl showed a radial polydactyly bifid at metacarpal shaft level. The ulnar thumb had delta middle phalanx with angular deformity (Figs. 20.27 and 20.28). A racquet- shaped incision was made along the radial thumb, and it was excised by dividing bony connection at metacarpal shaft level. Another straight incision was made

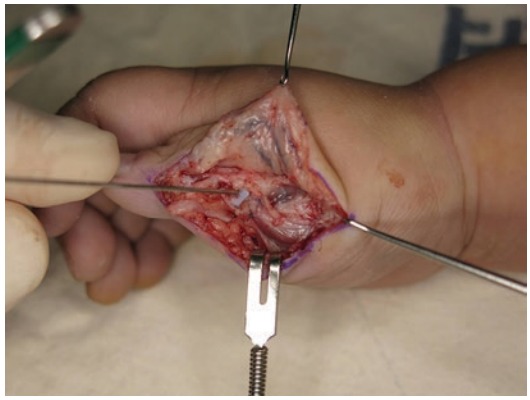

Fig. 20.22 The abductor pollicis brevis tendon detached from radial thumb as well as the previously raised ligamentoperiosteal flap was reinserted into the base of proximal phalanx

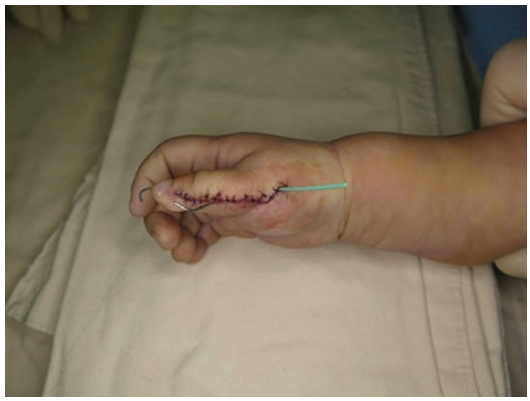

Fig. 20.23 A postoperative photo

along the radial side of the ulnar thumb to excise the delta middle phalanx. After excision of the delta bone, the radial collateral ligament was sutured in proper tension. When the patient's age is less than 6 years, simple excision of the delta bone yields a good result [35]. The younger the patients, better the surgical outcome. A longitudinal K-wire was inserted to protect reconstructed radial collateral ligament of IP joint (Fig. 20.29). Three years after the operation, alignment and range of motion were good (Figs. 20.30 and 20.31).

Combination Procedure (Modified Bilhaut-Cloquet Procedure)

The original Bilhaut-Cloquet procedure (BC procedure) consists of resection of the central portion of duplicated segment and the coaptation of outer parts of bone, soft tissue, and nail tissue for the treatment of radial polydactyly [36]. This procedure has advantage in obtaining a good-sized thumb with good IP joint stability. However,

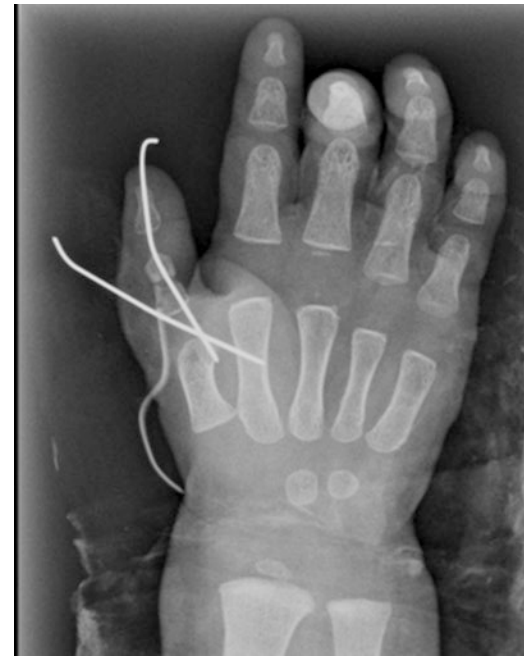

Fig. 20.24 Immediate postoperative radiograph

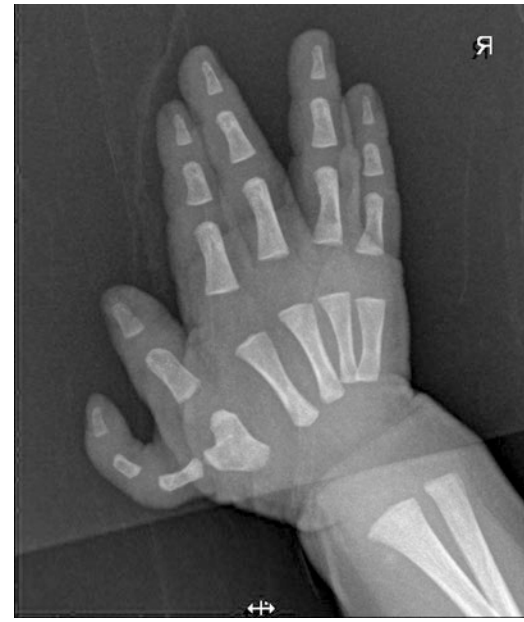

Fig. 20.25 A simple Wassel type VII polydactyly. Radial triphalangeal thumb was hypoplastic, and ulnar thumb showed good IP and MP joints with straight alignment

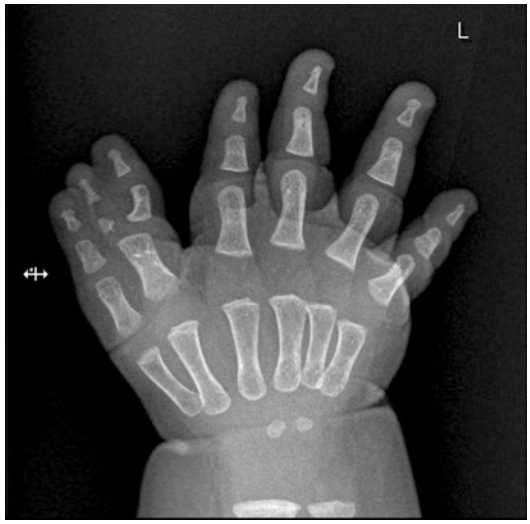

Fig. 20.26 A complex Wassel type VII polydactyly

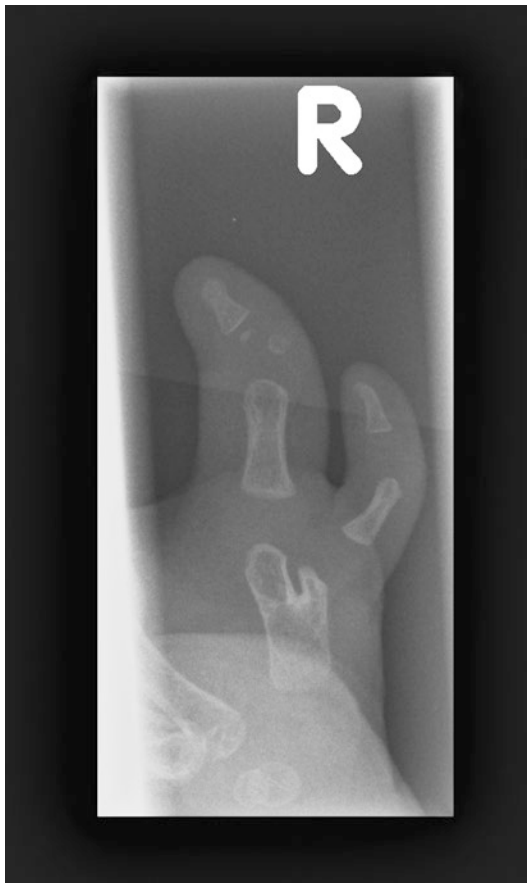

Fig. 20.27 A 12-month-old girl with Wassel type VII polydactyly. The ulnar triphalangeal thumb had delta middle phalanx causing angular deformity

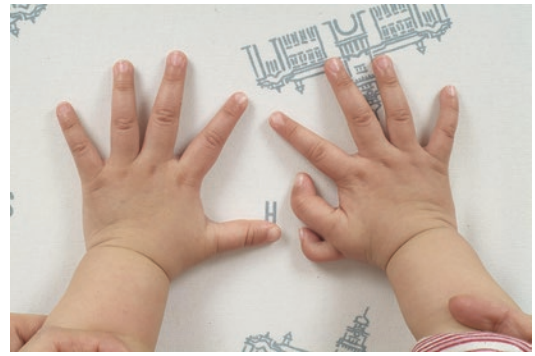

Fig. 20.28 Preoperative medical photo

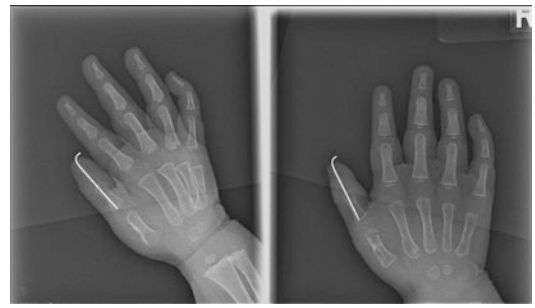

Fig. 20.29 Radial thumb was excised. The middle delta bone of the ulnar thumb was excised, and the collateral ligament was sutured in proper tension

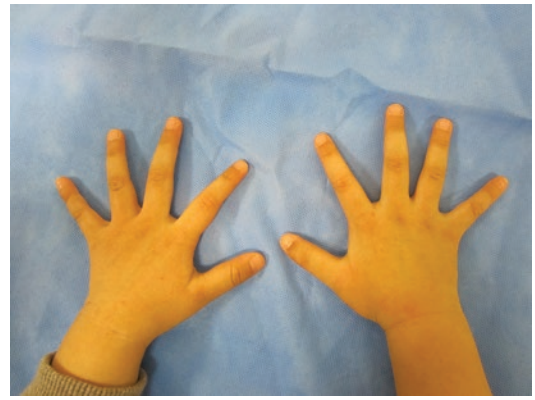

Fig. 20.30 Three years after the operation, alignment of the reconstructed thumb was straight

postoperative complications such as joint stiffness, physeal growth disturbance, and nail-plate deformity are common [22, 27, 37].

This original technique was modified to overcome these complications [38, 39]. There is no absolute indication for modified BC procedure.

However, when both thumbs are hypoplastic and show almost symmetric appearance, this procedure is indicated. Especially, when the nail width is less than two-thirds of contralateral normal side in unilateral cases, and when the nail width is less than that of index finger in bilateral cases, this modified technique is recommended. This modified procedure is different from the originally described method because it is an extra-articular procedure; the IP joint is reconstructed with one thumb and the other thumb contributes to only part of the distal phalanx for stability (Figs. 20.32 and 20.33). Both dorsal and volar incisions are necessary for this procedure. To prevent so called "seagull deformity" of the reconstructed nail, the contour of nail bed can be manipulated. For example, a rounder contour of the nail bed can be achieved by bending two parts more volarly. To make one smooth semicircular nail bed in the transverse plane, slight volar-axial

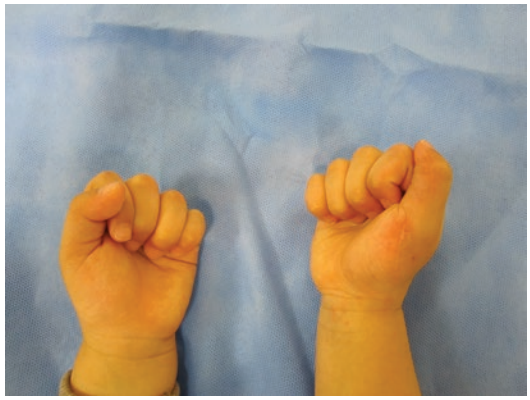

Fig. 20.31 Range of motion was good

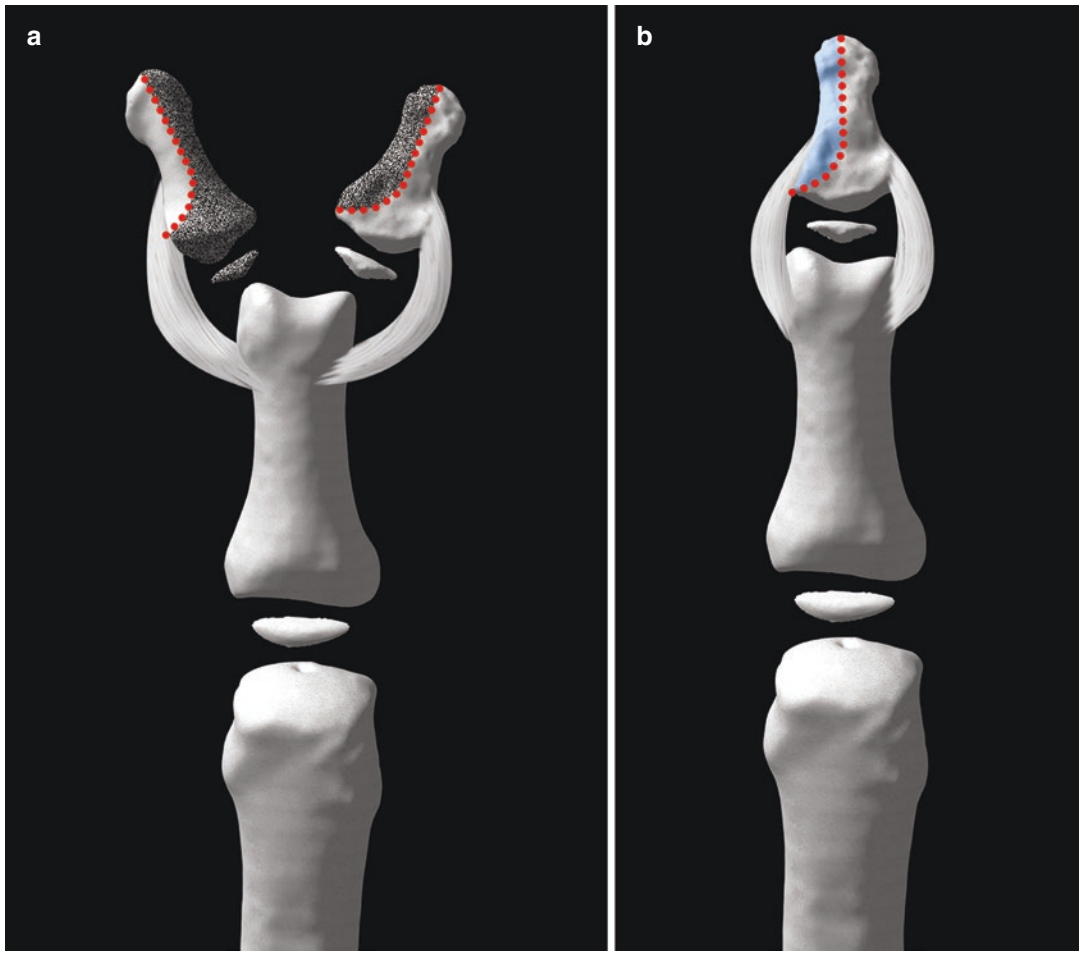

Fig. 20.32 (**a**, **b**) Modified BC procedure for Wassel type II. The central areas are resected, and the two distal phalangeal bones are combined extra-articularly to preserve IP joint motion and to prevent epiphyseal plate injury

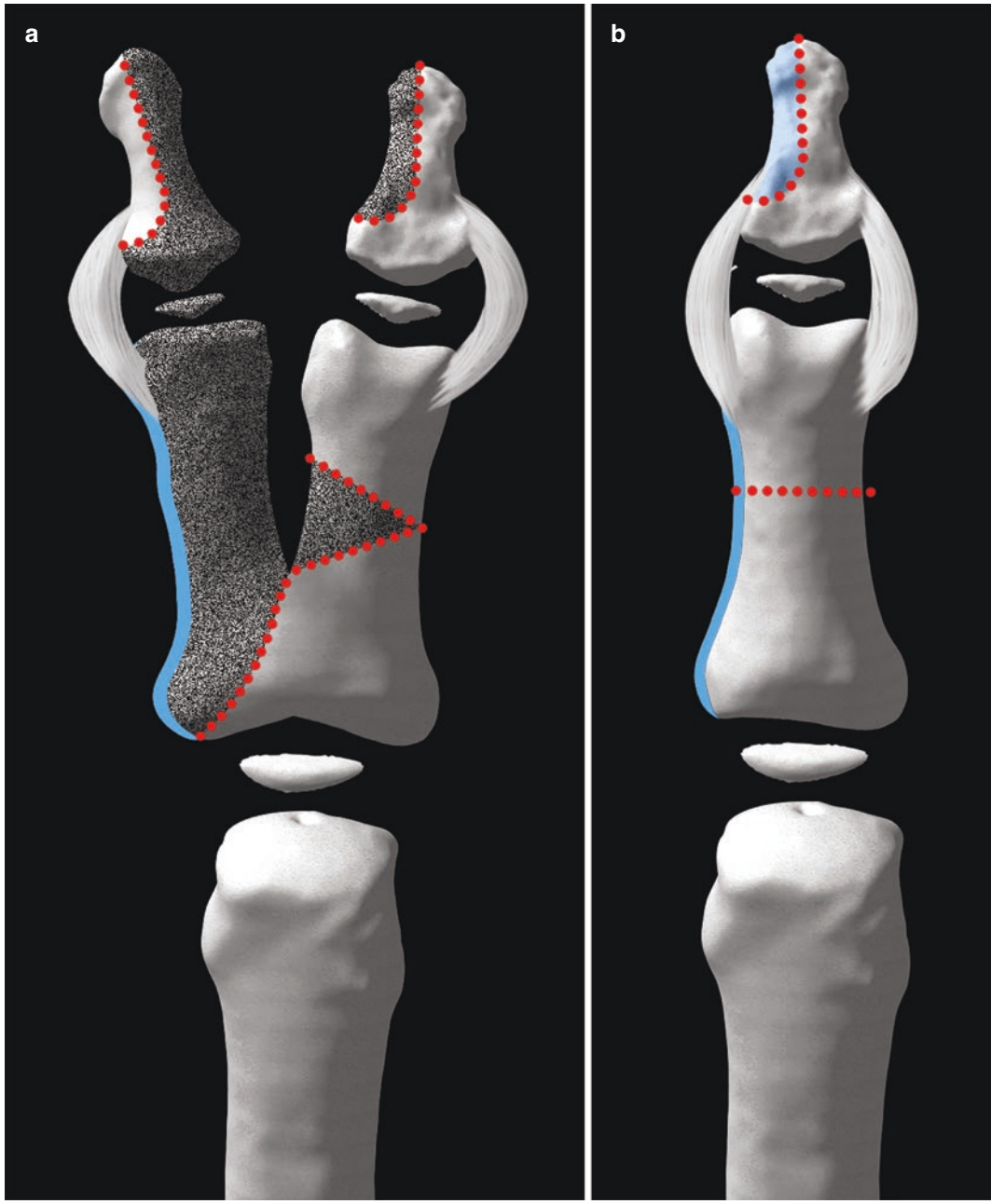

Fig. 20.33 (**a**, **b**) Modified BC procedure for Wassel type III. The corrective osteotomy of the proximal phalanx is performed when there is more than 20° of angular deformity

rotation is required (Fig. 20.34). Bony union between two distal phalangeal parts usually occurred within several months and rarely within a year.

For Wassel type IV polydactyly, the original technique had been tried [40–42], and the authors reported good alignment and good joint stability. The medial portions of two distal phalanges as well as those of the two proximal phalanges should be resected for classic BC operation in Wassel type IV. However, it is almost impossible for phalangeal bones of bifid thumbs to be mirror

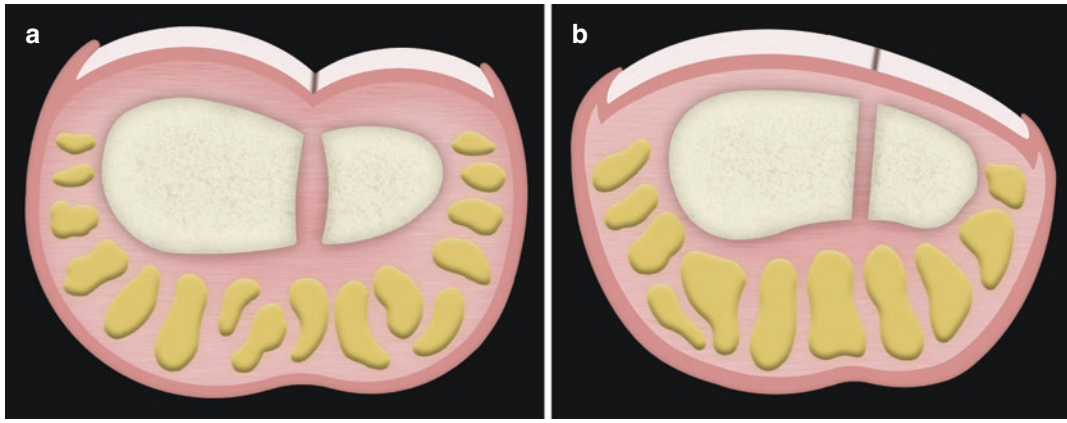

Fig. 20.34 (**a**, **b**) Slight volar-axial rotation is required to make smooth semicircular nail bed

images especially in terms of height. A step-off between fused two proximal phalangeal bones at the IP joint is inevitable when the MP joint was coapted congruously. Otherwise, shaving of distal articular cartilage or shortening of one proximal phalangeal bone at shaft level is necessary.

When two bisected proximal phalanges are coapted, articular surface of proximal portion should be congruous because the MP joint is more important than IP joint functionally. There should be length mismatch between two portions at the IP joint level if two bones are not exactly the same height. If distal articular portion of proximal phalanx of dominant thumb is preserved and the same part of proximal phalanx of shorter minor thumb is removed, reconstructed thumb will have a stable MP joint and mobile IP joint (Fig. 20.35). Previously mentioned modified BC technique is applied to at the IP joint and classic BC technique at the MP joint.

Surgical Technique (Wassel Types II, III) [38, 39]

A 2-year and 1-month-old boy showed Wassel type II thumb polydactyly on the left hand. The distal phalangeal epiphysis of the radial thumb showed an abnormal triangular shape [43], while that of the ulnar thumb looked normal (Fig. 20.36). Thus, the ulnar thumb was chosen to be the main thumb of which most of the parts, including the IP joint, would be preserved. The size of the nail of the polydactylic thumbs was smaller than those of index fingers (Fig. 20.37). Under tourniquet control, the nail plates were removed. Then soft tissues including skin and nail bed were removed along with the incision line. The base of the two distal phalanges was separated carefully. The main articulating digit, the ulnar side in this case, contained a major part of the distal phalangeal bone with the overlying nail bed. The radial minor thumb was made into a fillet flap containing only small extra-articular part of the distal phalangeal bone supporting the incised nail bed and the collateral ligament attached to the proximal phalanx. Articular facet of proximal phalanx for minor radial thumb was shaved. The radial side of the main ulnar digit tuft was also trimmed with a small rongeur to make a better approximation with remaining portion of minor thumb.

The two distal phalangeal bones can be approximated and maintained by 5–0 nylon suture, one or two transverse K-wires, or a spinal needle in a very small thumb. The nail fold as well as nail bed was repaired with 8–0 nylon sutures (Fig. 20.38). Removed nail was trimmed and reinserted into the reconstructed nail fold for internal splint. Two months after the operation, bony union was observed between two portions of distal phalanges and alignment was good (Fig. 20.39). Three months after the operation, the new nail grew well without deformity and IP joint motion was good (Figs. 20.40 and 20.41).

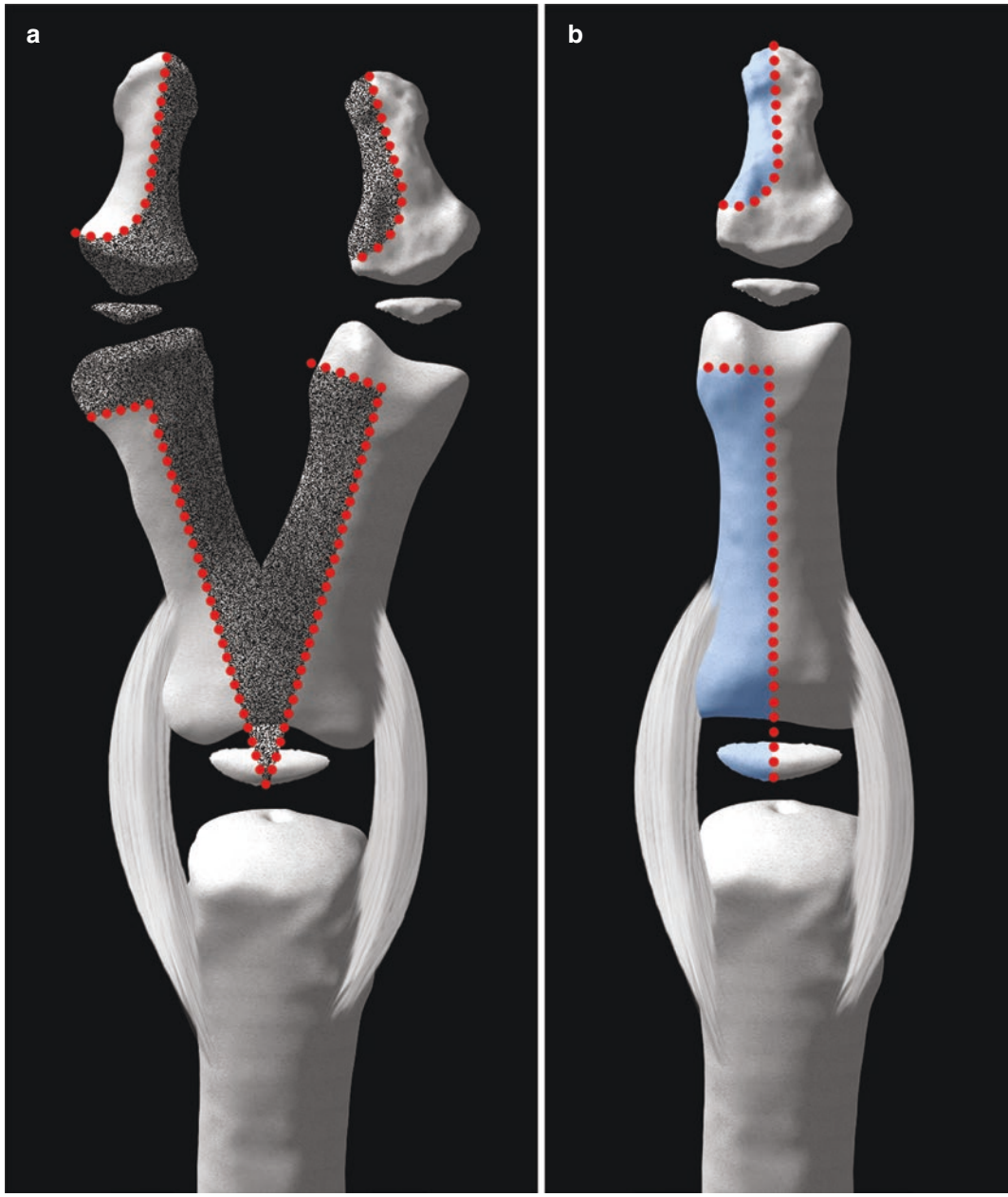

Fig. 20.35 (**a**, **b**) Modified BC procedure for Wassel type IV. The articular surface of the MP joint is adjusted first after removal of central portions of two proximal phalanges. There is length discrepancy between two portions at the IP joint level if two bones are not exactly the same height. If distal articular portion of proximal phalanx of dominant thumb is preserved, remaining procedure is the same with that of type II

In a Wassel type III polydactyly, all the procedures are same as those of Wassel type II except the minor thumb is osteotomized at its bifurcation level. When there is more than 20 degrees of angular deformity at the IP joint, a closed-wedge osteotomy is performed at the proximal phalanx of the retained thumb. One or two K-wires are inserted to stabilize the osteotomy site.

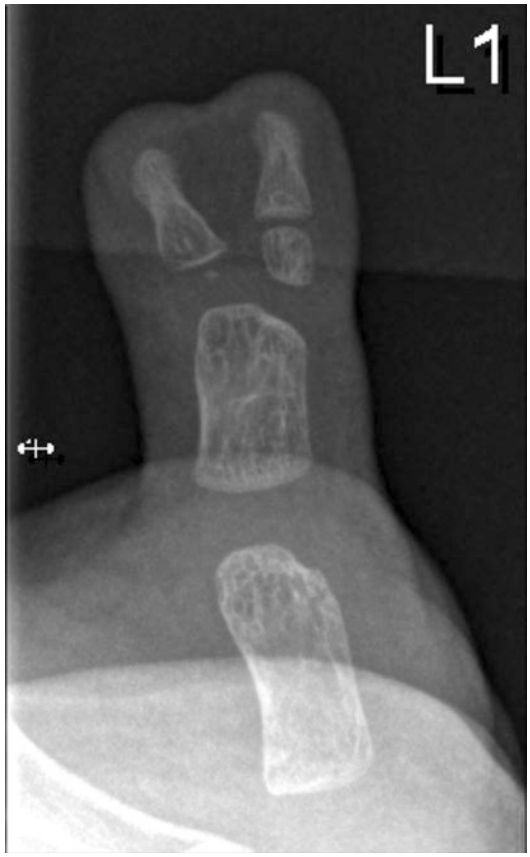

Fig. 20.36 The distal phalangeal epiphysis of the radial thumb showed abnormal triangular shape in this Wassel type II polydactyly

Fig. 20.37 The nail size of the polydactylic thumbs was smaller than those of index fingers

All the K-wires are removed 4–6 weeks after the operation, even if the bony bridge is not observed between coapted distal phalanges, because it will eventually show bony union.

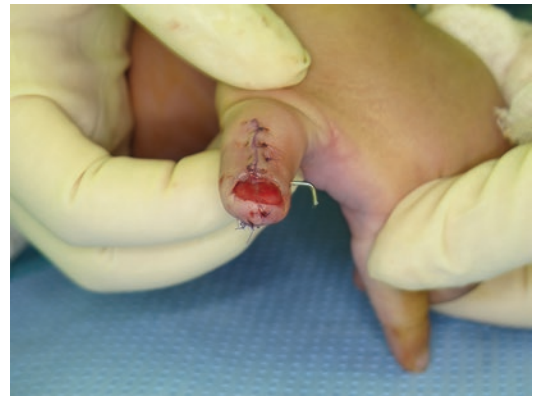

Fig. 20.38 A transverse K-wire was inserted for stability. The nail bed was repaired with 8–0 nylon sutures

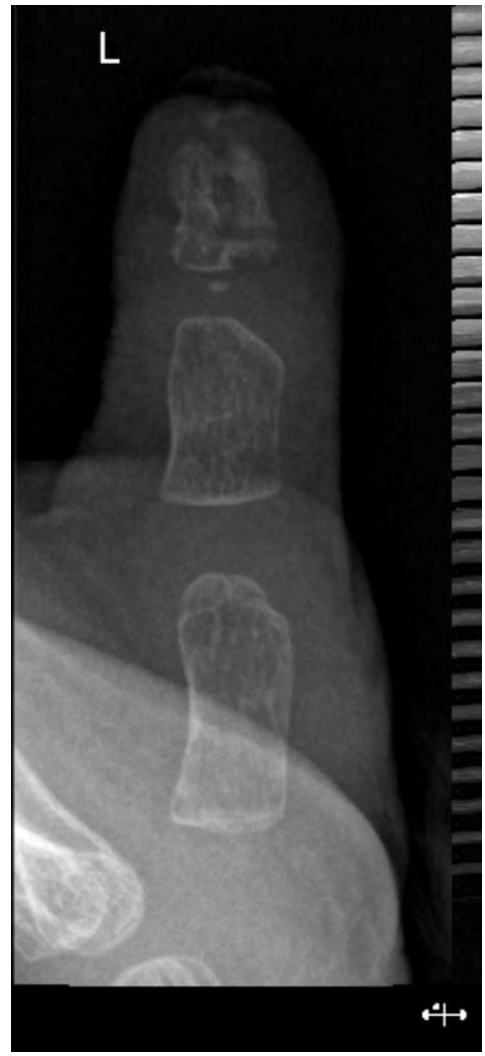

Fig. 20.39 Two months after the operation, bony union was achieved

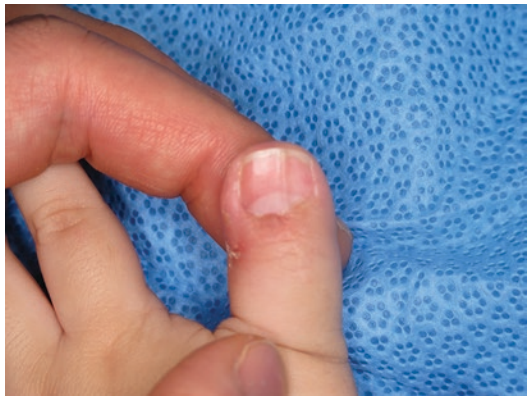

Fig. 20.40 Three months after the operation, the new nail grew well

Fig. 20.41 The contour of the nail was smooth

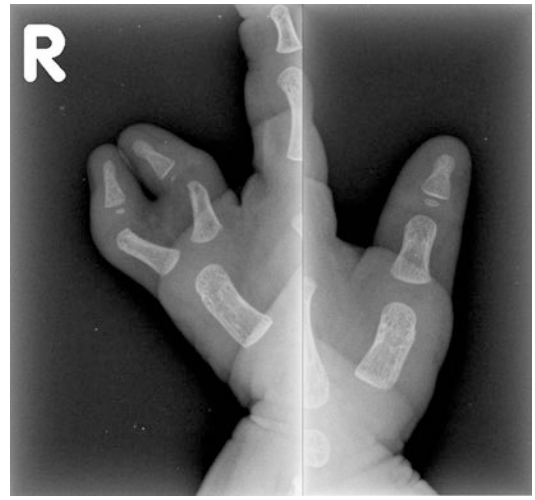

Fig. 20.42 Wassel type IV polydactyly of right thumb. Bony hypoplasia of polydactylic thumbs was observed

Fig. 20.43 The size of the nails of the polydactylic thumbs was smaller than those of index fingers

Surgical Technique (Wassel Type IV)

A 15-month-old boy showed Wassel type IV thumb polydactyly on right hand (Figs. 20.42 and 20.43). Dorsal and volar skin incisions were designed. Soft tissues were removed, and central portion of bifid proximal phalanges were resected. Two parts of proximal phalanges were coapted using 4–0 nylon to make MP joint congruously. The EPL and FPL tendons were realigned as previously described. For IP joint, same modified technique as in Wassel type II was applied. After skin closure, removed nail was trimmed and reinserted. Although immediate postoperative radiographs showed incongruous MP joint, the cartilaginous portions of coapted proximal phalanges were adjusted congruously (Fig. 20.44).

Four months after the operation, both IP and MP joints looked more congruous radiographically (Fig. 20.45). Three and half years after the operation, both IP and MP joints were getting more congruous (Figs. 20.46 and 20.47). The epiphysis of the distal phalanx grew well without angular deformity. Two epiphyseal centers were noted at proximal portion of proximal phalanx. Flexion arc of both MP and IP joints were almost equal with those of normal side (Figs. 20.48 and 20.49).

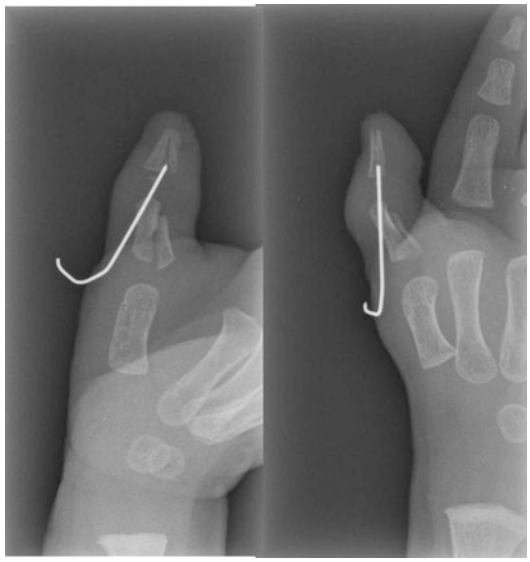

Fig. 20.44 Immediate postoperative radiographs after modified BC procedure

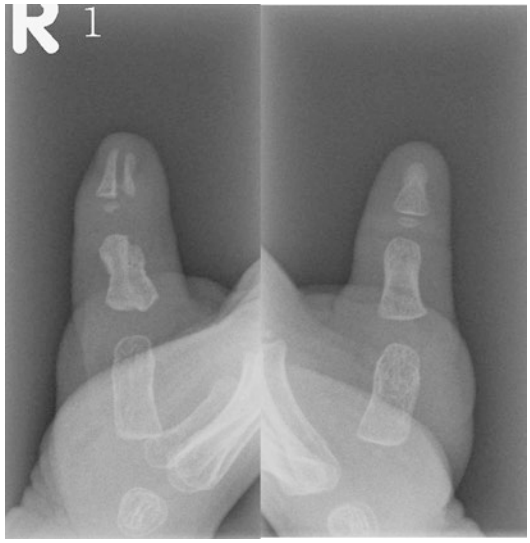

Fig. 20.45 At 4 months postoperatively, the MP joint became more congruous

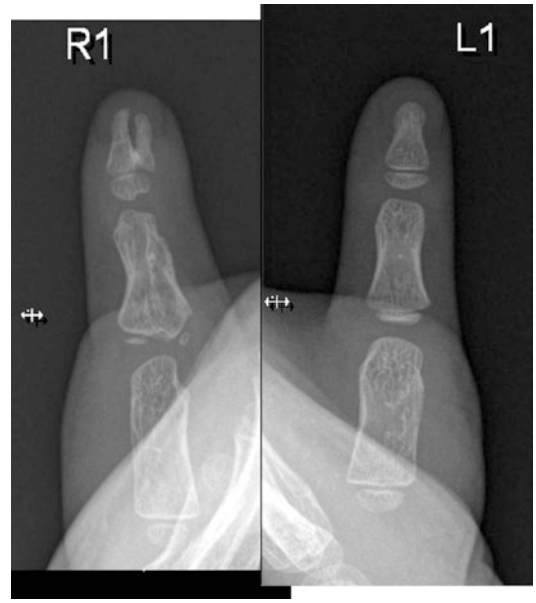

Fig. 20.46 Bony growth and alignment were good in AP view 3.5 years after the operation

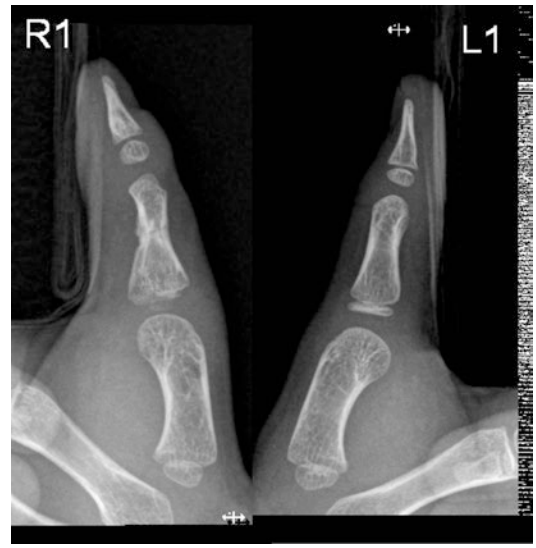

Fig. 20.47 Lateral views

On-Top Plasty

In certain patients with radial polydactyly, one thumb has a well-developed proximal part and a poorly developed distal part with absent or hypoplastic nail; on the other hand, the other thumb has a poorly developed proximal part and a better distal part, including nail and pulp. In these situations, combining parts from both thumbs, termed on-top plasty, can yield an acceptable aesthetic and functional result. In this technique, better distal part of one thumb is transposed to the better proximal part of the other thumb. The transposed

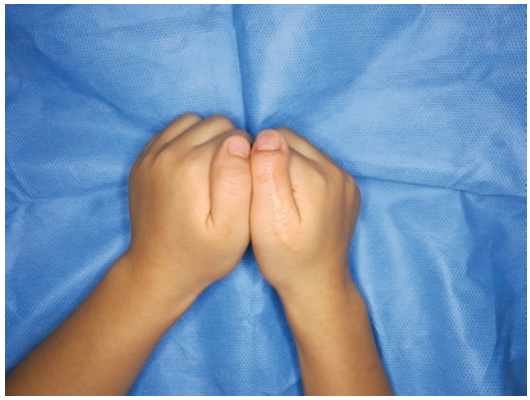

Fig. 20.48 Medical photos taken 31/2 years after the reconstruction

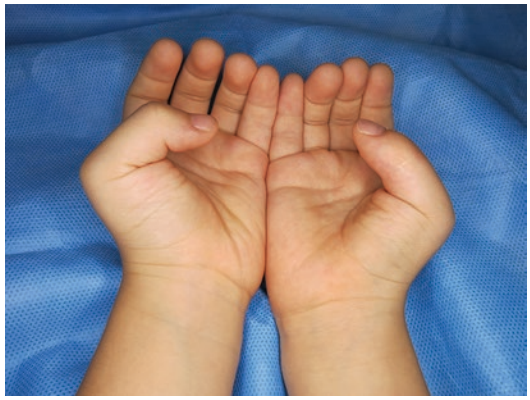

Fig. 20.49 Active range of motion was good at both IP and MP joints

distal portion should have its own neurovascular bundle to feed itself, like a local neurovascular flap. The location of feeding artery to the transposed distal part can be traced by ultrasonography. At least one artery is identifiable.

Surgical Technique

An 11-month-old girl showed bilateral Wassel type VII thumb polydactyly. Right side was operated by "excision and reconstruction" method. On left hand, radial-sided thumb had good proximal phalanx and MP joint, however distal phalangeal bone and nail were hypoplastic. The ulnar thumb had good nail, pulp, and distal phalangeal bone, but there was no bony connection with radial thumb proximally (Figs. 20.50 and 20.51). Preoperative sonography was performed to trace

Fig. 20.50 Radial thumb showed good proximal part, and the ulnar thumb good distal part

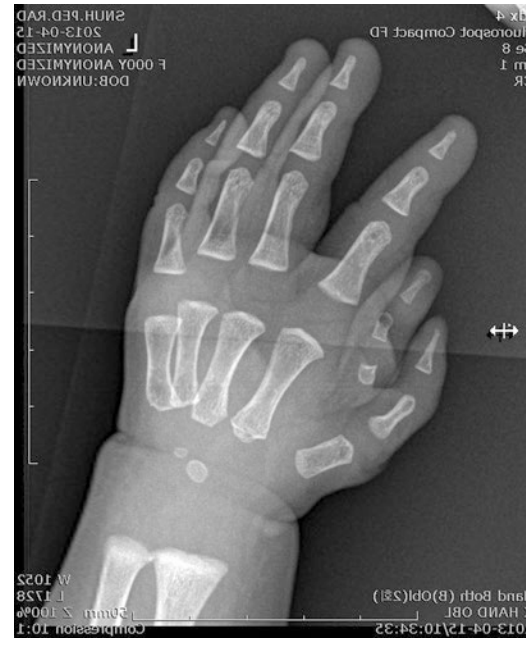

Fig. 20.51 The base of the ulnar thumb was not connected with the radial thumb

vascular supply to the ulnar thumb. Two vessels were identified dorsoradially and voloradially (Fig. 20.52). Skin incision was designed (Figs. 20.53 and 20.54). On the ulnar-floating thumb, only distal portion including nail and distal phalangeal bone except epiphysis was isolated with vascular pedicle, and vascular perfusion was confirmed after tourniquet release (Fig. 20.55). On the radial main thumb, distal portion including nail and distal phalangeal bone except epiphysis was removed. Then, vascular pedicled portion of ulnar thumb tip was transposed to the top of radial thumb. The vascular bundle was buried into the soft tissue of ulnar side of the radial thumb. A longitudinal K-wire was inserted to fix transposed part (Fig. 20.56). Immediate postoperative findings after the tourniquet release showed good alignment and circulation

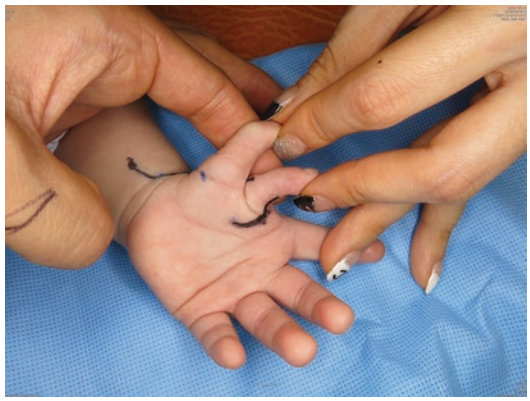

Fig. 20.52 Location of the vessels were identified by ultrasonography and marked

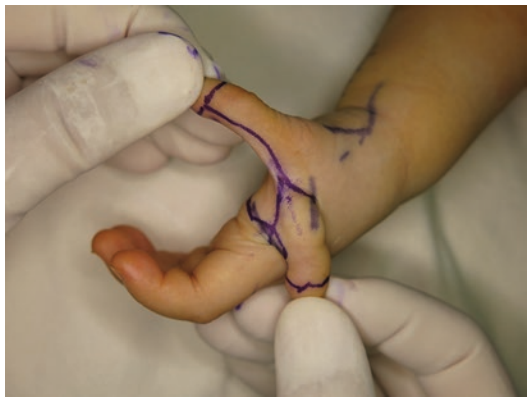

Fig. 20.53 Drawing of skin incision

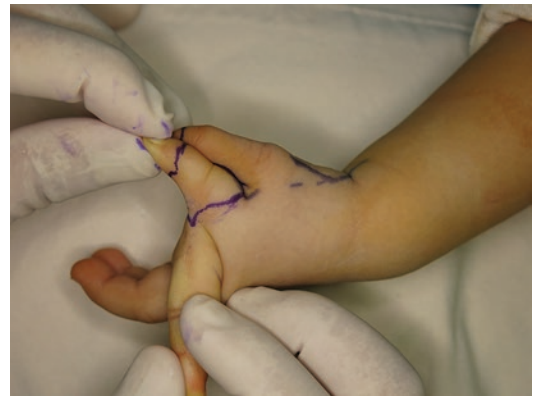

Fig. 20.54 Dorsal view of skin incision

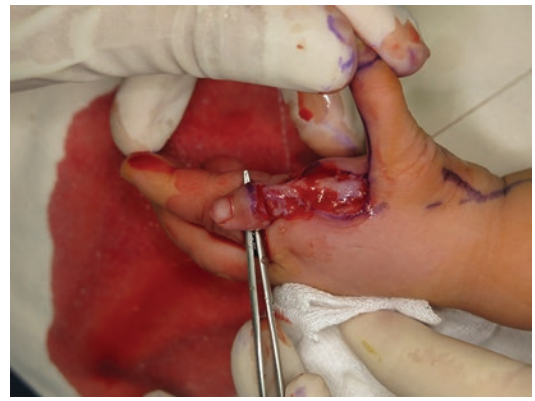

Fig. 20.55 Only distal portion of ulnar thumb was remained with vascular pedicles. Active bleeding and good circulation were noted after tourniquet release

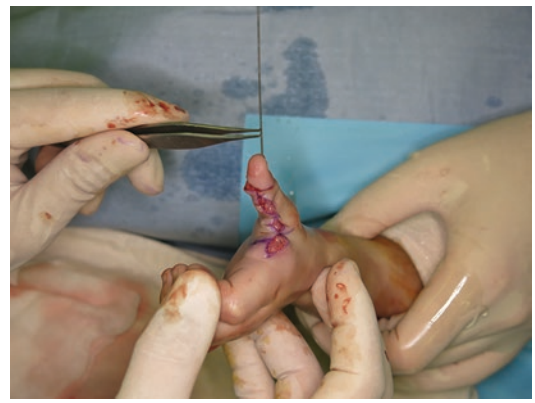

Fig. 20.56 The vascular pedicles were embedded on the ulnar side of the thumb. A K-wire was inserted for stability

(Figs. 20.57, 20.58, and 20.59). Two months after the operation, the circulation of her left thumb maintained well and the thumb functioned nicely (Fig. 20.60).

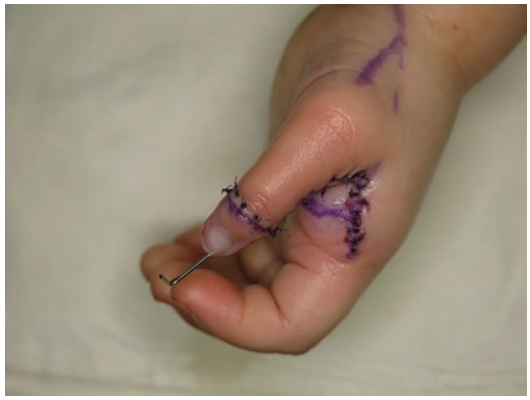

Fig. 20.57 Dorsal view of the reconstructed thumb

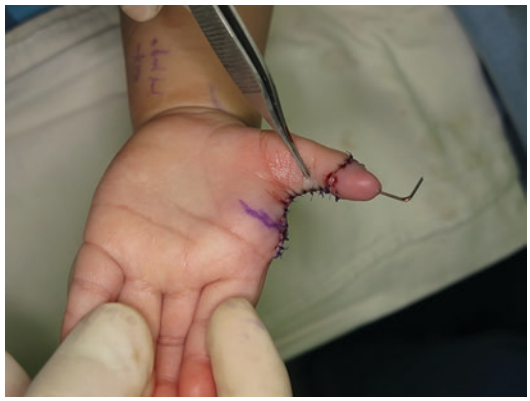

Fig. 20.58 First web space was well preserved

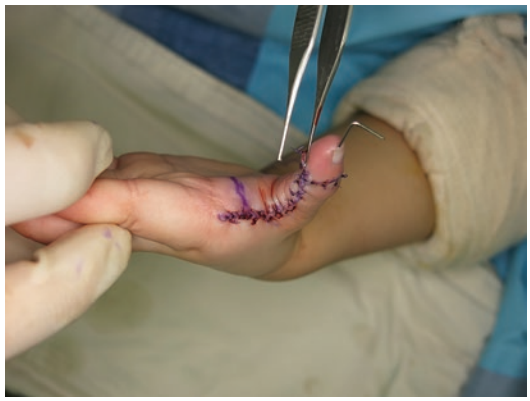

Fig. 20.59 After skin closure, the circulation of the transposed portion was well maintained

Fig. 20.60 Function and appearance were good 2 months after the operation

References

1. Swanson AB. A classification for congenital limb malformations. J Hand Surg Am. 1976;1(1):8–22.
2. Oberg KC, Feenstra JM, Manske PR, Tonkin MA. Developmental biology and classification of congenital anomalies of the hand and upper extremity. J Hand Surg Am. 2010;35(12):2066–76.
3. Sesgin MZ, Stark RB. The incidence of congenital defects. Plast Reconstr Surg Transplant Bull. 1961;27:261–7.
4. Temtamy SA, McKusick VA. The genetics of hand malformations. Birth Defects; Original Article Series V. 1978;14(i-xviii):1–619.
5. Goldfarb CA, Wall LB, Bohn DC, Moen P, Van Heest AE. Epidemiology of congenital upper limb anomalies in a midwest United States population: an assessment using the Oberg, Manske, and Tonkin classification. J Hand Surg Am. 2015;40(1):127–32 e1–2.
6. Wassel HD. The results of surgery for polydactyly of the thumb. A review. Clin Orthop Relat Res. 1969;64:175–93.
7. Ogino T, Minami A, Fukuda K, Kato H. Congenital anomalies of the upper limb among the Japanese in Sapporo. J Hand Surg Br. 1986;11(3):364–71.
8. Baek GH, Chung MS, Park YB, Yoo KH. The relative incidence of congenital anomalies of the hand. J Korean Orthop Assoc. 1997;32(4):796–801.
9. Wood VE. Polydactyly and the triphalangeal thumb. J Hand Surg Am. 1978;3(5):436–44.
10. Umair M, Ahmad F, Bilal M, Ahmad W, Alfadhel M. Clinical genetics of polydactyly: an updated review. Front Genet. 2018;9:447.
11. Al-Qattan MM, Al Abdulkareem I, Al Haidan Y, Al BM. A novel mutation in the SHH long-range regulator (ZRS) is associated with preaxial polydactyly, triphalangeal thumb, and severe radial ray deficiency. Am J Med Genet A. 2012;158A(10):2610–5.

12. Daluiski A, Yi SE, Lyons KM. The molecular control of upper extremity development: implications for congenital hand anomalies. J Hand Surg Am. 2001;26(1):8–22.
13. Hill P, Gotz K, Ruther U. A SHH-independent regulation of Gli3 is a significant determinant of anteroposterior patterning of the limb bud. Dev Biol. 2009;328(2):506–16.
14. Al-Qattan MM. The distribution of the types of thumb polydactyly in a Middle Eastern population: a study of 228 hands. J Hand Surg Eur Vol. 2010;35(3):182–7.
15. Tonkin MA. Thumb duplication: concepts and techniques. Clin Orthop Surg. 2012;4(1):1–17.
16. Manske MC, Kennedy CD, Huang JI. Classifications in brief: the Wassel classification for radial polydactyly. Clin Orthop Relat Res. 2017;475(6):1740–6.
17. Flatt AE. Extra thumbs. In: Flatt AE, editor. The care of congenital hand anomalies. St Louis,MO: Quality Medical Publishing; 1977. p. 120–35.
18. Buck-Gramko D, Behrens P. [Classification of polydactyly of the hand and foot] [in German]. Handchir Mikrochir Plast Chir. 1989;21:195–204.
19. Miura T. Triphalangeal thumb. Plast Reconstr Surg. 1976;58(5):587–94.
20. Chung MS, Baek GH, Gong HS, Lee HJ, Kim J, Rhee SH. Radial polydactyly: proposal for a new classification system based on the 159 duplicated thumbs. J Pediatr Orthop. 2013;33(2):190–6.
21. Evanson BJ, Hosseinzadeh P, Riley SA, Burgess RC. Radial polydactyly and the incidence of reoperation using a new classification system. J Pediatr Orthop. 2016;36(2):158–60.
22. Townsend DJ, Lipp EB Jr, Chun K, Reinker K, Tuch B. Thumb duplication, 66 years' experience–a review of surgical complications. J Hand Surg Am. 1994;19(6):973–6.
23. Waters PM, Bae DS. Pediatric hand and upper extremity surgery. A practical guide. 1st ed. Philadelphia: Lippincott Williams & Wilkins; 2012. p. 41.
24. Goldfarb CA, Patterson JM, Maender A, Manske PR. Thumb size and appearance following reconstruction of radial polydactyly. J Hand Surg Am. 2008;33(8):1348–53.
25. Kozin SH. Deformities of the thumb. In: Wolfe SW, Hotchikiss RN, Pederson WC, Kozin SH, editors. Green's operative hand surgery. 6th ed. Philadelphia: Elsevier Churchill Livingstone; 2011. p. 1383.
26. Jobe MT. Congenital anomalies of the hand. In: Canale ST, Beaty JH, editors. Campbell's operative orthopaedics. 12th ed. Philadelphia: Elsevier Mosby; 2013. p. 3755.
27. Tada K, Yonenobu K, Tsuyuguchi Y, Kawai H, Egawa T. Duplication of the thumb. A retrospective review of two hundred and thirty-seven cases. J Bone Joint Surg Am. 1983;65(5):584–98.
28. Cheng JC, Chan KM, Ma GF, Leung PC. Polydactyly of the thumb: a surgical plan based on ninety-five cases. J Hand Surg Am. 1984;9(2):155–64.
29. JSSH Congenital Hand Committee. Evaluation sheet for polydactyly of the thumb [in Japanese]. J Japan Soc Surg Hand. 2007;24:422.
30. Dijkman RR, van Nieuwenhoven CA, Selles RW, Hovius SE. Comparison of functional outcome scores in radial polydactyly. J Bone Joint Surg Am. 2014;96(6):463–70.
31. Leber GE, Gosain AK. Surgical excision of pedunculated supernumerary digits prevents traumatic amputation neuromas. Pediatr Dermatol. 2003;20(2):108–12.
32. Manske PR. Treatment of duplicated thumb using a ligamentous/periosteal flap. J Hand Surg Am. 1989;14(4):728–33.
33. Tupper JW. Pollex abductus due to congenital malposition of the flexor pollicis longus. J Bone Joint Surg Am. 1969;51(7):1285–90.
34. Lister G. Pollex abductus in hypoplasia and duplication of the thumb. J Hand Surg Am. 1991;16(4):626–33.
35. Hovius SE, Zuidam JM, de Wit T. Treatment of the triphalangeal thumb. Tech Hand Up Extrem Surg. 2004;8(4):247–56.
36. Bilhaut M. Guerison d'un poucebifide par un nouveau procedeoperatoire. Congr Fr Chirg. 1889;4:576–80.
37. Miura T. Duplicated thumb. Plast Reconstr Surg. 1982;69(3):470–81.
38. Baek GH, Gong HS, Chung MS, Oh JH, Lee YH, Lee SK. Modified Bilhaut-Cloquet procedure for Wassel type-II and III polydactyly of the thumb. J Bone Joint Surg Am. 2007;89(3):534–41.
39. Baek GH, Gong HS, Chung MS, Oh JH, Lee YH, Lee SK. Modified Bilhaut-Cloquet procedure for Wassel type-II and III polydactyly of the thumb. Surgical technique. J Bone Joint Surg Am. 2008;90 Suppl 2 Pt 1:74–86.
40. Hartrampf CR, Vasconez LO, Mathes S. Construction of one good thumb from both parts of a congenitally bifid thumb. Plast Reconstr Surg. 1974;54(2):148–52.
41. Samson P, Salazard B, Magalon G. The "Bilhaut-Cloquet" technique for treatment of thumb duplication. Handchir Mikrochir Plast Chir. 2004;36(2–3):141–5.
42. Tonkin MA, Bulstrode NW. The Bilhaut-Cloquet procedure for Wassel types III, IV and VII thumb duplication. J Hand Surg Eur Vol. 2007;32(6):684–93.
43. Baek GH, Chung MS, Gong HS, Lee S, Lee YH, Kim HH. Abnormal triangular epiphysis causing angular deformity of the thumb. J Hand Surg Am. 2006;31(4):544–8.

Ulnar Polydactyly and Ulnar Dimelia

21

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Overview

Ulnar polydactyly represents one of the most frequent hand congenital anomalies while ulnar dimelia is one of the most unusual congenital upper limb abnormalities. Ulnar polydactyly is common in many families particularly in families of African ancestry. Both conditions demonstrate variable pathologic anatomy due to failure of differentiation of the anterior-posterior axis of the upper limb. Additional congenital abnormalities may be associated with each of these conditions. Ulnar polydactyly and ulnar dimelia may be diagnosed prenatally by ultrasound. Both diagnoses are made based upon the morphologic appearance of the limb at birth. Appropriate diagnostic work-up should consider associated conditions. Surgical reconstruction of the affected extremity should improve the aesthetic appearance of the hand while preserving or improving upper extremity function.

Ulnar Polydactyly

Ulnar polydactyly, also known as postaxial polydactyly, includes a spectrum of disorders involving duplication of digits or parts of digits along the ulnar side of the hand. In contrast, radial, or preaxial, polydactyly involves the thumb, while central polydactyly involves the index, middle, or ring fingers. Ulnar polydactyly arises owing to failure of differentiation of the anterior-posterior axis of the hand plate during embryologic formation of the upper limb [1]. The epidemiology, genetics, and treatment of ulnar polydactyly are, in many ways, dissimilar from either radial or central polydactyly [2, 3]. Ulnar polydactyly is classified as *Class III/Duplication* using the International Federation of Societies for Surgery of the Hand (IFSSH) Classification [4]. The condition is categorized as *Class 1B2 Malformations/Failure of Axis of Formation of Hand Plate Anterioposterior Axis* according to the modified Oberg, Manske, Tonkin (OMT) Classification [5].

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Classification

Supernumerary digits in ulnar polydactyly usually present as one of two forms, described by Temtamy and McKusiak as Type A and Type B [6]. Type-A ulnar polydactyly digits are well-developed digits located on the ulnar border of the small finger, whereas Type B describes a hypoplastic, pedunculated, or small finger nubbin. Several additional classification schemes are described in Table 21.1 [2, 6–10].

Epidemiology

Ulnar polydactyly, the most frequent congenital hand difference in African-American children occurs in approximately 1 in 150 newborns [3].

Table 21.1 Classification schemes utilized in ulnar polydactyly

Temtamy classification [6]	Type A: Well formed and functioning digit on ulnar side of small finger Type B: Small nonfunctioning digit that may be pedunculated or a nubbin
Stelling classification [7]	Type 1: digit with soft tissue only Type 2: digit with phalangeal elements Type 3: digit with phalangeal and metacarpal elements
Buck-Gramcko classification [9] "universal" classification	Type V rud: digit with soft tissue only Type V distal phalanx: digit with bifid distal phalanx Type V distal interphalangeal (DIP) joint: digit with two distal phalanges articulating at DIP joint Type V middle phalanx: digit with bifid middle phalanx Type V proximal interphalangeal (PIP) joint: digit with two middle phalanges articulating at PIP joint Type V proximal phalanx: digit with bifid proximal phalanx Type V metacarpal-phalangeal (MCP) joint: digit with two proximal phalanges articulating at MCP joint Type V metacarpal: digit with bifid metacarpal Type V carpometacarpal (CMC) joint: digit with two metacarpals articulating with the CMC joint
Rayan classification [2]	Type I: small "wart-like" skin nubbin without a nail or bone Type II: digit with small nail and bone with or without a joint that has no tendons and no function Type III: digit that is more developed than type II with hypoplastic or absent PIP joint and articulation with MCP joint or bifid 5th metacarpal Type IV: fully developed 6th digit with a 6th metacarpal Type V: others; including ulnar polydactyly with syndactyly and other bony abnormalities
Al-Qattan classification [10] "modified Rayan"	Type I: small nubbin without bone or nail Type IIA: Pedunculated nonfunctioning digit with narrow pedicle (<3 mm) Type IIB: Pedunculated nonfunctioning digit with wider pedicle (>3 mm) Type IIIA: Well formed functioning digit articulating with bifid metacarpal or partially duplicated 5th metacarpal Type IIIB: Well formed functioning digit with proximal phalanx fused to 5th metacarpal Type IV: digit with separate 6th metacarpal Type V: others; including polysyndactyly and triplication of small finger
Pritsch classification [8] for Type A only	Type I: fully developed 6th metacarpal that articulates at CMC joint ("metacarpal type") Type II: digit on lateral side of fifth digit with intercalated distal metacarpal remnant ("metacarpal-phalangeal type") Type III: digit from hypoplastic 6th metacarpal or fused to 5th metacarpal ("phalangeal type") Type IV: digit from metacarpal-phalangeal joint ("intercalated type") Type V: digit from bifid proximal phalanx ("fully developed type")

Although this condition is far less common in Caucasian (1:1400), Mexican (1:700), and Middle Eastern patients (1:1000), it is, nonetheless, one of the most frequently encountered congenital abnormalities of the upper limb. It has been noted that ulnar polydactyly is associated with different congenital abnormalities in children of different racial backgrounds [10–12].

In African-American children, the condition is usually inherited in an autosomal- dominant pattern and is rarely associated with other hand anomalies, congenital syndromes or nonsyndrome systemic abnormalities. Most African-American children demonstrate Type-B ulnar polydactyly. Cases are usually bilateral (70%). The left hand is more commonly affected in unilateral cases [2, 11]. There is equal sex distribution [10, 11].

In patients of non-African descent, ulnar polydactyly is usually sporadic. Only 5% of patients of non-African descent demonstrate a recognizable pattern of inheritance. Non-African descent patients demonstrate both Type-A and Type-B ulnar polydactyly. Twenty percent of cases are bilateral and males are more commonly affected than females [11]. Non-African patients also demonstrate a higher incidence of associated hand conditions including polysyndactyly, mixed polydactyly, and isolated syndactyly than do African- American children. Foot involvement (i.e., lateral toe polydactyly) may also be present in some children. Cases may also be associated with other congenital syndromes [13–16]. Associated syndromes and their inheritance patterns are listed in Table 21.2. Other congenital abnormalities not associated with one of the listed syndromes are uncommon [17].

Isolated, nonsyndromic ulnar polydactyly is strongly associated with genetic inheritance patterns. Both autosomal-dominant and autosomal-recessive patterns have been described. Genetic analysis has linked ulnar polydactyly to chromosomes 7, 13, and 19 [14, 18–22]. However, the exact pattern of inheritance of ulnar polydactyly is uncertain and most likely more complex than simple Mendelian genetics [11, 23]. Environmental exposure has been suggested as posing a risk for the development of ulnar polydactyly [24].

Pathogenesis

Although ulnar polydactyly is linked to failure of differentiation of the anterior-posterior axis of the developing limb bud, the exact mechanism is unknown. Embryologic limb development occurs in a coordinated fashion along the three spatial axes in a complex series of steps that begin with limb bud formation [1]. Embryologic formation of the upper limb is detailed in elsewhere in this book (Chap. 1). As the limb bud develops and lengthens along the proximal-distal axis, the zone of polarizing activity (ZPA) is established in the posterior mesoderm. Sonic hedgehog (SHH), elaborated by the ZPA, influences digital development and identity along the anterior-posterior axis. SHH contributes to the unique formation of the ulnar-sided structures of the forearm, wrist, and hand including the ulna, the ulnar two columns of the carpal bones, and the small finger, ring finger, and the ulnar half of the middle finger. Deficiency of SHH leads to ulnar ray deficiency and overexpression of SHH leads to radial polydactyly [15]. Ulnar polydactyly has been linked to the Gli-3 transcription factor, an important protein in the signaling pathway of SHH located on chromosome 7 [25–29]. The Gli-3 protein exists in an active form (Gli-3A) and a repressor form (Gli-3R). Gli-3A exists primarily in the posterior mesoderm and displays the same gradient as SHH with decreasing concentrations anteriorly. Gli-3R has the opposite gradient with higher concentrations in the anterior mesoderm and decreasing concentrations posteriorly. Syndromes associated with ulnar polydactyly have been associated with defects in the Gli-3 gene as well as with defective processing of the Gli-3 protein into its active form [15, 28, 30]. The normal balance of Gli-3 is disturbed when there is a relative increase in Gli-3R compared to Gli-3A. It has been proposed that this imbalance contributes to the formation of ulnar polydactyly [15].

Table 21.2 Syndromes associated with ulnar polydactyly [13–16]

Name	Associated anomalies	Inheritance
Ellis-van Creveld syndrome	Dwarfism, short limbs, small chest, dental abnormalities, cardiac defects	Autosomal recessive
Smith-Lemli-Opitz syndrome	Abnormal facies, microcephaly, intellectual disability, cardiac, renal, gastrointestinal, and genital malformations, hypotonia	Autosomal recessive
McKusick-Kaufman syndrome	Genital malformations (hydrometrocolpos), cardiac defects	Autosomal recessive
Trisomy 13/Patau syndrome	Intellectual disability, cardiac defects, brain/spinal cord abnormalities, microophthalmia, cleft lip/palate, hypotonia	Sporadic
Short rib-polydactyly I-III	Small chest, short limbs, cardiac defects, polycystic kidney disease, cardiac, gastrointestinal, and genital abnormalities	Autosomal recessive
Orofaciodigital syndrome	Abnormal facies, oral and dental abnormalities, cleft lip/palate, polycystic kidney disease (type I only)	Type I: X-linked dominant Others: autosomal recessive
Bardet-Biedl syndrome	Visual loss, obesity, intellectual disability, hypogonadism, abnormal facies, cardiac, hepatic, and gastrointestinal abnormalities	Autosomal recessive
Meckel syndrome	Occipital encephalocele, other neural tube defects, polycystic kidney disease, cirrhosis	Autosomal recessive
Greig cephalopolysyndactyly syndrome	Abnormal facies, macrocephaly, intellectual disability, large hallux/thumb	Autosomal dominant
Pallister-Hall syndrome	Brain abnormalities (hypothalamus hamartoma), bifid epiglottis, imperforate anus, renal abnormalities	Autosomal dominant
Weyers acrofacial dysostosis	Dental abnormalities, malformed nails, shortened limbs	Autosomal dominant
Joubert syndrome	Brain abnormalities (molar tooth sign), hypotonia, ataxia, intellectual disability, abnormal facies, retinal dystrophy, renal, hepatic, and endocrine abnormalities	Autosomal recessive, rare X-linked recessive
Simpson-Golabi-Behmel syndrome	Abnormal facies, polythelia, diaphragmatic hernia, umbilical hernia, renal abnormalities, hepatosplenomegaly, intellectual disability, solid-organ malignancy	X-linked dominant
Hydrolethalus syndrome	Abnormal facies, cleft lip/palate, hydrocephalus, brain abnormalities, cardiac defects, airway stenosis, omphalocele	Autosomal recessive
Acrocallosal syndrome	Macrocephaly, corpus callosum agenesis, abnormal facies, cleft lip/palate, cardiac abnormalities	Autosomal recessive
Asphyxiating thoracic dystrophy/Jeune syndrome	Small chest, short ribs, short limbs, pelvic abnormalities, respiratory failure	Autosomal recessive
Focal dermal hypoplasia/ Goltz-Gorlin syndrome	Multiple skin abnormalities, cutaneous papillomas, ocular abnormalities, dental abnormalities, cleft lip/palate	X-linked dominant

Anatomy

Type-B ulnar polydactyly includes rudimentary supernumerary digits that arise from the ulnar border of the small finger (Fig. 21.1). Because these digits lack bony elements and tendons they are nonfunctional. The digits may be as small as a wart-like bump on the ulnar side of the small finger proximal phalanx or may take the form of a somewhat more developed digit with a fibrocartilaginous ossicle and a hypoplastic nail [3, 31]. The small, wart-like bumps, or rudimentary polydactyly, are considered to be remnant stumps from digits that were auto-amputated in-utero [32, 33]. "Pacifier polydactyly" refers to a specific Type-B polydactyly demonstrated by a very large and edematous soft-tissue nubbin that is consistently sucked by the patient [34]. All Type-B supernumerary digits, including rudimentary polydactyly, contain a neurovascular pedicle.

Type-A ulnar polydactyly includes more developed digits with variable anatomy (Fig. 21.2). Type-A digits always contain bony

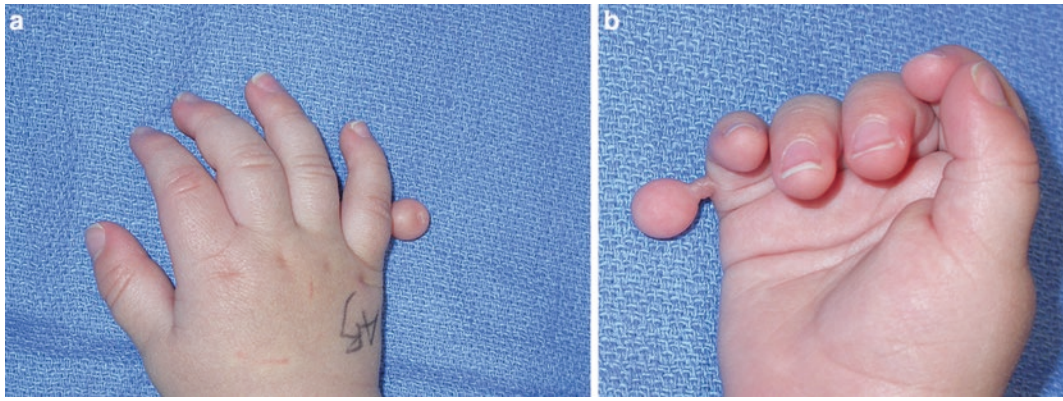

Fig. 21.1 (**a**) Dorsal and (**b**) volar views of a child with Type B ulnar polydactyly demonstrating a large pedunculated mass with a long stalk. There is a rudimentary nail present on dorsal aspect

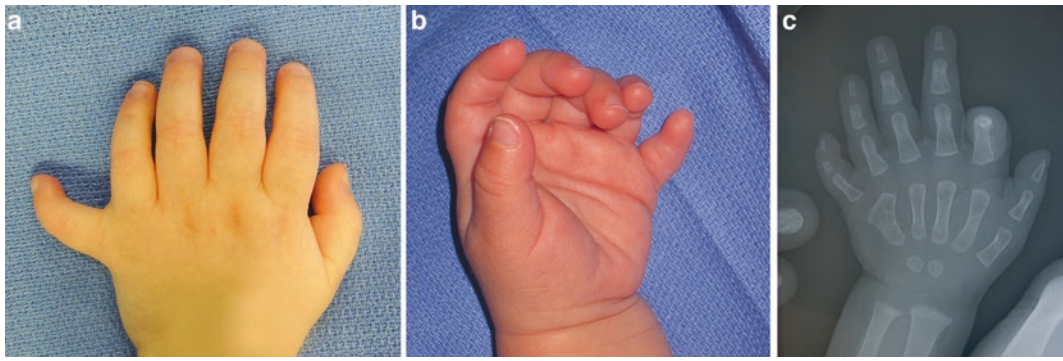

Fig. 21.2 (**a**) Dorsal and (**b**) volar views of a child with Type-A ulnar polydactyly. The extra digit is fully formed with bony elements. There is some ulnar angulation of the digit compared to the adjacent small finger. (**c**) Hand radiographs demonstrate the proximal phalanx of the polydactylous digit is articulating with an abnormally broad metacarpophalangeal joint along the ulnar side of the joint. The joint surface is sloped ulnarly, which explains the angulation of the extra digit

elements and may contain anomalous flexor and extensor tendons including the insertion for the abductor digiti minimi (ADM) and flexor digiti minimi brevis (FDMB) muscles. The interphalangeal joints are often hypoplastic and stiff. Digits that extend to or beyond the metacarpophalangeal (MCP) joint, either with a bifid metacarpal or a duplicated proximal phalanx articulating with a common metacarpal-phalangeal joint, will include the insertion for the ulnar collateral ligament of the metacarpal-phalangeal joint. A sixth metacarpal may include the insertions of the opponens digiti minimi (ODM) and be surrounded by the muscle bellies of the ADM and FDMB muscles. Type-A digits contain digital nerves and arteries.

Diagnosis

Ulnar polydactyly, particularly Type A, may be diagnosed prenatally during routine second trimester ultrasound [16]. Remaining cases of ulnar polydactyly are diagnosed during routine postnatal physical exams. Rudimentary ulnar polydactyly can be diagnosed postnatally by careful examination of the skin on the ulnar border of the hand. Physical examination should focus on elements associated with syndromes that include ulnar polydactyly (see Table 21.2). The exam should include the lower extremities as polydactyly of the foot may also be present [12]. In children with Type-A ulnar polydactyly, anterior-posterior radiographs clarify the bony

anatomy of the ulnar digits. Family history should be reviewed. Referral to a geneticist should be considered in patients with evidence of congenital syndromes or isolated familial ulnar polydactyly. Referral to other pediatric specialists should precede surgical treatment of the ulnar polydactyly.

Treatment

The families of patients with Type-A ulnar polydactyly are often surprised by their child's hand difference. The treatment of ulnar polydactyly is not an emergency. Type-A ulnar polydactyly with a fully formed sixth ray may be functional. The family may opt for surgery to give the hand a more "normal" appearance. In some cultures, ulnar polydactyly is seen as a supernatural trait and individuals with extra digits were often given deferential treatment [35].

Many newborns with Type-B ulnar polydactyly are treated by ligation in the nursery without any hand surgery consultation. Small, pedunculated digits are commonly treated by suture ligation by the nursery staff, pediatricians, obstetricians, and neonatal intensivists. The ischemic digit falls off days to weeks after the suture is applied [3] (Fig. 21.3). Small vascular clips applied to the pedicle of the digit have also been used to cause ischemia of the digit. It has been reported that in untreated patients, the digit may auto-amputate and fall off without intervention [2]. Newborns with more completely developed forms of ulnar polydactyly are usually referred to a hand surgeon [36].

Open excision of Type-B digits in the nursery or office is an alternative to ligation that avoids the distress that some experience observing the necrotic digit [37, 38]. The patient is soothed with a pacifier and the hand anesthetized with local anesthesia. The area is prepped and the supernumerary digit is excised in an elliptical pattern. Nerves are sharply divided. The base of the wound is coagulated using a battery cautery, electrocautery, or topical silver nitrate and closed using simple absorbable suture. Topical antibiotic ointment or Steri-Strips may be applied to the area as a dressing. The area usually heals with a small scar that is rarely problematic.

Because Type-A polydactyly generally requires treatment under general anesthesia surgery is delayed until the child is 6–12 months old. The goal of surgery is to reconstruct an optimal single small finger. Many bone and soft-tissue elements are excised while other elements are retained with the residual small finger. The incision should be designed using a racquet shape around the more ulnar digit, preserving as much skin as possible. The incision can be extended

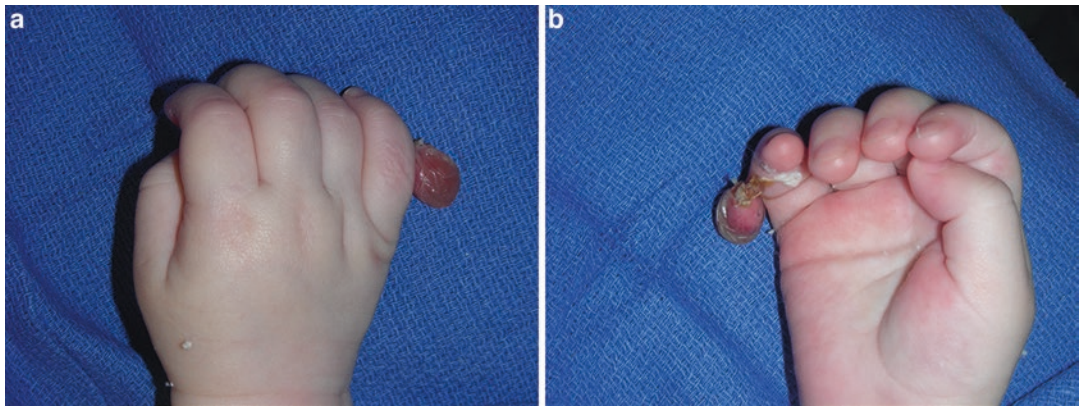

Fig. 21.3 (**a**) Dorsal and (**b**) volar views of a child treated with suture ligation of Type- B ulnar polydactyly. One week after the suture was placed, the digit demonstrates significant edema and necrosis. The stalk can be seen to be separating from the ulnar aspect of the small finger. The digit subsequently fell off and the area went on to heal without complication

proximally in the midlateral line of the finger and hand along the junction of the glabrous and non-glabrous skin. The skin is incised and sharp and blunt dissection is used to expose the bony elements of the digit. The bony elements are isolated from the surrounding subcutaneous tissue. Anomalous flexor and extensor tendons are sharply dissected, incised, and allowed to retract into the hand. The neurovascular bundles to the extra digit are identified. Traction neurectomies are performed on the digital nerves and the arteries are cauterized using bipolar cautery. The skin flaps are trimmed to allow for a linear closure that should lie in the midlateral line. Standing cutaneous deformities ("dog-ears") should be corrected by extending the incision longitudinally or along flexor creases.

Type-A ulnar polydactyly that extends to or proximal to the 5th metacarpal-phalangeal joint deserves special attention. The hypothenar muscles, including the insertion of the ODM and muscle bellies of the ADM and FDMB should be preserved and dissected from the extra metacarpal in the subperiosteal plane. In cases where the polydactyly extends proximal to the metacarpal-phalangeal joint, the ADM insertion on the more ulnar proximal phalanx is preserved with a periosteal sleeve. The ADM insertion is then sutured to the base of the radial-proximal phalanx to assure small finger abduction. If the polydactyly includes two proximal phalanges articulating with the small metacarpal at the MCP joint, the insertion of the ulnar collateral ligament on the base of the extra proximal phalanx should also be preserved with a periosteal sleeve. After excision of the ulnar digit, the ulnar collateral ligament should be transferred to the base of the retained proximal phalanx. When the metacarpal is bifid, osteotomy of the metacarpal creates a more normal contour of the residual small finger metacarpal. Angulation of the metacarpal should be corrected with closing wedge osteotomies and Kirschner wire fixation. The ulnar collateral stability of the reconstructed metacarpal-phalangeal joint of the small finger should be tested. If additional stability is necessary, suture capsulorrhaphy with pin fixation of the MCP joint should be considered. The extrinsic flexor and extensor tendons should be centralized if eccentric.

Complications

Treatment-related complications are more frequent in suture ligation than in surgical excision [2, 39]. First, unless the suture is tied exactly at the base of the pedunculated digit, where it originates from the skin of the small finger, the skin that remains that is proximal to the suture may persist as a visible and palpable bump (Fig. 21.4); this occurs in up to 40% of patients who undergo suture ligation [2, 3]. A neuroma often forms a prominence at the amputation site. Improvement in contour after excision of the residual bump and traction neurectomies of the nerves has been demonstrated by several studies [40–42]. The risk of prominent neuromas and surgical scars are minimized by using a vascular clip rather than a suture or by performing open excision [43, 44]. Additional reported complications associated with suture ligation include bleeding, infection, and necrosis without amputation [2, 41].

Complications from treatment of Type-A ulnar polydactyly are uncommon. Infection, bleeding, and wound healing difficulties have been reported but may be minimized with a well-

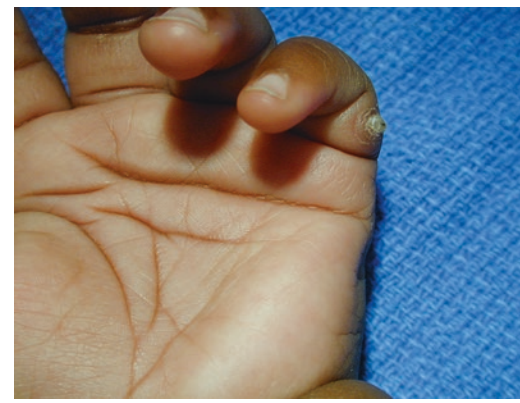

Fig. 21.4 A scar remained on the ulnar aspect of the small finger after suture ligation of Type-B ulnar polydactyly. This area may be painful and contain a neuroma. Surgical correction including re-excision and traction neurectomies should be considered in patients who have problematic scars after suture ligation

planned and executed operation [2, 45]. Reconstruction of ulnar polydactyly tends to less often result in symptomatic joint instability or stiffness compared to radial polydactyly. Nonetheless, cases with postoperative prominence of small finger- metacarpal head, instability of the metacarpal-phalangeal joint, and intrinsic tightness have been reported [46].

Ulnar Dimelia

Ulnar dimelia is a rare form of duplication in which the ulnar side of the forearm, wrist, and hand is represented on both the preaxial as well as postaxial side of the limb. As with ulnar polydactyly, the condition is a result of abnormal differentiation along the anterior-posterior axis of the developing limb bud. Ulnar dimelia is included in the IFSSH *Class III/Duplication* category [4]. The condition is classified as Class 1A2*Malformations/Failure of Axis of Formation of Entire Upper Limb Anterioposterior Axis* using the modified OMT Classification [5].

Classification

Most commonly, ulnar dimelia is characterized by duplication of the ulna, absence of the radius, absence of the thumb, and seven or eight digits symmetric about the midline. Because each patient demonstrates unique anatomic structural variations, a spectrum of mirror hand-multiple hand anomalies has been suggested [47]. A classification system of ulnar dimelia limbs is shown in Table 21.3. Type 1A is the most common form while the others (Type 1B-Type 5) are exceedingly rare [47].

Table 21.3 Classification for mirror hand-multiple hand spectrum

Type	Name	Description
1A	Ulnar dimelia	Multiple fingers with two well-formed ulnae
1B	Ulnar dimelia	Multiple fingers with well-formed medial ulna, lateral ulna is hypoplastic
2	Intermediate type	Multiple fingers with two ulnae and a radius. Central ulna is vestigial [66]
3A	Intermediate type	Multiple fingers with one ulna and well-formed radius
3B	Intermediate type	Multiple fingers with one ulna and a hypoplastic radius
4A	Laurin-Sandrow syndrome	Bilateral multiple fingers, with two ulnae, complex syndactyly, multiple toes, nasal deformities
4B	Martin syndrome	Bilateral multiple fingers with a radius and an ulna, complex syndactyly, multiple toes, nasal deformities
5	Multiple hand	Complete hand duplication including thumb with normal forearm anatomy

Adapted from Al-Qattan et al. [47], Copyright 1998, with permission from Elsevier

Epidemiology

Ulnar dimelia is one of the most rare forms of upper extremity congenital difference. Most cases have been detailed as isolated reports or series with just over 60 cases reported in the literature [48]. Although ulnar dimelia is usually sporadic and unilateral [49–60], it is a component of autosomal-dominant syndromes including Laurin-Sandrow and Martin syndromes [47, 61–63].

Pathogenesis

The exact mechanism leading to ulnar dimelia has yet to be discovered. It is recognized that the ZPA is critical to defining the anterior-posterior axis of the developing limb bud; errors in differentiation of the ZPA are theorized to be important to the etiology of ulnar dimelia [64]. Several genes have been identified that result in atypical mirror hand (Type 3A/B) in animals including TWIST1, ALX4, and GLI-3 [65]. These genes can be associated with an abnormal increase in SHH activity on the anterior aspect of the limb bone leading to hypoplasia of the radius. Classic Type 1A ulnar dimelia may be a result of an error in the prepatterning stage of limb development and may involve abnormal expression of the genes HOXB8, GLI-3, HAND2 [65]. Type 4 is

most likely related to gene mutations in SHH while Type 5 may represent a true duplication of the ZPA [47].

Anatomy

The anatomy of ulnar dimelia is highly variable. The abnormality involves the entire upper extremity. Because the radius is absent, typical descriptions of anatomic structures should not be based on their location on the "radial" or "ulnar" sides of the forearm or hand. Instead, structures may be designated by their position on the medial (postaxial) or lateral (preaxial) side of the extremity when the limb is imagined in an anatomic position of supination.

Proximal elements of the arm may be abnormal including the scapula, clavicle, humerus, and glenohumeral joint [52, 54, 56]. The distal humerus articulates with both ulnas. The lateral aspect of the distal humerus exhibits a hypoplastic capitellum, which often resembles a poorly formed trochlea. The biceps and triceps may be underdeveloped or represented by fibrous bands [56, 66, 67]. The biceps may abnormally insert onto the distal humerus [68].

The forearm contains two parallel ulnae like bones that are rotated from 70° to 180° to each other [60, 69]. The proximal portion of the lateral ulna often contains a broad articulation, not unlike an olecranon [67]. However, since it is malrotated in the plane of the lateral hypoplastic trochlea, elbow motion is limited. The elbow is typically extended with a variable arc of passive and active flexion. Distally, the articular surfaces of the lateral or both ulnae are broad and often resemble the articular surface of a distal radius [51, 60, 67]. The absence of a proximal or distal radioulnar joint and the inability of the medial ulna to rotate result in negligible pronation or supination between the two forearm bones.

In the forearm, flexor muscles tend to originate from both proximal ulnae. The medial musculature tends to be more developed with a normal appearing flexor carpi ulnaris. The lateral wrist flexor may be absent or abnormally insert into the wrist capsule [66]. The wrist is typically flexed and deviated to either the medial or the lateral side. The presence of pronator teres and pronator quadratus have been described [66]. The flexor digitorum superficialis (FDS) and flexor digitorum profundus (FDP) may have common muscle bellies and have variable origins on the forearm bones. The FDS and FDP tendons are often present in each digit, though adjacent digits may share a common, bifurcated tendon. Function of the digital flexors can be highly variable and the proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints are often stiff [52]. The extensor tendons are thin and may be duplicated to the central digit. Often the wrist and finger extensor muscles are absent with tendons that do not extend proximal to the wrist [66].

The carpus is symmetric with duplication of the ulnar elements including two pisiforms, two triquetrums, and two hamates. The central lunate or capitate may be fused or separate [51, 52, 70]. The scaphoid and trapezium are absent. A hypoplastic trapezoid may be present at the distal aspect of the carpus articulating with the distal capitate and central metacarpals [52, 66]. The ulnocarpal joint is narrow and incongruent. The carpus may form a fibrous pseudoarthrosis in a volarly subluxed and flexed position [66].

The hand is broad and flat with absent thenar and hypothenar contours. Seven or eight digits may be arranged in separate clusters on the medial and lateral aspect of the hand. Each digit may have an individual metacarpal or two adjacent digits may share a metacarpal. The metacarpals lack the normal cascade and are aligned in a single plane from medial to lateral. The fourth-most medial digit is often the longest digit. Digits are usually triphalangeal though biphalangeal digits have been reported [59, 68]. Syndactyly and clinodactyly may be present [52, 54, 56, 59]. Finger flexion is usually limited due to stiffness of the PIP and DIP joints. Intrinsic muscle function may be poor.

A large medial ulnar nerve innervates the more medial one and a half digits, like a normal ulnar nerve. An additional lateral ulnar nerve with an accompanying artery supplies the more lateral digits, or the sensory branch of the radial nerve may innervate them. The median nerve supplies the central digits although it may

bifurcate in the forearm [66]. Electromyography demonstrates substantial cross innervation of the intrinsic muscles from both medial and lateral nerves to the median nerve [69].

The arterial anatomy of the ulnar dimelia hand is variable. The arterial anatomy may be asymmetric within the hand with a dominant medial ulnar artery supplying the majority of the digits. A smaller lateral artery perfused only the lateral two and a half of the seven digits in one-studied hand. Another description demonstrated a large medial ulnar artery and a central median artery without a lateral vessel [66]. This asymmetry is interesting given the relative symmetry of bone and other soft-tissue elements in ulnar dimelia. The arteries do not seem to communicate in a superficial arch, though a deep communication may be present [51, 66, 67]. Anomalies in the common digital arteries have also been described [71].

Diagnosis

Due to the distinctly abnormal appearance of the limb with ulnar dimelia, the clinical diagnosis is relatively straightforward and can often be established by prenatal ultrasound.

Treatment

Ulnar dimelia is so uncommon, that most hand surgeons will not encounter a single case in their practices. Hand and upper extremity surgeons should recognize the characteristic anatomic features of ulnar dimelia. Treatment begins with family counseling. They should be educated on the sporadic nature of ulnar dimelia though a brief family history should be included to ensure a syndromic form is not present.

A full physical exam including a comprehensive assessment of the upper extremity needs to be performed. Shoulder abnormalities are frequent in children with ulnar dimelia. All joints from the shoulder to the fingertip should be assessed for passive and active range of motion. Treatment should be designed to facilitate positioning of the hand in space, to normalize the appearance of the hand, and to maximize hand function. Thus, close observation of the child in the outpatient office is essential to understand the native function of the upper extremity. Video assessments may also be of benefit. The parents often have insight into the child's successes and struggles with specific activities and should be encouraged to share their experiences. Repeat physical examinations may be necessary to accurately characterize the specific deficiencies present in a patient with ulnar dimelia [57].

Standard radiographs to include the hand, wrist, forearm, elbow, and shoulder will help delineate the bony and joint anatomy of the involved extremity. Large areas of unossified cartilage about the elbow make definition of pathologic elbow anatomy difficult in the very young child. Syndromic patients should have consultation with appropriate pediatric subspecialists and genetic counselors.

Initial treatment should be designed to improve the wrist and elbow position and digital range of motion [51]. Passive range of motion with stretching and splinting should be initiated to maximize passive joint motion. Once motion gain has plateaued with therapy, surgical reconstruction should be considered.

There are several reasons to consider operative treatment for ulnar dimelia. The elbow often lacks active or passive flexion making hand-to-mouth feeding activities impossible. The wrist is fixed in flexion and lacks active extension. The fingers, particularly the lateral digits, are usually stiff, resulting in weak flexor function. Though the hand lacks traditional thumb opposition, the lateral cluster of digits are pronated in relation to the medial digits, allowing some large object-grasping activities. Finally, the unusual appearance of the mirror hand with seven or eight digits and absent thumb attracts unwanted curious attention resulting in social challenges for the child.

Surgical treatment of the elbow aims to improve elbow flexion. The proximal portion of the lateral ulna abuts against the dysplastic distal humerus and blocks elbow and forearm motion. The biceps is often replaced with a fibrous cord. When passive motion is present, active motion depends upon the forearm flexor muscles. Several procedures have been described to improve elbow flexion. Subperiosteal resection of the

proximal portion of the lateral ulna may permit the medial forearm to flex and extend at the residual-medial ulnotrochlear joint [68, 72] (Figs. 21.5 and 21.6). Others studies have shown modest improvement in supination and pronation with excision of the proximal lateral ulna [71]. The child should be monitored closely since regrowth of the proximal ulna may recreate the bony block [52]. Repeat resection should be undertaken and should include resection of the anterior distal humerus [68, 71]. Reconstruction of the lateral-collateral ligament of the elbow may be necessary. Tendon transfer of the pectoralis major muscle for elbow flexion should be considered in patients with good-passive but poor-active elbow range of motion [69]. It is essential to preoperatively confirm function of the pectoralis prior to transfer since many patients with ulnar dimelia have hypoplasia of chest musculature. If an abnormal insertion of the biceps tendon onto the distal humerus is detected, transfer of the biceps insertion to the anterior forearm may also be of benefit [68]. If the forearm is positioned in an extreme of pronation or supination, rotational osteotomy of the one or both ulnae may bring the hand into neutral rotation or a slightly pronated position. Resecting the lateral proximal ulna may also provide improved radioulnar joint motion [73].

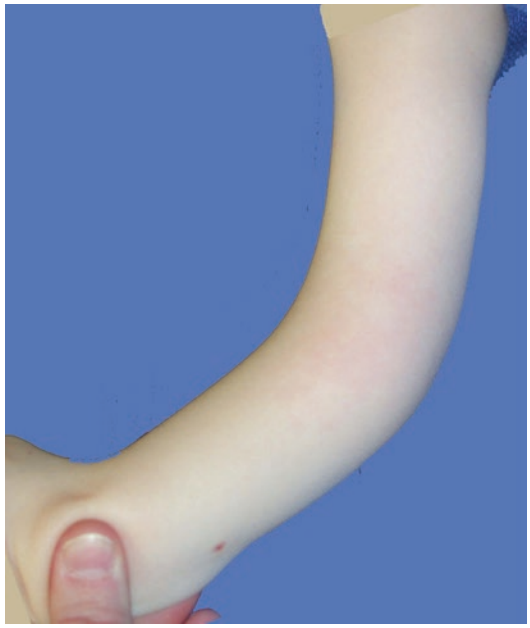

Fig. 21.5 Preoperative view of a child with ulnar dimelia with incomplete elbow flexion. The hand is to the left of the picture. Passive and active flexion of the elbow was limited to approximately 30°

Surgery of the wrist is designed to address the flexed and deviated posture of the hand and establish active wrist extension. Procedures to

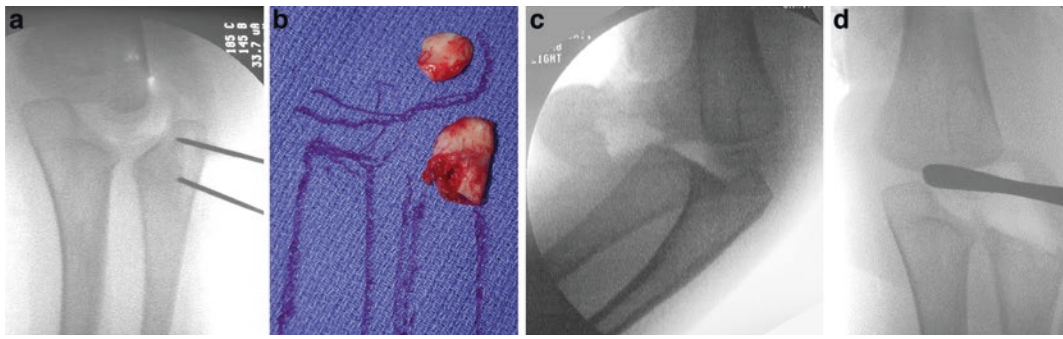

Fig. 21.6 Intraoperative views of the corrective surgery to improve elbow flexion. (**a**) Anterior fluoroscopic images of the abnormal elbow joint with two ulnae articulating with the humerus. The proximal aspect of the lateral ulna is blocking motion. Two Kirschner wires have been placed in the proximal lateral ulna designating the area to be resected. Subperiosteal dissection was used to expose this portion of the lateral ulna. After resection of this portion of the lateral ulna, full flexion was still restricted by an anterior projection from the articular surface of the hypoplastic capitellum. This was similarly excised. (**b**) The bony fragments removed demonstrating their relationship to the surrounding joint. (**c**) Anterior and (**d**) lateral fluoroscopic images of the elbow joint after excision of the proximal lateral ulna and portion of the capitellum. Full passive elbow flexion was achieved at the completion of the bony excision

release the flexion deformity and to augment wrist extension include palmar skin z-plasty, fractional lengthening of the flexor carpi ulnaris tendons, volar capsulotomy, dorsal capsule plication, extensor tendon shortening, and proximal row carpectomy [68, 72]. Tendon transfer can confer active extension of the wrist. The transfer may be inserted into the extensor carpi radialis, if present, or directly into the second metacarpal. Donor motors include the flexor carpi ulnaris or residual flexor or extensor tendons from amputated fingers during digital reduction surgery [51, 54, 59, 68, 72]. Though wrist arthrodesis can help position the wrist and improve grip strength, it should be reserved for extreme cases not amenable to contracture release and tendon transfers [48].

The abnormal appearance of the seven- or eight-digit hand should be considered. The goals of hand reconstruction should include reduction in the number of digits to create a five-digit hand that includes an opposable digit in the thumb position.

The medial four digits are retained and will serve as the index through small fingers. The fourth-most medial digit (index) is not shorter than the third-most medial digit (middle finger) but rather is the longest of the fingers, creating a somewhat abnormal appearance. The lateral cluster of three or four digits should be reduced to a single digit taking the role and position of a thumb. Determining which digit should be retained and which digits should be deleted requires careful examination of joint mobility and observation of the child at play to determine which fingers are most readily reconstructed to function as a thumb.

The amputation of two fingers in a seven-digit hand or of three fingers in an eight-digit hand normalizes the number of digits (Figs. 21.7, 21.8, and 21.9).

Early techniques for thumb reconstruction involved merely amputating the redundant digits and leaving one to function as the thumb [52, 54, 55, 57]. Because the lateral cluster of digits are often pronated compared to the medial cluster, the retained digit was often adequately positioned to allow for opposition. Splinting the reconstructed thumb in abduction can improve the position [54]. Another technique involved creating a syndactyly between two of the lateral digits to make a broad and strong thumb [56, 74].

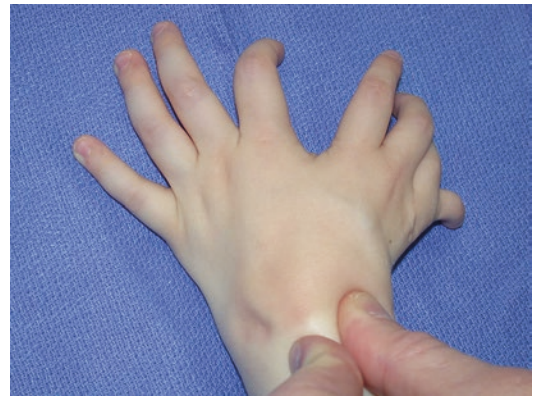

Fig. 21.7 Mirror hand with eight digits divided into two clusters. The lateral cluster is separated from the medial cluster by a central web and is slightly pronated in comparison to the remainder of the hand

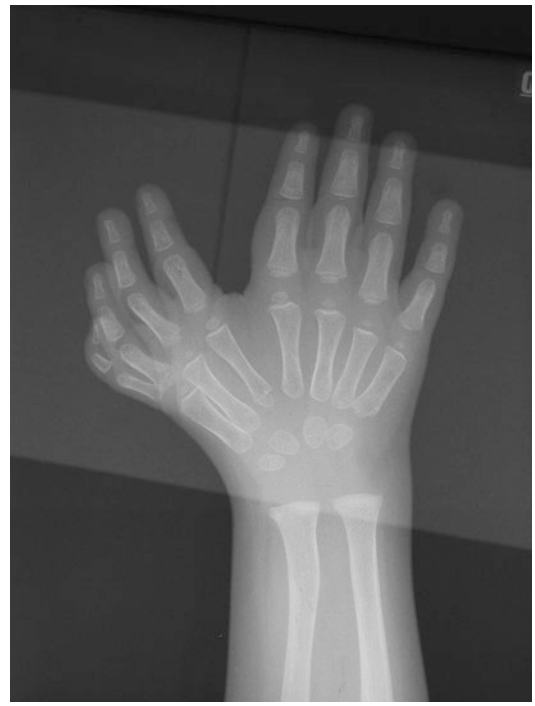

Fig. 21.8 Anterior-posterior radiograph of the hand demonstrating seven metacarpals and eight phalanges. The most lateral two digits articulate with a common metacarpal. Two capitates and two hamates are present at the carpal level. The distal articular surfaces of the medial and lateral ulna are broad like the articular surface of a normal radius

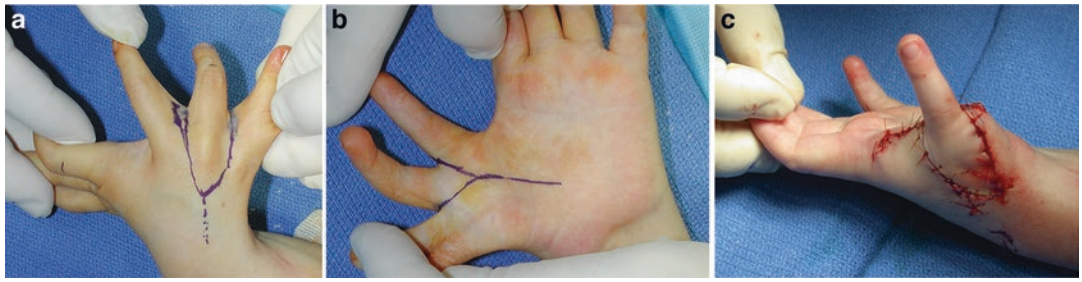

Fig. 21.9 After clinical evaluation of the child, the third-most lateral digit was chosen for pollicization. (**a**) Dorsal and (**b**) volar views of the racquet incision used to isolate the pollicized digit. The remaining digits were amputated. (**c**) View of the completed pollicization. The digit is shorter and better positioned to function as a thumb. The remaining skin was used to create a first webspace and resurface the pollicized digit

Other authors have described a two-stage technique with the reconstruction beginning with reduction to a five-fingered hand and using redundant skin and subcutaneous tissue to resurface the first webspace [51]. The second stage involved rotational and shortening osteotomy of the metacarpal of the preserved lateral digit to a position that provides opposition with the medial cluster of digits. Some authors still recommend this technique with adequate long-term results [72]. The advantage of this technique is that it is simple and carries a low risk of vascular compromise. However, the reconstructed thumb will be triphalangeal and may appear too long compared to the contralateral thumb.

Pollicization of one of the lateral digits in the hand with ulnar dimelia is usually elected [50, 59, 68–71, 75]. Though many digits and many musculotendinous units are available for this reconstruction, pollicization in these hands remains challenging. Some differences between pollicization in ulnar dimelia and pollicization in thumb hypoplasia should be mentioned. Amputation of the redundant digits should be designed to preserve sufficient skin to resurface the new first webspace between the retained digit and the index finger. A modified pollicization of the retained digit repositions it in palmar abduction and pronation. Neurovascular structures are dissected free to allow digital repositioning. The blood supply of the retained digit should be carefully defined since aberrant arterial anatomy has been described in ulnar dimelia [71]. In most pollicization procedures, the majority of the metacarpal of the pollicized digit is resected. In ulnar dimelia pollicization, the extent of metacarpal resection depends upon the relationship of the pollicized digit to the adjacent index finger. The anchorage of the metacarpal head facilitates appropriate positioning of the digit relative to the medial fingers. Intrinsic muscles are sutured to the pollicized digit to further balance its position. After removal of the skeletal elements of the deleted digits, the surgeon will identify numerous redundant flexor and extensor tendons. While it is possible to use these tendons to augment wrist extension or opposition, it should be recognized that many of the tendons of the lateral digits have a common muscle belly [71]. One must assure that the excursion of the extrinsic flexor and extensor tendons to the pollicized digit is not compromised by tendon transfer of another tendon from the common muscle belly.

Preoperative modeling, three-dimensional printing, and simulation surgery may assist with surgical planning [76]. An excellent review of pollicization in ulnar dimelia should be reviewed for additional technical details of this procedure [71].

Complications

Reconstruction of the upper extremity in patients with ulnar dimelia results in a more normal appearance. Though there is seemingly an abundance of tissue, these procedures are challenging since the soft tissues are often dysplastic and

stiff. Complications may occur. Even following surgical release of the elbow with excision of the proximal lateral ulna, stiffness may occur with regrowth of the bone. Vascular compromise of a pollicized digit has been reported but may be avoided if arterial anomalies are recognized prior to digit transposition [77]. The reconstructed thumb may be either too long or too short and opposition may be weak necessitating further tendon transfer.

References

1. Al-Qattan MM, Kozin SH. Update on embryology of the upper limb. J Hand Surg Am. 2013;38(9):1835–44.
2. Rayan GM, Frey B. Ulnar polydactyly. Plast Reconstr Surg. 2001;107(6):1449–54; discussion 55–7.
3. Watson BT, Hennrikus WL. Postaxial type-B polydactyly. Prevalence and treatment. J Bone Joint Surg Am. 1997;79(1):65–8.
4. Swanson AB, Swanson GD, Tada K. A classification for congenital limb malformation. J Hand Surg Am. 1983;8(5 Pt 2):693–702.
5. Tonkin MA, Tolerton SK, Quick TJ, Harvey I, Lawson RD, Smith NC, et al. Classification of congenital anomalies of the hand and upper limb: development and assessment of a new system. J Hand Surg Am. 2013;38(9):1845–53.
6. Temtamy SA, McKusick VA. Synopsis of hand malformations with particular emphasis on genetic factors. Birth Defects. 1969;3:125–84.
7. Stelling F. The upper extremity. Orthopedic surgery in infancy and childhood. Baltimore: Williams & Wilkins; 1963. p. 304–8.
8. Pritsch T, Ezaki M, Mills J, Oishi SN. Type A ulnar polydactyly of the hand: a classification system and clinical series. J Hand Surg Am. 2013;38(3):453–8.
9. Buck-Gramcko D, Behrens P. [Classification of polydactyly of the hand and foot]. Handchir Mikrochir Plast Chir. 1989;21(4):195–204.
10. Al-Qattan MM, Al-Shanawani B, Al-Thunayan A, Al-Namla A. The clinical features of ulnar polydactyly in a middle eastern population. J Hand Surg Eur Vol. 2008;33(1):47–52.
11. Castilla EE, da Graca Dutra M, Lugarinho da Fonseca R, Paz JE. Hand and foot postaxial polydactyly: two different traits. Am J Med Genet. 1997;73(1):48–54.
12. Holmes LB, Nasri H, Hunt AT, Toufaily MH, Westgate MN. Polydactyly, postaxial, type B. Birth Defects Res. 2018;110(2):134–41.
13. Simmons BP. Polydactyly. Hand Clin. 1985;1(3):545–65.
14. Umm e K, Basit S, Kamran-ul-Hassan Naqvi S, Ansar M, Ahmad W. Genetic mapping of an autosomal recessive postaxial polydactyly type A to chromosome 13q13.3-q21.2 and screening of the candidate genes. Hum Genet. 2012;131(3):415–22.
15. Al-Qattan MM, Al-Motairi MI. The pathogenesis of ulnar polydactyly in humans. J Hand Surg Eur Vol. 2013;38(9):934–9.
16. Bromley B, Shipp TD, Benacerraf B. Isolated polydactyly: prenatal diagnosis and perinatal outcome. Prenat Diagn. 2000;20(11):905–8.
17. Castilla EE, Lugarinho R, da Graca Dutra M, Salgado LJ. Associated anomalies in individuals with polydactyly. Am J Med Genet. 1998;80(5):459–65.
18. Galjaard RJ, Smits AP, Tuerlings JH, Bais AG, Bertoli Avella AM, Breedveld G, et al. A new locus for postaxial polydactyly type A/B on chromosome 7q21-q34. Eur J Hum Genet. 2003;11(5):409–15.
19. Galjaard RJ, van der Linde HC, Eussen BH, de Vries BB, Wouters CH, Oostra BA, et al. Isolated postaxial polydactyly type B with mosaicism of a submicroscopic unbalanced translocation leading to an extended phenotype in offspring. Am J Med Genet A. 2003;121a(2):168–73.
20. Radhakrishna U, Blouin JL, Mehenni H, Patel UC, Patel MN, Solanki JV, et al. Mapping one form of autosomal dominant postaxial polydactyly type A to chromosome 7p15-q11.23 by linkage analysis. Am J Hum Genet. 1997;60(3):597–604.
21. Radhakrishna U, Wild A, Grzeschik KH, Antonarakis SE. Mutation in GLI3 in postaxial polydactyly type A. Nat Genet. 1997;17(3):269–71.
22. Zhao H, Tian Y, Breedveld G, Huang S, Zou Y, Y J, et al. Postaxial polydactyly type A/B (PAP-A/B) is linked to chromosome 19p13.1-13.2 in a Chinese kindred. Eur J Hum Genet. 2002;10(3):162–6.
23. Zguricas J, Heutink P, Heredero L, Deurloo J, Oostra BA, Snijders PJ, et al. Genetic aspects of polydactyly. Handchir Mikrochir Plast Chir. 1996;28(4):171–5.
24. Man LX, Chang B. Maternal cigarette smoking during pregnancy increases the risk of having a child with a congenital digital anomaly. Plast Reconstr Surg. 2006;117(1):301–8.
25. Daluiski A, Yi SE, Lyons KM. The molecular control of upper extremity development: implications for congenital hand anomalies. J Hand Surg Am. 2001;26(1):8–22.
26. Ni F, Han G, Guo R, Cui H, Wang B, Li Q. A novel frameshift mutation of GLI3 causes isolated postaxial polydactyly. Ann Plast Surg. 2019;82(5):570–3.
27. Palencia-Campos A, Martinez-Fernandez ML, Altunoglu U, Soto-Bielicka P, Torres A, Marin P, et al. Heterozygous pathogenic variants in GLI1 are a common finding in isolated postaxial polydactyly A/B. Hum Mutat. 2020;41(1):265–76.
28. Al-Qattan MM, Shamseldin HE, Salih MA, Alkuraya FS. GLI3-related polydactyly: a review. Clin Genet. 2017;92(5):457–66.
29. Verma PK, El-Harouni AA. Review of literature: genes related to postaxial polydactyly. Front Pediatr. 2015;3:8.
30. Al-Qattan MM. A novel frameshift mutation of the GLI3 gene in a family with broad thumbs with/without

big toes, postaxial polydactyly and variable syndactyly of the hands/feet. Clin Genet. 2012;82(5):502–4.
31. Hare PJ. Rudimentary polydactyly. Br J Dermatol. 1954;66(11):402–8.
32. Shapiro L, Juhlin EA, Brownstein MH. "Rudimentary polydactyly": an amputation neuroma. Arch Dermatol. 1973;108(2):223–5.
33. Kitayama Y, Tsukada S, Ishikura N, Ide Y, Kojima M. Rudimentary polydactyly: report of five cases. J Hand Surg Am. 1985;10(3):382–5.
34. Kanter WR, Upton J. "Pacifier polydactyly": a transitional form between pedunculated polydactyly and rudimentary polydactyly. Plast Reconstr Surg. 1989;84(1):136–9.
35. Wrobel GD, Helmke C, Nash L, Awe JJ. Polydactyly and the Maya: a review and a case from the site of Peligroso, upper Macal River Valley, Belize. Anc Mesoam. 2012;23:131–42.
36. Dodd JK, Jones PM, Chinn DJ, Potokar T, Laing H. Neonatal accessory digits: a survey of practice amongst paediatricians and hand surgeons in the United Kingdom. Acta Paediatr (Oslo, Norway: 1992.). 2004;93(2):200–4.
37. Comer GC, Potter M, Ladd AL. Polydactyly of the hand. J Am Acad Orthop Surg. 2018;26(3):75–82.
38. Carpenter CL, Cuellar TA, Friel MT. Office-based post-axial polydactyly excision in neonates, infants, and children. Plast Reconstr Surg. 2016;137(2):564–8.
39. Chopan M, Sayadi L, Chim H, Buchanan PJ. To tie or not to tie: a systematic review of postaxial polydactyly and outcomes of suture ligation versus surgical excision. Hand (New York, NY). 2018:1558944718810885.
40. Heras L, Barco J, Cohen A. Unusual complication of ligation of rudimentary ulnar digit. J Hand Surg Br. 1999;24(6):750–1.
41. Patillo D, Rayan GM. Complications of suture ligation ablation for ulnar polydactyly: a report of two cases. Hand (New York, NY). 2011;6(1):102–5.
42. Mullick S, Borschel GH. A selective approach to treatment of ulnar polydactyly: preventing painful neuroma and incomplete excision. Pediatr Dermatol. 2010;27(1):39–42.
43. Leber GE, Gosain AK. Surgical excision of pedunculated supernumerary digits prevents traumatic amputation neuromas. Pediatr Dermatol. 2003;20(2):108–12.
44. Mills JK, Ezaki M, Oishi SN. Ulnar polydactyly: long-term outcomes and cost-effectiveness of surgical clip application in the newborn. Clin Pediatr. 2014;53(5):470–3.
45. Taghinia AH, Upton J. Polydactyly. In: Weiss AC, editor. Textbook of hand and upper extremity surgery. Chicago: American Society for Surgery of the Hand; 2013. p. 1006–16.
46. Light TR, Buck-Gramcko D. Ulnar polydactyly. In: Buck-Gramcko D, editor. Congenital malformations of the hand and forearm. London: Churchill-Livingstone; 1998. p. 265–9.
47. Al-Qattan MM, Al-Thunayan A, De Cordier M, Nandagopal N, Pitkanen J. Classification of the mirror hand-multiple hand spectrum. J Hand Surg Br. 1998;23(4):534–6.
48. Chinegwundoh JO, Gupta M, Scott WA. Ulnar dimelia. Is it a true duplication of the ulna? J Hand Surg Br. 1997;22(1):77–9.
49. Burman M. An historical perspective of double hands and double feet. The survey of the cases reported in the 16th and 17th centuries. Bull Hosp Joint Dis. 1968;29(2):241–54.
50. Gropper PT. Ulnar dimelia. J Hand Surg Am. 1983;8(4):487–91.
51. Gorriz G. Ulnar dimelia--a limb without anteroposterior differentiation. J Hand Surg Am. 1982;7(5):466–9.
52. Harrison RG, Pearson MA, Roaf R. Ulnar dimelia. J Bone Joint Surg Br. 1960;42-b:549–55.
53. Hinojosa JF, Lascombes P, Prevot J. [Cubital dimelia. Apropos of a case with review of the literature]. Chirurg Pediatr. 1988;29(1):52–4.
54. Pintilie D, Hatmanu D, Olaru I, Panoza G. Double ulna with symmetrical polydactyly. Case report. J Bone Joint Surg Br. 1964;46:89–93.
55. Lichtblau PO. Mirror hand: one stage reconstruction. Orthop Rev. 1981;10(12):77–80.
56. Davis RG, Farmer AW. Mirror hand anomaly; a case presentation. Plast Reconstr Surg Transplant Bull. 1958;21(1):80–3.
57. Kelley JW. Mirror hand. Plast Reconstr Surg Transplant Bull. 1962;30:374–7.
58. Afshar A. Ulnar dimelia without duplicated arterial anatomy. J Bone Joint Surg Br. 2010;92(2):293–6.
59. Yang SS, Jackson L, Green DW, Weiland AJ. A rare variant of mirror hand: a case report. J Hand Surg Am. 1996;21(6):1048–51.
60. Jameel J, Khan AQ, Ahmad S, Abbas M. Ulnar dimelia variant: a case report. J Orthop Traumatol. 2011;12(3):163–5.
61. Laurin CA, Favreau JC, Labelle P. Bilateral absence of the radius and tibia with bilateral reduplication of the ulna and fibula. A case report. J Bone Joint Surg Am. 1964;46:137–42.
62. Sandrow RE, Sullivan PD, Steel HH. Hereditary ulnar and fibular dimelia with peculiar facies. A case report. J Bone Joint Surg Am. 1970;52(2):367–70.
63. Martin RA, Jones MC, Jones KL. Mirror hands and feet with a distinct nasal defect, an autosomal dominant condition. Am J Med Genet. 1993;46(2):129–31.
64. Tickle C, Towers M. Sonic hedgehog signaling in limb development. Front Cell Dev Biol. 2017;5:14.
65. Al-Qattan MM. Preaxial polydactyly of the upper limb viewed as a spectrum of severity of embryonic events. Ann Plast Surg. 2013;71(1):118–24.
66. Barton NJ, Buck-Gramcko D, Evans DM. Soft-tissue anatomy of mirror hand. J Hand Surg Br. 1986;11(3):307–19.
67. Askari M, Christensen KN, Heath S, Moran SL, Lachman N. Presentation of soft tissue anatomy of mirror hand: an anatomical case report with implications for surgical planning. Surg Radiol Anat. 2016;38(7):855–62.

68. Tsuyuguchi Y, Tada K, Yonenobu K. Mirror hand anomaly: reconstruction of the thumb, wrist, forearm, and elbow. Plast Reconstr Surg. 1982;70(3):384–7.
69. Harpf C, Hussl H. A case of mirror hand deformity with a 17-year postoperative follow up. Case report. Scand J Plast Reconstr Surg Hand Surg. 1999;33(3):329–33.
70. Tomaszewski R, Bulandra A. Ulnar dimelia-diagnosis and management of a rare congenital anomaly of the upper limb. J Orthop. 2015;12(Suppl 1):S121–4.
71. Barton NJ, Buck-Gramcko D, Evans DM, Kleinert H, Semple C, Ulson H. Mirror hand treated by true pollicization. J Hand Surg Br. 1986;11(3):320–36.
72. Al-Qattan MM, Al-Kahtani AR, Al-Sharif EM, Al-Otaibi NJ. Thumb reconstruction without formal pollicization in mirror hand deformity: a series of four cases. J Hand Surg Eur Vol. 2013;38(9):940–7.
73. Takagi T, Seki A, Takayama S. Elbow and forearm reconstruction in patients with ulnar dimelia can improve activities of daily living. J Shoulder Elb Surg. 2014;23(3):e68–72.
74. Bocca M, Ferraris E, Boccardo E. Polydactyly: the creation of a functional thumb in cases of mirror hand. Panminerva Med. 1968;10(4):164–70.
75. Gaba S, John N, Bhogesha S, Singh O, Vemula GK. Mirror hand: an uncommon neglected case managed with pollicisation. World J Plast Surg. 2017;6(2):263–5.
76. Podolsky DJ, Borschel GH. Preoperative modeling for mirror hand: simplifying a difficult problem using 3-dimensional printing and simulation. Plast Reconstr Surg Glob Open. 2019;7(1):e1929.
77. Pilkington S, Hearth M, Richards AM, Hobby JA. Laurin-Sandrow syndrome – a surgical challenge. Br J Plast Surg. 2000;53(1):68–70.

Part V

Overgrowth, Amniotic Band, and Generalized Anomalies

Macrodactyly

22

Joseph Hardwicke, Janak Ashwin Bechar, and Ruth Lester

Definition

Macrodactyly (Greek *makros*, large, and *daktylos*, digit) is a descriptive term for a congenital malformation consisting of a significant increase in the length and girth of most or all of a digit compared to its contralateral digit (if unaffected), or compared to what would be expected for age/body build. The increased girth is accompanied by an increase in the dorsoventral dimension and the lateral dimension of the digit [1]. The phalanges, tendons, nerves, vessels, subcutaneous fat, nails, and skin can all be enlarged [2].

The condition may present in an isolated digit, or multiple digits, and be unilateral or bilateral, symmetric or asymmetric, and simultaneously affect both hands and feet [3]. Previous terminologies that have been used to describe this condition include *megalodactyly*, *pachydactyly*, *gigantomegaly, dactylomegaly, digital gigantism, macrodactylia fibrolipomatosis, macrodystrophia lipomatosa,* and *local gigantism* [1, 4–6], with the last two terms usually referring to enlargement extending beyond the digit to involve more proximal structures. With even more proximal extension of overgrowth, macrodactyly can be seen as digital involvement in cases of hemihypertophy. Disappointingly, descriptors such as *banana fingers* [7] and *monstrous* [8] have been linked to this condition.

Other authors reserve the term *macrodactyly* for non-syndromic, congenital enlargement of a digit or digits that occurs in isolation without associated limb hemihypertrophy or vascular anomaly [4]. For the purposes of this chapter, *macrodactyly* will be used to describe subjective congenital digital enlargement of all causation, which may present at birth, or after, and in isolation, or in association with other signs or syndrome, sometimes referred to as *pseudomacrodactyly* [9]. It is our opinion that to limit this review to non-syndromic cases, or cases that do not extend beyond the digit or digits, will impact on the appreciation of the multidisciplinary management of the more complex cases. Although the majority of patients will present with isolated macrodactyly, a surgeon in a center treating such patients must be prepared to apply principles learned from these to all cases of enlarged digits.

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History

The English philosopher and physician John Locke (1632–1704) may have been the first to describe a case of macrodactyly in his medical journals from 1675 to 1679 [10, 11]. Due to the rarity of macrodactyly of the hands and feet, it is usually reported on a case-by-case basis [2]. Between Polaillon (1884) and Humphry (1891), a total of 36 cases are presented from the literature between 1840 and 1891, although there is an overlap of citations [12, 13]. Sir George Murray Humphry describes six specimens from the Pathological Museum at the University of Cambridge, with a further 19 cases from the literature are also included in this review [13]. With the interpretation of the cases by today's standards, there appear to be examples of macrodactyly secondary to vascular anomaly, neurofibromatosis, and Proteus syndrome, as well as progressive and static forms of the disease.

The next comprehensive review of macrodactyly was by Barsky in 1967 [2]. This review of 64 cases of upper limb macrodactyly consists of eight original descriptions and a review of the literature to that date, which relies heavily on the work of Polaillon. With the exclusion of cases prior to 1884, only 30 extra cases were published in intervening years. Macrodactyly of the upper and lower limb continues to be reported on a case-by-case basis and we estimate that fewer than 500 cases have been reported worldwide to date.

Classification

Macrodactyly is a congenital limb anomaly of overgrowth (IV) according to the modified Swanson/International Federation of Societies for Surgery of the Hand [14–16]. A recent reclassification has been proposed as dysplasia–hypertrophy–macrodactyly or dysplasia–hypertrophy–upper limb and macrodactyly, according to the Oberg-Manske-Tonkin (OMT) system, to reflect both the axis of formation/differentiation and the part of the limb predominantly affected [17].

In its own right, macrodactyly has been subclassified in numerous ways. With no known unifying biological theory as to the causation, or progression, the only consistent feature is the subjective description of the enlarged digit. As such, there is overlap between classification systems, which must be considered as imperfect at the present time [4]. A brief review of the most commonly applied systems from the medical literature reveals three broad classes: relating to the tissues involved, rate of growth, or affiliation with different clinical signs or syndromes. Based upon these, we suggest a new inclusive classification system for macrodactyly.

To be classed as true macrodactyly, all elements of the digit must be enlarged [2, 18, 19]. This classification has been adapted to note that it is only tissues that respond late in development to neurogenic influence are enlarged, thus the tendon and blood vessels may be of normal size [20]. Digital enlargement may also occur secondarily to tumor or vascular anomalies and would be considered as pseudomacrodactyly [9], although the presentation and subsequent management may be similar in part (Fig. 22.1). There is no evidence that links outcomes with true or pseudomacrodactly.

The relative growth of the digit, compared to unaffected digits, may be considered as either static or progressive [2, 21], and may be symmetric or asymmetric [18, 22] (Fig. 22.2). In the static type, enlargement is present at birth and the affected limb grows in proportion to the child. In the progressive type, some overgrowth may be noted at birth, but around 2 years of age there is evidence of slow, unrestricted, and disproportionate digital enlargement, which continues until closure of the epiphyses [23].

In our review of 32 patients with macrodactyly, approximately two-thirds had the static type, which is different from the findings of other authors [3, 4]. In our cohort of 20 patients, six required no surgical intervention. It has been observed that such patients usually present later with good function [21] but we did not note any significant difference in age at presentation between the static and progressive subtypes, although it was noted that those with static

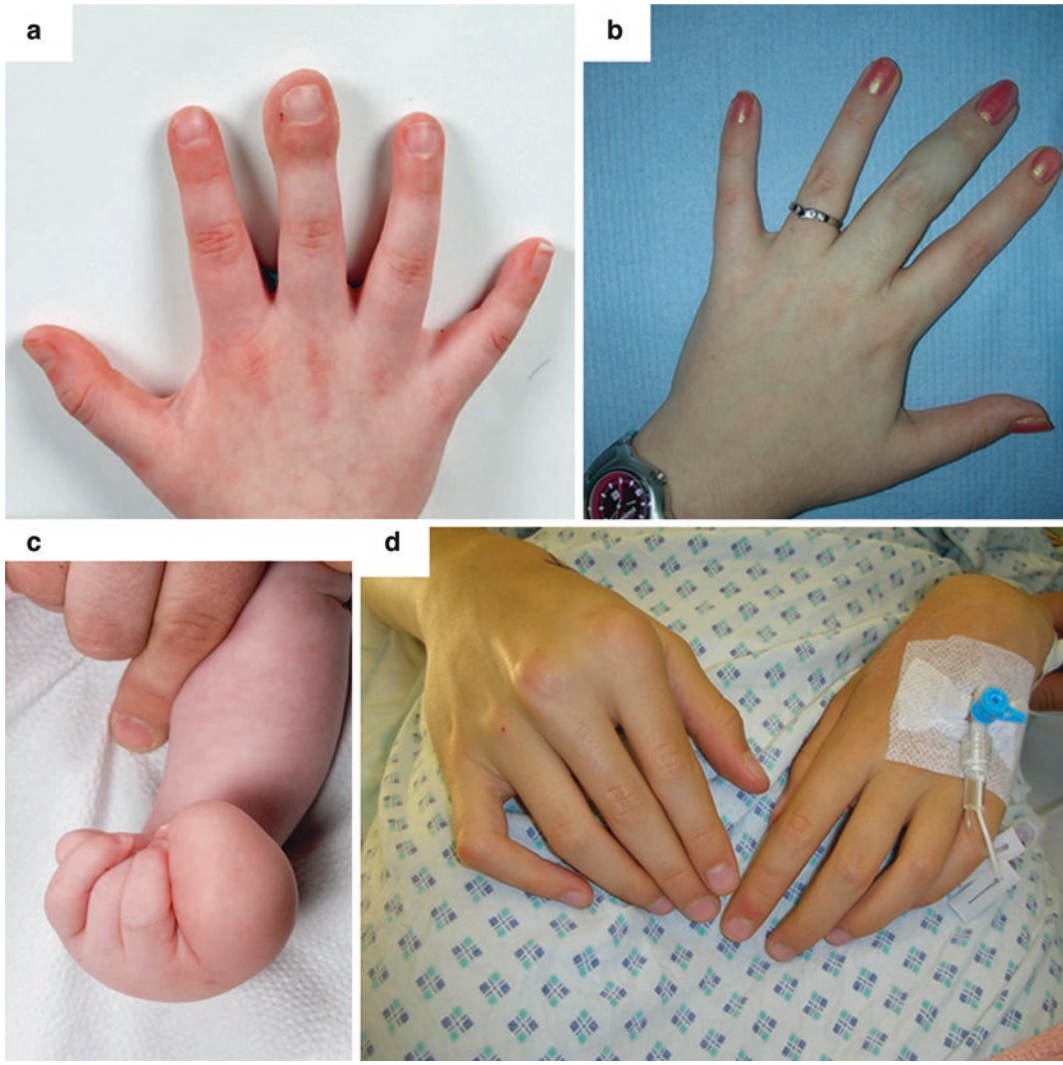

Fig. 22.1 Enlargement of the fingers or hand secondary to vascular malformations: (**a**) A lymphatic malformation of the tip of the middle finger. (**b**) An arteriovenous malformation of a finger leading to macrodactyly. (**c**) A venous malformation causing macrodactyly of the middle finger. (**d**) Muscle hypertrophy of the hand associated with a lymphatic malformation

disease required fewer operations overall, which was significant. These findings are echoed by Cerrato et al. [4]. It is difficult to classify into a static or a progressive type before the age of two, as the only significant indicator of the prognosis in macrodactyly is by regular observation in the first few years of life.

The most comprehensive classifications to date are based upon the original work of Kelikian, and later modified by Dell, Flatt, and Upton [7, 23–26] (Table 22.1). Lipomatous macrodactyly is the most common form of overgrowth in the literature and is differentiated from nerve territory-orientated macrodactyly (NTOM) by the absence of infiltration of the digital nerves upon microdissection and neurovascular structures are of normal caliber. NTOM was introduced by Kelikian [26] to differentiate the digital nerve involvement from that observed in neurofibromatosis-associated macrodactyly, and

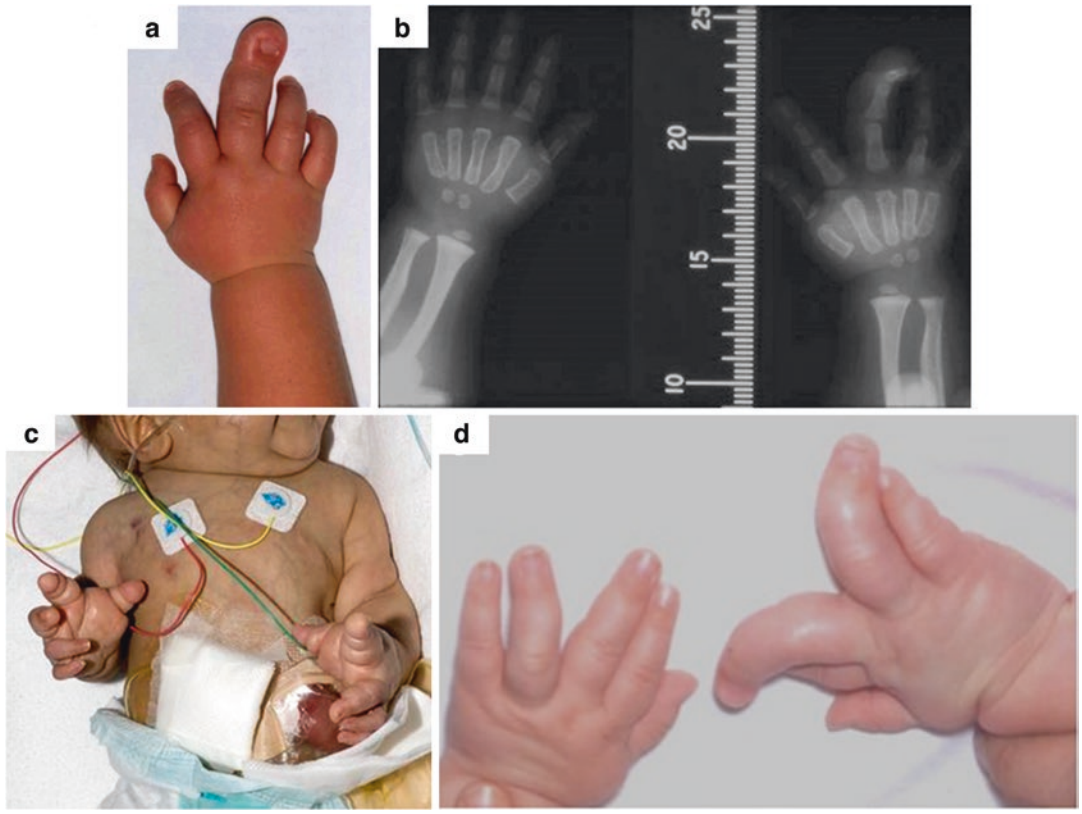

Fig. 22.2 The multiple variations of upper limb macrodactyly: (**a**) Progressive unilateral macrodactyly of the right middle finger. (**b**) Radiograph of the hands with the superimposition of a measure to allow for serial growth recording. (**c**) Bilateral, symmetrical macrodactyly in a child with an "unknown" syndrome that was fatal. (**d**) Bilateral, asymmetric macrodactyly

Table 22.1 Classifications of macrodactyly

Author(s) (year of publication)	Holmes (1869)	Richardière (1891)	De Laurenzi (1962) Barsky (1967)	Kelikian (1974)	Upton (1990) Flatt (1994)	Upton (2006)
	Symmetric	True	Static	Lipomatous macrodystrophy	Gigantism and (nerve-orientated) lipofibromatosis	Nerve territory-orientated macrodactyly
	Asymmetric	False	Progressive	Neurofibromatosis	Gigantism and neurofibromatosis	Lipomatous macrodactyly
				Nerve territory-orientated macrodactyly	Gigantism and digital hyperostosis	Neurofibromatosis
				Hyperostotic variety	Gigantism and hemihypertrpohy	Hyperostosis
						Hemihypertrophy
						Proteus syndrome
						Vascular malformations

Table 22.2 A system for the classification of macrodactyly

Characteristic	Classification			
(1) Growth	Static		Progressive	
(2) Associations	Isolated		Associated syndrome or anomalies	
(3) Structure	Lipomatous	Nerve territory-orientated	Hyperostotic	Vascular malformation

to emphasize the relationship between the enlargement of the nerve along with the bone and soft tissues. It is a common type of macrodactyly that is unilateral in 90% of cases. As with lipomatous macrodactyly, it does not usually show a pattern of inheritance, nor association with other malformations [25–27]. The median nerve territory is more often affected, with 85% of cases of macrodactyly affecting the thumb, index, or middle fingers [27]. Our recent review shows a similar distribution with involvement of these digits in 63% of cases and out of the 32 cases presented, 27 were lipomatous or NTOM macrodactyly [3]. Cerrato et al. presented 21 cases of macrodactyly, of which 12 were NTOM and 9 lipomatous. No significant difference in patients, progression, number of operations, distribution, or associated anomalies was found [4].

Digital hyperostosis, or *hyperostotic digital gigantism,* also described by Kelikian, is a rare form of macrodactyly that is nonhereditary, and may present later [26, 28]. There is bilateral enlargement of the digits, which may be symmetric or asymmetric, without gross enlargement of the digital nerves or fat, but it can present in the median nerve distribution, with concurrent NTOM [7, 29]. Palpable periarticular osteochondral masses arise from the volar plates of the metacarpals and phalanges, similar to the pattern seen in neurofibromatosis, and can lead to profound loss of motion [7, 23]. The joint involvement seen in hyperostosis and neurofibromatosis or Proteus syndrome will presumably lead to poorer functional outcomes, although this is not evidenced in the literature. The remaining subclasses associated with other anomalies or syndromes are discussed later.

The real value of a medical classification is to provide prognostic information, or to group patients for prospective analysis. With a confused variety of systems available for macrodactyly built upon phenotypic, intraoperative, histological, radiological, or genetic findings, the most effective classification should be based upon outcomes. It has been shown that patients with static disease need significantly fewer operations than those with progressive, although it must be acknowledged that the patient cohorts on which these assumptions are made were small and prone to variability [3, 4]. Macrodactyly associated with other anomalies or syndromes may also have poor functional outcomes due to joint involvement, flexion contracture, and other morbidity secondary to the syndrome involved.

With this established, we suggest a new three-layer classification based upon (1) growth progression, (2) associated anomalies, and (3) structures involved (Table 22.2). This encompasses all types of macrodactyly reported to date and can provide information about prognosis and allow grouping of similar patients for subsequent analysis. As such, a (1) static, (2) isolated, (3) lipomatous macrodactyly can be assumed to have a better prognosis in terms of function, fewer operations, and fewer surgical complications than a (1) progressive, (2) syndrome-associated, (3) hyperostotic macrodactyly.

Incidence

Macrodactyly is classed as a rare disease by the Office of Rare Disease Research, and thus affects less than 200,000 people in the USA [30]. With rare conditions, such as macrodactyly, a true population incidence is hard to calculate. The classic description by Flatt, of an incidence of 0.9% of all congenital hand anomalies is based upon the author's personal study of 2758 patients, with 28 cases of macrodactyly in 26 patients [7]. This figure, although widely published, has no reference to the overall incidence in the general population. A similar number was found in Hong Kong in the 1980s, with two cases of macrodactyly from a

cohort of 326 patients with congenital upper limb anomalies, equating to 0.5% [31].

Congenital anomalies occur in 1–2% of newborns, with 10% of these affecting the upper limb [7]. National population studies from Sweden have also shown an incidence of upper limb anomalies to be approximately 1/500 [32–34] and one can therefore extrapolate the incidence of upper limb macrodactyly (~1% of the total) to be around 1/50,000, but this is based upon many assumptions. Lower limb macrodactyly has been estimated to have an incidence of 1/18,000 [35]. In a large UK teaching hospital, one expects to see one to two new cases of upper limb macrodactyly per year, which echoes historic findings [36].

Associations

There are many reported associations of macrodactyly with other clinical signs or syndromes. In isolated non-syndromic macrodactyly, there can be concurrence of local anomalies such as syndactyly (occurring in 10% of patients) [29], clinodactyly, or curvature of the enlarged digit. There is also a very rare entity of syndactyly associated with dorsal macrodactyly (Fig. 22.3).

Of the many reported syndromes that have presented with macrodactyly, none have it per se as a syndrome-defining feature. It is usually classified as part of an overgrowth component of the disease, which can be classified into (1)

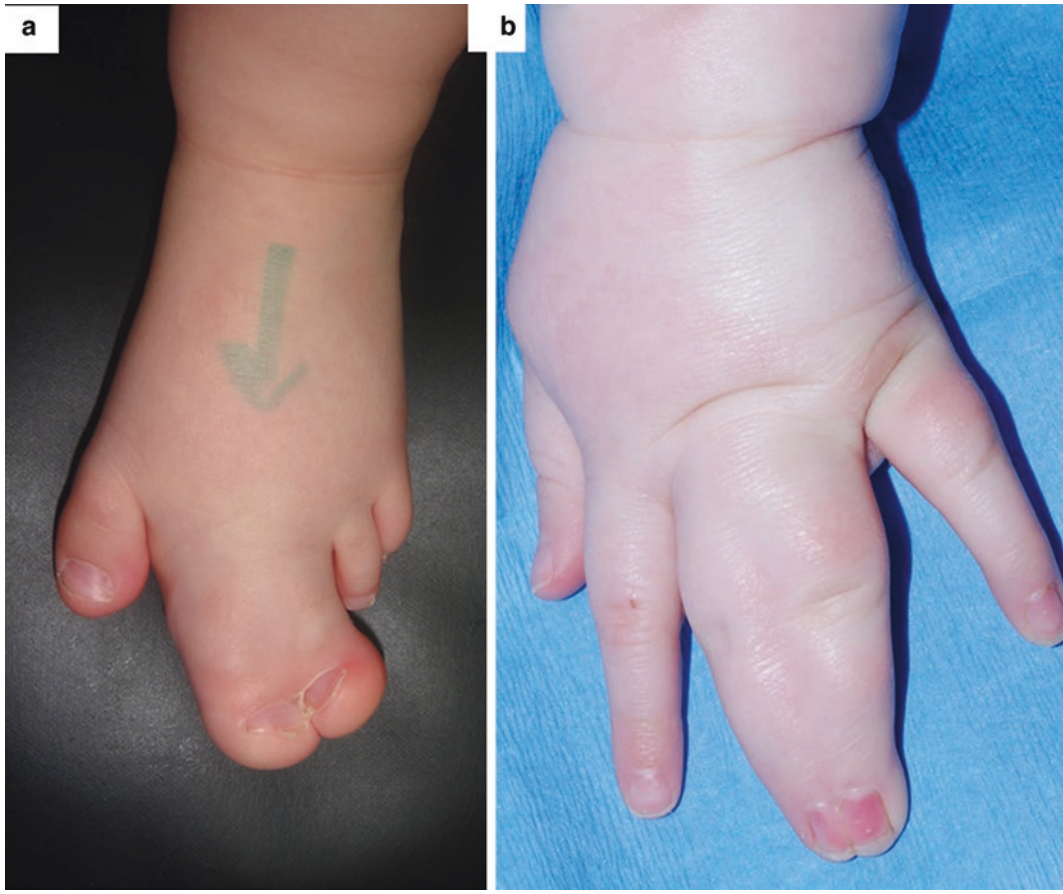

Fig. 22.3 Non-syndromic macrodactyly with associated malformations: (**a**) Macrosyndactyly of the 2nd and 3rd toes. (**b**) Subtle dorsal macrosyndactyly

Table 22.3 Syndromes associated with macrodactyly

(1)	Phakomatoses	Neurofibromatosis type 1 and 2	
		Hamartoma syndromes	Proteus syndrome
			Tuberous sclerosis
(2)	Osteochondrodysplasias	Enchondromatoses	Maffucci syndrome
			Ollier syndrome
		Monostotic fibrous dysplasia	
(3)	Specific overgrowth syndromes	Beckwith-Wiedemann syndrome	
(4)	Vascular anomalies	Vascular malformations	Klippel-Tranaunay syndrome
			Maffucci syndrome
			CLOVES syndrome

phakomatoses, (2) osteochondrodysplasias, (3) specific overgrowth syndromes, or (4) secondary to a vascular anomaly (Table 22.3).

Phakomatoses

The phakomatoses (or "neurocutaneous syndromes") include neurofibromatosis type 1 and 2 (NF1 and NF2) and the hamartoma syndromes.

NF1 and NF2 have both been associated with macrodactyly [7, 23, 25]. NF1 is the most commonly reported syndrome presenting with digital enlargement, as well as enlargement involving the upper and lower limbs, torso and head, and neck. It has an autosomal dominant inheritance pattern, with an incidence of 1/3000 [37–39] and has specific diagnostic criteria [40]. Digital enlargement is frequently bilateral and presents in a similar manner to the previously described NTOM or can be related to plexiform Schwannomatosis [41]. It may also present with features of hyperostosis [25]. As has been shown in hyperostotic macrodactyly, bony involvement can lead to limitation of movement and function. Growth is usually progressive and resection of the neurofibromas, or involved nerves, has been shown to limit advancement of the disease [42–44]. One must always consider the risk of malignant transformation and development of neurofibrosarcoma in the peripheral nerve [45, 46].

NF2 also has an autosomal dominant inheritance pattern but is 20 times less common than NF1. It manifests as bilateral vestibular Schwannomas, spinal cord meningiomas, or ependymomas and cataracts [47, 48]. Peripheral nerve involvement is rare, but macrodactyly secondary to a NF2 peripheral nerve Schwannoma has been reported [49].

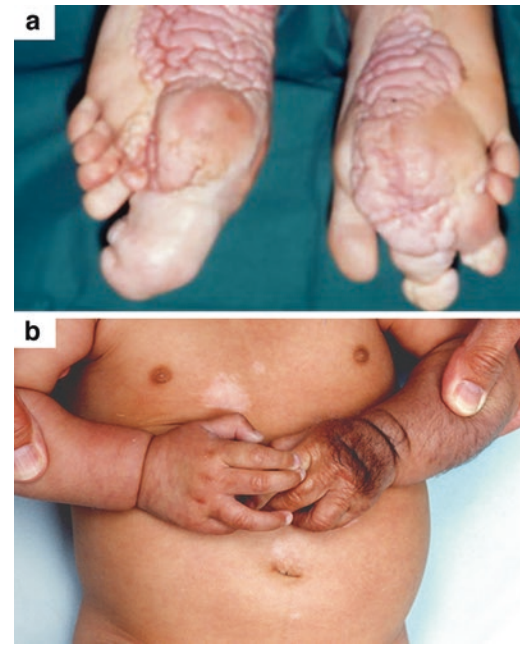

Fig. 22.4 Macrodactyly in association with hamartoma syndromes: (**a**) Bilateral macrodactyly of the toes and thickening of the plantar surfaces of the feet associated with Proteus syndrome. (**b**) Enlargement of the left hand associated with tuberous sclerosis

Hamartomas are benign focal malformations that resemble a neoplasm in the tissue of its origin [50]. Multiple hamartomas are associated with syndromes such as Proteus syndrome and Tuberous Sclerosis (Fig. 22.4), both presenting with soft tissue and bone overgrowth [51, 52]. Proteus syndrome was described as a discrete

clinical entity in 1979 [53] and assigned its name in 1983 [54] with reference to the Greek god who was gifted with the power to change his appearance at will. It is rare, and the first description is now attributed to Treves with his presentation of Joseph Merrick (the Elephant Man) to the Pathological Society of London in 1885 [55, 56]. It is not inherited and displays genetic mosaicism [57–60]. After neurofibromatosis, it is the most widely reported syndrome associated with macrodactyly [61–65]. In this condition, macrodactyly can be highly variable, progressive, and asymmetric. Disproportionate growth throughout the body begins between the ages of 6 and 18 months and leads to severe overgrowth and flexion contractures and the hands, which, when combined with glabrous hyperplasia can preclude functional use of the hand [23, 66].

Tuberous sclerosis complex is an autosomal dominant disorder characterized by hamartomatous malformations in various organs such as brain, kidney, heart, and lung [67, 68]. Macrodactyly is rarely reported in association, with only 10 cases identified up to 2000 [69]. There is a hyperostosis with cortical bone cysts, although the joints appear to be spared [70, 71]. The patients may have associated symptoms such as epilepsy or learning disability as a result of the primary diagnosis of tuberous sclerosis [72, 73].

Osteochindrodyplasias

The osteochondrodyplasias that may present in infancy include the enchondromatoses and fibrous dysplasia, which may present with digital enlargement secondary to bone overgrowth.

Muffuci syndrome and Ollier disease are both enchondromatoses, characterized by multiple enchondromas that are almost exclusively localized in the metaphysis of long bones and in the small bones of the hands and feet [74–77]. Enchondromas can result in severe growth abnormalities (more severe than those observed in multiple exostosis) and fingers often show irregular morphology and size, although are rarely reported in the literature [76, 78]. Radiological findings include ovoid, cystic, and highly radiolucent lesions, elongated parallel to the major axis of the bone, originating near the physis and migrating toward the diaphyses with growth [76, 79, 80]. Debulking of the enchondromas and hemangiomas forego amputation and can result in a hand that is improved in appearance and less prone to trauma [81].

Fibrous dysplasia may be monostotic or polyostotic in presentation or have associated endocrinopathy in McCune-Albright syndrome. Rarely reported monostotic involvement in the digit [82] must be considered in the differential diagnosis of macrodactyly.

Overgrowth Syndromes

Overgrowth syndromes can be associated with hemihypertophy, of which macrodactyly can be a component. Beckwith–Wiedemann syndrome (BWS) is a rare and complex disorder of overgrowth with undetermined inheritance [83]. It was classically described as macrosomia, macroglossia, and an abdominal wall defect [84–86], but more recently has been noted to include hemihyperplasia [87, 88]. Hemihypertrophy macrodactyly presents similarly to Proteus syndrome but with more uniform soft tissue overgrowth and muscular hypertrophy. The palm and hand are less enlarged in proportion to the ipsilateral forearm, due to increased muscle bulk, but in extreme cases can be fixed in flexion at the wrist with digits in ulnar deviation due to muscular imbalance, which becomes more obvious during adolescence [23]. Isolated muscle hypertrophy of the hand including muscular hyperplasia, aberrant muscles, ulnar drift of the fingers in the metacarpophalangeal (MP) joints, flexion contractures of the MP joints, and enlargement of the metacarpal spaces is extremely rare but we have seen two cases associated with a lymphatic malformation (see Fig. 22.1d) and localized gigantism of the upper limb (Fig. 22.5).

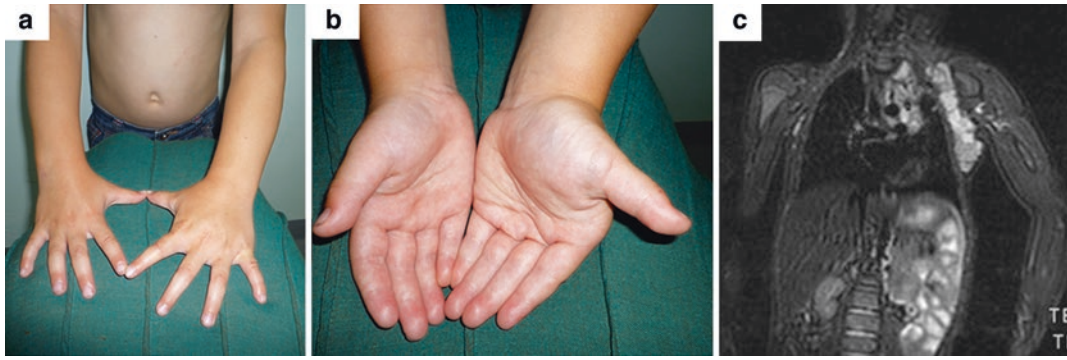

Fig. 22.5 Enlargement of the right-hand musculature with sparing of the digits, in association with hemihypertrophy: (**a**) Dorsal view. (**b**) Anterior view. (**c**) Magnetic resonance imaging of the left upper limb showing generalized soft tissue hypertrophy

Vascular Anomaly Syndromes

Vascular anomaly syndromes that are associated with digital enlargement include Klippel-Tranaunay syndrome (KTS) and CLOVES syndrome. The anomalies that are present are vascular malformations (VM) as per the International Society for the Study of Vascular Anomalies [89, 90]. Macrodactyly in such cases may be diagnosed and managed with a different strategy, focusing on destruction or disruption of the VM prior to surgical debulking. KTS was described in 1900 with three characteristic features: a vascular nevus; hypertrophy of all of the tissues, particularly the skeleton; and ipsilateral varicosities [91, 92]. McGrory reviewed 108 patients with KTS and found 26 had macrodactyly (79 digits) of the upper or lower limb, among other congenital hand and foot anomalies. There was predilection for the radial side of the hand and medial foot [93].

CLOVES syndrome consists of: Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevi, and Skeletal abnormalities [94]. It can span the classifications, being part of either the overgrowth or vascular anomaly subset. The presence of high flow lesions in these patients suggests that it may be clinically related to KTS, and as such we have classified it here. The presence of truncal lipomatous mass and a characteristic pattern of macrodactyly differentiates CLOVES from other syndromic forms of overgrowth [94, 95]. The macrodactyly consists of progressive soft tissue overgrowth in predominance to bone overgrowth, which may be nonprogressive and non-distorting in nature [96, 97], which is markedly different from that found in Proteus syndrome. Review of the historical literature reveals probable CLOVES syndrome that may previously have been described as gigantism [95] or Proteus syndrome [94].

Genetics

The majority of isolated, non-syndromic macrodactyly, whether of the progressive or static subtype, is sporadic in nature with no known underlying genetic causation recorded on the Online Mendelian Inheritance in Man database [98]. At present, there is no modern molecular insight into macrodactyly and there are no cellular or animal models of macrodactyly [99]. Candidate genes have been proposed (Table 22.4) that include those coding for Bone Morphogenetic Proteins 5 and 7 (BMP5 & 7), Transforming Growth Factor Beta 3 (TGF-B3), Wnt (wingless-type) signaling pathway proteins (Wnt-2, Wnt-5A), pleiotrophin (PTN) [99], Natriuretic Peptide Receptor 2 (NPR2) [100], and phosphoinositide-3-kinase (PI3K) [101].

BMP5 & 7, TGF-B3, Wnt-2, and Wnt-5A are all overexpressed in macrodactyly, but PTN had the greatest fold-change when reported [99].

Table 22.4 Genes associated with non-syndromic and syndromic macrodactyly

	Gene	Chromosome location	Encoded protein	Syndrome	Gene(s)	Chromosome location	Encoded protein(s)
Non-syndromic macrodactyly	*BMP5*	6p12.1	Bone morphogenetic protein 5	**Neurofibromatosis type 1**	*NF1*	17q11.2	Neurofibromin
	BMP7	20q13.31	Bone morphogenetic protein 7	**Neurofibromatosis type 2**	*NF2*	22q12.2	Merlin
	TGFB3	14q24.3	Transforming growth factor beta 3	**Proteus syndrome**	*AKT1*	14q32.33	RAC alpha serine/threonine-protein kinase
	WNT2	7q31.2	Protein Wnt-2	**Proteus-like syndrome**	*PTEN*	10q23.31	Phosphatase and tensin homolog
	WNT5a	3p14.3	Protein Wnt-5a	**SOLAMEN syndrome**	*PTEN*	10q23.31	Phosphatase and tensin homolog
	PTN	7q33	Pleiotrophin	**Tuberous sclerosis**	*TSC1*	9q34.13	Hamartin
					TSC2	16p13.3	Tuberin
	NPR2	9p13.3	Natriuretic Peptide Receptor 2	**Beckwith-Wiedemann syndrome**	*CD KNIC, H19, IGF2, KCNQ10T1*	11p15.5	Cyclin-dependent kinase inhibitor 1C, Insulin-like growth factor 2
	PIK3CA	3q26.32	Phosphoinositide-3-kinase	**CLOVES syndrome**	*PIK3CA*	3q26.32	Phosphoinositide-3-kinase

PTN is a promising candidate for the pathogenesis of macrodactyly because it promotes growth of nearly all the tissues affected by macrodactyly: PTN is necessary for neurite outgrowth and maturation in the central nervous system [102–104]. In the peripheral nervous system, it promotes nerve regeneration following injury [105]. PTN is highly expressed in bone and cartilage and is upregulated in response to mechanical loading [106–108]. It is an angiogenic factor, and supports endothelial cell proliferation [109].

Overproduction of C-type natriuretic peptide (CNP) due to a chromosomal translocation was reported to cause skeletal dysplasia associated with tall stature [110, 111]. In addition, acromesomelic dysplasia, characterized by dwarfism and short limbs, is caused by loss of function mutations in the *NPR2* gene [112]. In a study by Miura et al., a three-generation family of tall stature and macrodactyly of the great toes had a gain of function mutation in the *NPR2* gene [100].

PI3K is an upstream regulator of the AKT-mTOR cell-signaling pathway, which has been implicated in non-syndromic macrodactyly and CLOVES syndrome [101, 113]. The PI3K/AKT/mTOR pathway is important in apoptosis and carcinogenesis [114, 115] and muscular hypertrophy [116].

In syndrome-associated macrodactyly, especially those with an autosomal dominant inheritance pattern, individual genes have been identified (see Table 22.4). A mutation in the *NF1* gene that encodes for neurofibromin, leads to the development of NF1 [117, 118]. The *NF2* gene encodes for merlin (also known as schwannomin) and mutations lead to the development of NF2 [47, 48, 119]. Although its exact function is unknown, merlin is likely also involved in controlling cell movement, cell shape, and communication between cells [120–122], with mutations leading to the development of Schwannomas, which may be associated with macrodactyly [49].

Proteus syndrome is caused by a mutation in the *AKT1* gene that encodes for RAC-alpha serine/threonine-protein kinase (AKT1), which regulates cell growth, proliferation, and apoptosis [123]. A mutation in *AKT1* leads to the abnormal growth characteristics of Proteus syndrome [66, 124]. Mutations in the *PTEN* gene, which encodes for Phosphatase and Tensin homolog (PTEN), have been associated with asymmetric overgrowth but do not meet the strict guidelines for a diagnosis of Proteus syndrome [125–127]. Instead, these individuals have Proteus-like syndrome, which is considered part of a larger group of disorders called PTEN hamartoma tumor syndromes. Segmental Overgrowth, Lipomatosis, Arteriovenous Malformation, and Epidermal Nevus (SOLAMEN) syndrome, another variant within this group with mosaic PTEN mutations, has presented with macrodactyly [128].

Tuberous sclerosis complex is caused by mutations in the *TSC1* or *TSC2* genes, which encode hamartin and tuberin, respectively [67]. The proteins act as tumor suppressors, and with loss of function mutations leads to the growth of tumors in many different organs and tissues [68, 72], which may lead to macrodactyly [69]. The genetic causes of BWS are complex [83, 129], and involve several genes that are intrinsic to normal growth, including the *CDKN1C*, *H19*, *IGF2*, and *KCNQ1OT1* genes [129–133]. The CLOVES syndrome is linked to *PIK3CA* gene mutations [113, 134] and is negative for *PTEN* gene mutations [94], which allows differentiation from similarly presenting PTEN hamartoma syndromes (e.g., SOLAMEN syndrome).

Imaging

Prenatal diagnosis of macrodactyly has been reported. Yuksel et al. present a case of macrodactyly of the second toe of the left foot, diagnosed at 24 weeks gestation on obstetric ultrasound scan (USS), with no other anomalies diagnosed [135]. Rypens et al. report a case of Proteus syndrome, diagnosed antenatally on USS, which presented with macrodactyly of the left middle finger and an associated massive axillary lymphangioma [136]. The evidence relating to the imaging of macrodactyly is not evident in the literature. In most cases, the diagnosis can be ascertained from the clinical history and examination after birth. If there is doubt as to the diagnosis, or if there is disproportionate growth of a

previously *unaffected* digit, especially in adulthood, or after closure of the epiphyses, radiological investigation would be recommended.

Management

This section is inevitably anecdotal. Macrodactyly consists of a variety of conditions with many variations in presentation and growth patterns. It presents an almost unique situation whereby there is significant unpredictability of outcome with or without surgery. The management of macrodactyly demonstrates the need for very close observation of the child and detailed discussions with the parents and eventually the child throughout their growing years. It also requires considerable flexibility from a surgeon who has to consider the use of a wide variety of procedures and techniques. The aims of surgery are to allow a child to develop with minimum hindrance from their enlarged digit(s), e.g., by enabling them to be comfortable in shoes or to remove a digit, which is hindering their development of manipulative skills. This is done by attempting to reduce the disparity of the circumferential and longitudinal dimensions of the affected digit(s) when compared with the unaffected [25], with preservation of sensation, blood supply and function, as far as is possible [23].

In terms of principles of surgery, the senior author currently uses a lateral approach to each individual digit tackling one side at a time with an interval of a few months between each operative procedure. With this approach, bone and soft tissues surgical reduction can be combined. Palmar or plantar soft tissue debulking can be carried out using a variety of incisions, including zigzag and longitudinal [7, 23, 26], as well as the use of skin grafts in the reconstruction [137]. The position of scars rarely causes a problem even when using a longitudinal plantar incision [3].

The need for repeated procedures must be highlighted in the cases of progressive macrodactyly. The eventual decision to carry out a ray amputation (Fig. 22.6) should not be considered a failure in management as it may take many years and several operations to arrive jointly at this decision, which can transform the quality of life for these patients. In the vast majority of cases of surgically treated macrodactyly, the functional and cosmetic outcome will be acceptable to the patient [3].

The surgical management of macrodactyly can be classified by the treatment of the different tissues involved, i.e., soft tissue (skin and nerve) debulking, shortening of bone, correction of angulation of a digit; or attempting to arrest abnormal excessive growth by destruction of the growth plate. Macrodactyly associated with other anomalies, such as vascular anomalies, need to be treated individually according to problems reported by parents and/or child.

Skin and Soft Tissue

Excess fat can be radically reduced both dorsally and from around the nerve through a lateral incision. In isolated non-syndromic macrodactyly, there can be concurrent syndactyly (occurring in 10% of patients) [29]. Syndactyly separation using either a volar or dorsal flap technique can be employed. If the fat is radically debulked at the same time, there is usually enough skin for direct closure without the need for skin grafts.

Nerve

McCarroll initially reported the cessation of abnormal growth after nerve excision in neurofibromatosis-associated macrodactyly [44]. Kelikian advocated excision of tortuous redundant digital nerve after neurolysis (defatting) and showed return of sensation by 3 months in six out of seven individuals, although no mention of continual growth is made [26]. Multiple authors have refuted nerve excision as a method of growth arrest based on long-term outcomes, but this does include cases of partial nerve resection [42, 138–140]. The nerve can be radically debulked by a careful dissection and excision of infiltrated fat leaving only a small residual thickness of nerve tissue. Troublesome neuromata are rarely seen.

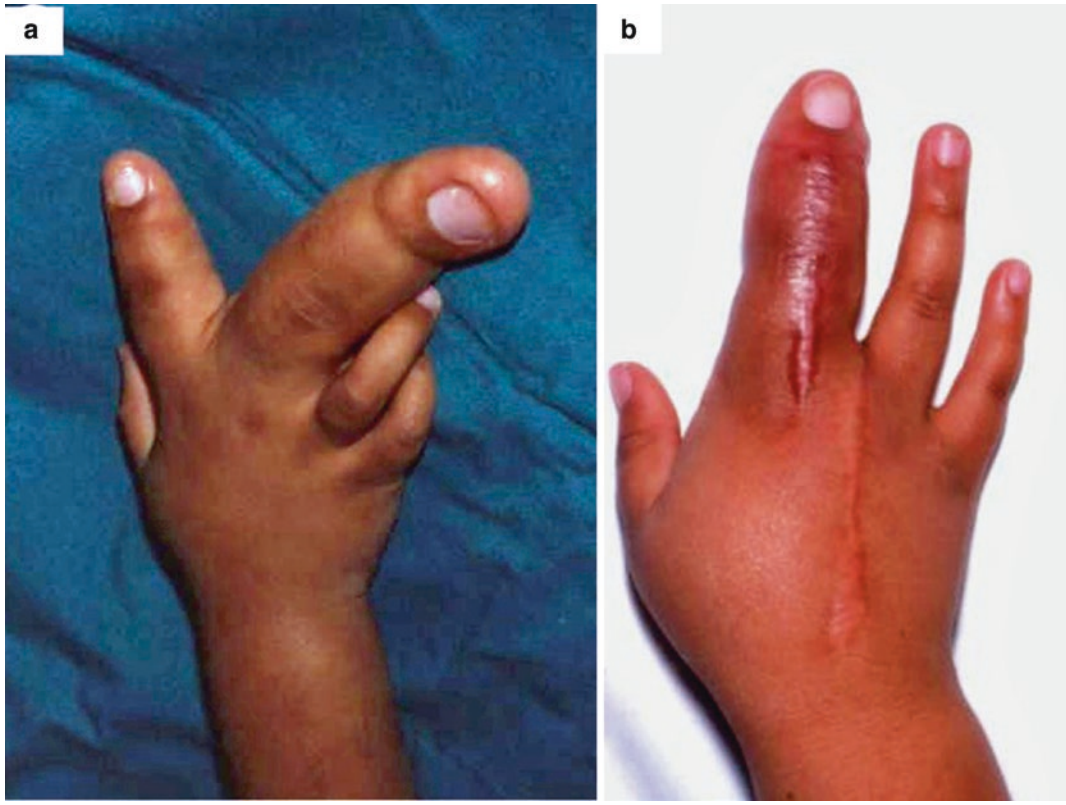

Fig. 22.6 Macrodactyly of the index and middle fingers: (**a**) Progressive macrodactyly of the right middle finger with the index finger affected to a lesser degree. (**b**) Postoperative image after ray amputation of the middle finger and soft tissue debulking of the index finger

Although the sensation of the digit may be reduced, this does not cause any functional problems as the digit is unlikely to be used during fine manipulation.

Nerve compression symptoms are reported in conjunction with enlargement of nerves in macrodactyly at both the cubital [141, 142] and carpal tunnel [143, 144]. Carpal tunnel syndrome is rare in children [145, 146] but has been reported in association with macrodactyly [147–151]. Release of the carpal tunnel and neurolysis has been shown to give symptomatic improvement [149]. The carpal tunnel decompression and neurolysis can be performed through an extended carpal tunnel incision, or in conjunction with other debulking procedures (Fig. 22.7).

Bones, Joints, and Epiphyses

Surgery to the bone including the joints can correct width, length, and angulation of a digit. If the epiphysis is included in the bony excisions, then ongoing growth of the length of the digit will be slowed down. Epiphyseal destruction will halt longitudinal growth if all centers involved in the enlargement of the digit are completely destroyed [23]. Early methods employed wiring or stapling of the growth plate [2] or the use of a motorized drill [152]. The use of a burr may not reliably destroy all growth centers and so some authors have moved to complete excision [7, 150]. Circumferential growth will continue and so will need addressing using osteotomy and bone trim-

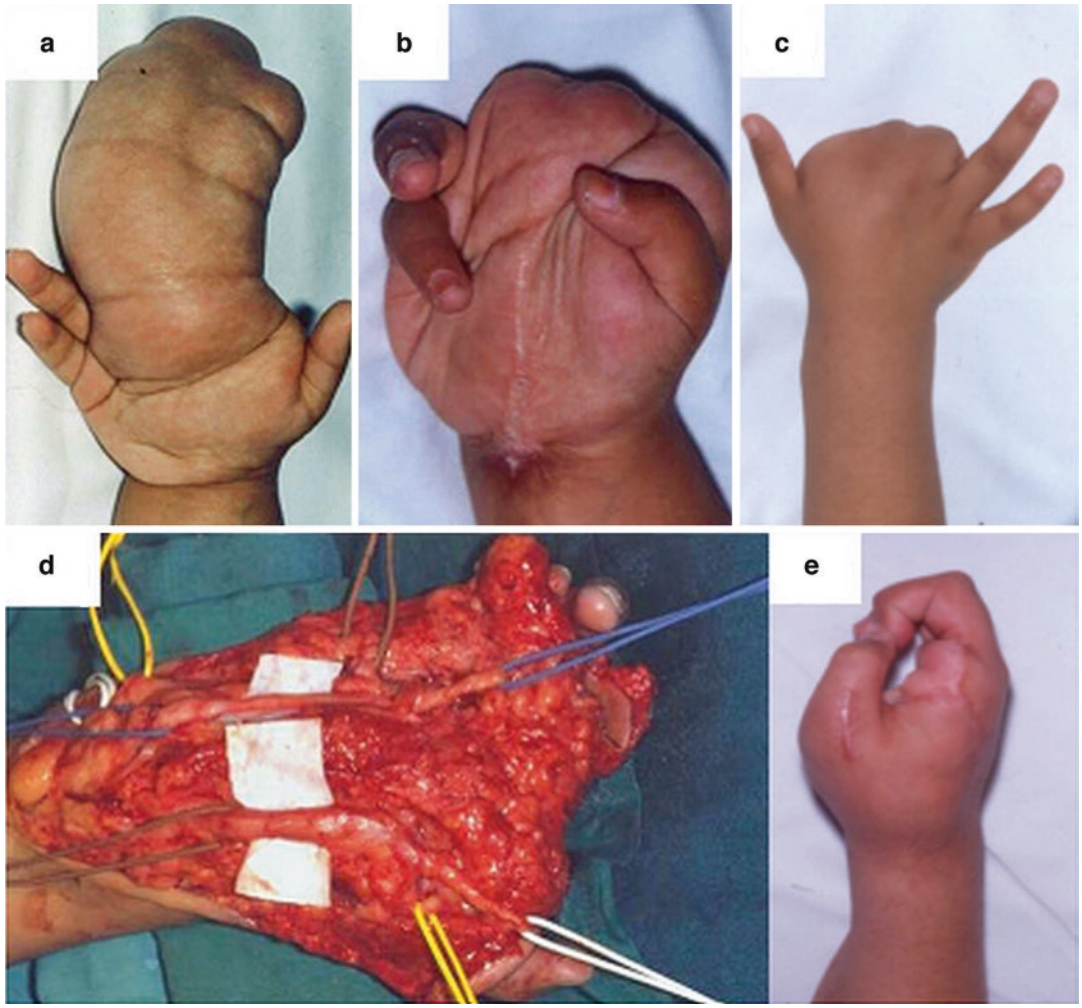

Fig. 22.7 Macrodactyly presenting with syndactyly of the index and middle fingers. (**a**) Gross macrosyndactyly with angulation leading to a nonfunctional hand. (**b**) The digits were initially amputated at MCP joint level but the hand remained encumbered. (**c**) Dorsal view. (**d**) A double ray amputation with debulking of the soft tissues of the palm was performed in conjunction with carpal tunnel decompression. (**e**) Lateral view showing a successful pinch grip

ming as described below. Epiphysodesis has been shown to be more reliable in longitudinal growth arrest from long-term follow-up than other methods, such as nerve excision [138].

Width reduction Through the lateral incision used to debulk the soft tissue, enlarged phalangeal bones can be trimmed in the longitudinal direction. Joints are very often already stiff and therefore preservation of collateral ligaments becomes irrelevant. Bulky deposits of bone around the PIP joints can be trimmed and this can improve the range of movement of the joint without reducing the stability. In cases of hyperostotic macrodactyly, early diagnosis and resection of the osteochondral masses before significant impairment of joint function has occurred is advised [23, 25, 28].

Length reduction Length reduction should involve preservation of the nail bed, rather than just simple terminalization of the digit. The

method attributed to Barksy shortens the middle phalanx with arthrodesis of the distal interphalangeal joint, transporting the distal phalanx and nail bed proximally, with plan for later soft tissue correction and narrowing of the nail bed if required [2] (Fig. 22.8). Tsuge described the "reverse" of this technique, with creation of a dorsal flap carrying the nail bed on one-third of the distal phalanx. The remainder of the distal phalanx is excised with the pulp and the nail bed transported proximally to the recipient middle phalanx, again with a plan for soft tissue correction at a later stage [153] (Fig. 22.9). However, simple excision of an already stiff distal interphalangeal joint will reduce the length of a digit, slow down the growth (by excision of the epiphysis), and improve the function and appearance of the digit. If this is carried out in association with a soft tissue debulking, any excess skin in the longitudinal direction will reduce spontaneously during the healing process. A single longitudinal/oblique K-wire can be used for fixation and removed in the outpatient department at around 6 weeks post-op.

Nail size and tip projection The nail width can be reduced at the same time as trimming of the bone and soft tissue debulking through a lateral incision. This may need to be carried out on one side only. At the same time, the excision of soft tissue around the tip of the digit can be performed close to the distal nail bed. The other side of the nail and further tip reduction can be performed 6 months later with debulking and narrowing of the digit through a lateral approach on the other side of the digit (Fig. 22.10).

Correction of angulation Closing wedge osteotomies at various sites in the phalanx will correct angulation and reduce the length of a digit or digits. A careful assessment of the x-ray and level of the angulation will determine where the osteotomy should take place. This can include the excision of the epiphysis. A whole stiff joint can be excised with minimal detriment to the function of the digit (i.e., an arthrodesis; Fig. 22.11). A single oblique K-wire is usually sufficient to encourage bone healing and can be simply removed in the clinic at around 6 weeks post-op.

Thumb The Millesi technique for thumb reduction is a combination of longitudinal and axial osteotomy of the distal phalanx with partial excision of the phalanx to provide shortening of the digit and narrowing nail bed in one stage (Fig. 22.12). This is further combined with oblique osteotomy of the proximal phalanx to allow shortening while maintaining the insertions of the extrinsic thumb flexor and extensor tendons [154]. It is also possible to consider a complete central resection of the bone and soft tissues.

Ray Amputation

In cases of progressive macrodactyly, the option for amputation should be raised early on in the treatment of the disease, especially if numerous operations and hospital admissions are anticipated. The parents and eventually the child need to be able to discuss this option freely but there is often a reluctance to consider this unless other attempts at surgical debulking have been tried in the first place. In the management of macrodactyly of the foot, ray amputation is often the best way to enable normal shoe fitting during the child's growing years. There should be no hesitation in carrying this operation out even in a young child, but significant soft tissue debulking both dorsally and on the plantar or volar side need to be carried out at the same time. Longitudinal scars in this condition are not a problem on the sole of the foot. Historically, amputation of the thumb was strongly discouraged, with Kelikian favoring arthrectomy and fusion of the first metacarpophalangeal joint [26]. More recently, digital transfer and free toe transfer have been used in the management of multi-digit macrodactyly affecting the thumb, middle, and index fingers [4].

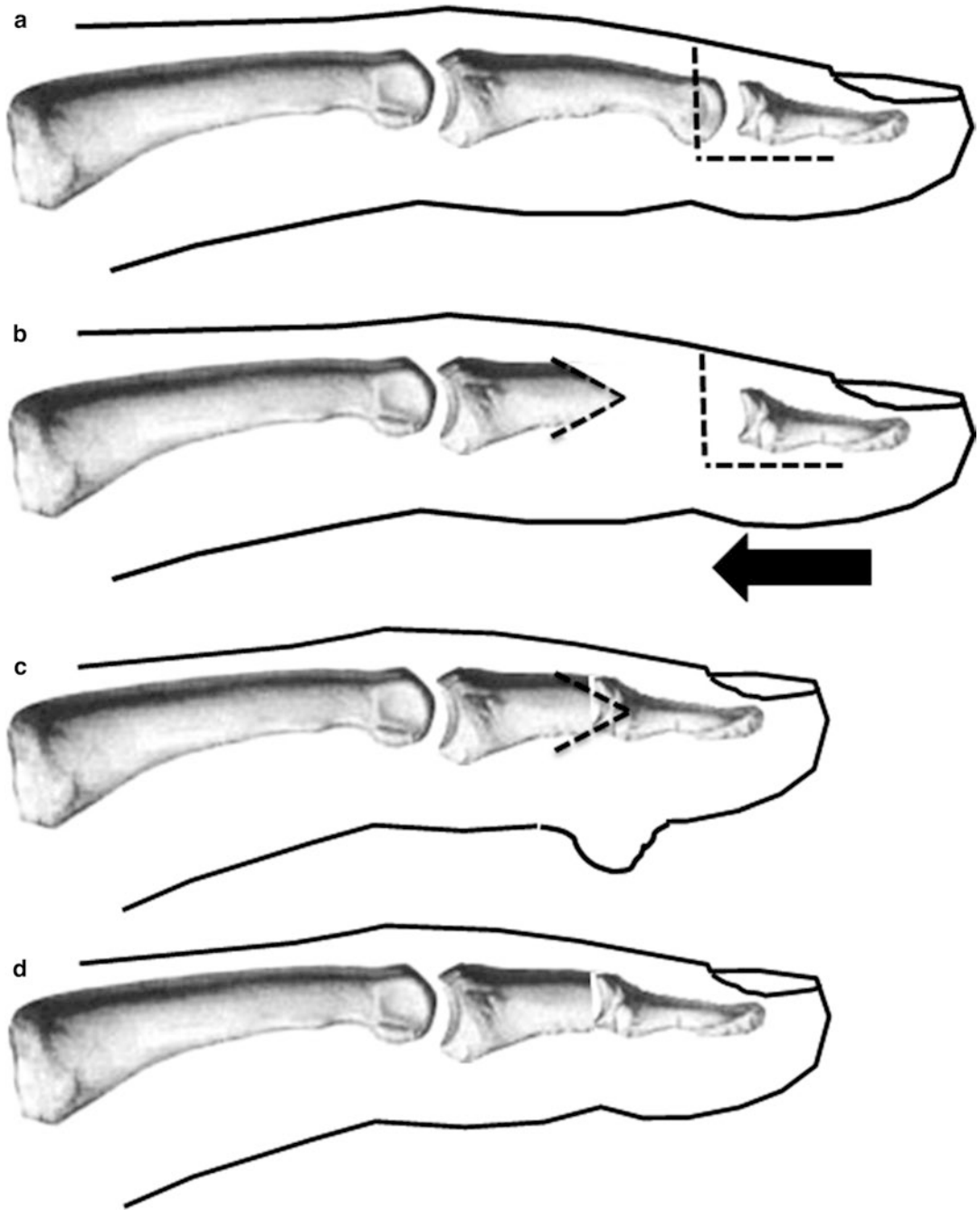

Fig. 22.8 Length reduction according to Barsky: (**a**) The enlarged digit with the skin incision as a dashed line. (**b**) The distal part of the middle phalanx is excised, proximal portion spiked, and distal phalanx hollowed out. (**c**) The distal phalanx is transported proximally with a resulting volar hump. (**d**) The volar hump is excised at a later date. (Adapted from [2])

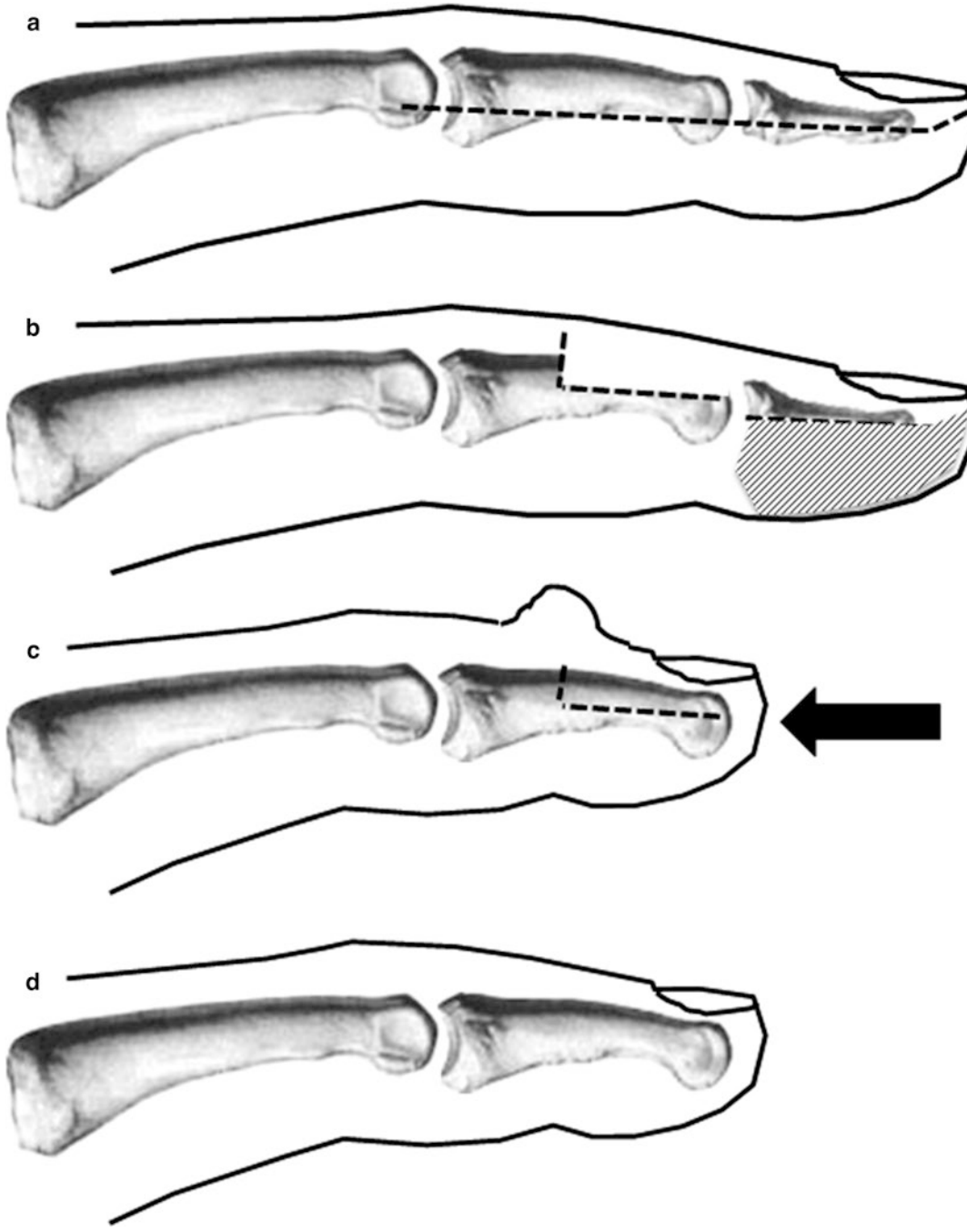

Fig. 22.9 Length reduction according to Tsuge: (**a**) Mid-lateral incisions to raise a dorsal flap to transport the nail. (**b**) The dorsal one-third of the distal phalanx is raised with the nail and redundant pulp and distal phalanx excised (shaded). (**c**) The distal phalanx and nail is transposed proximally, resulting in a dorsal hump. (**d**) The dorsal hump is excised at a later date. (Adapted from [153])

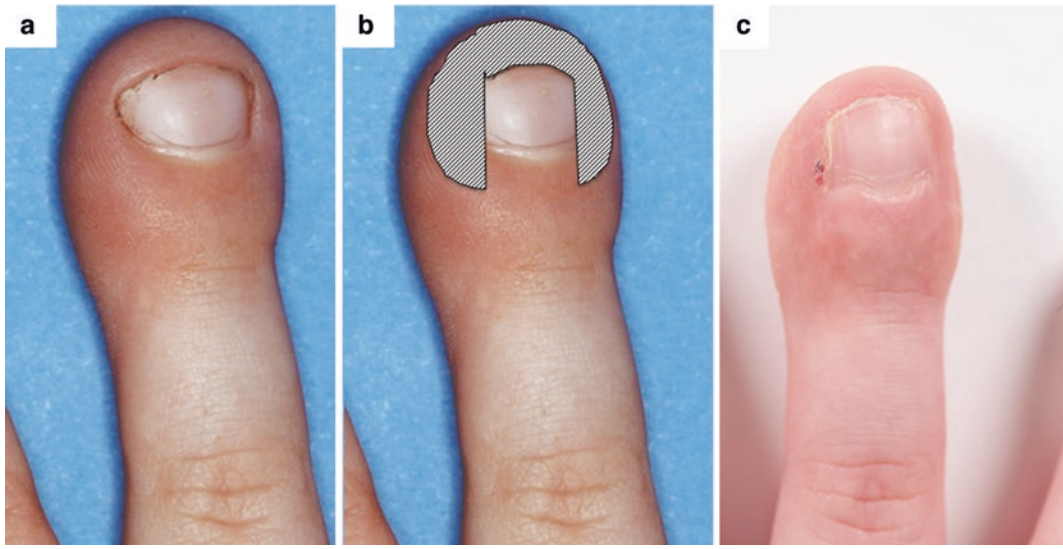

Fig. 22.10 Author's preferred method of reducing the nail: (**a**) Preoperative view. (**b**) Bilateral partial Zadek's procedure with bony and soft tissue reduction of the distal phalanx and finger tip. Excision area is shaded. (**c**) Postoperative view

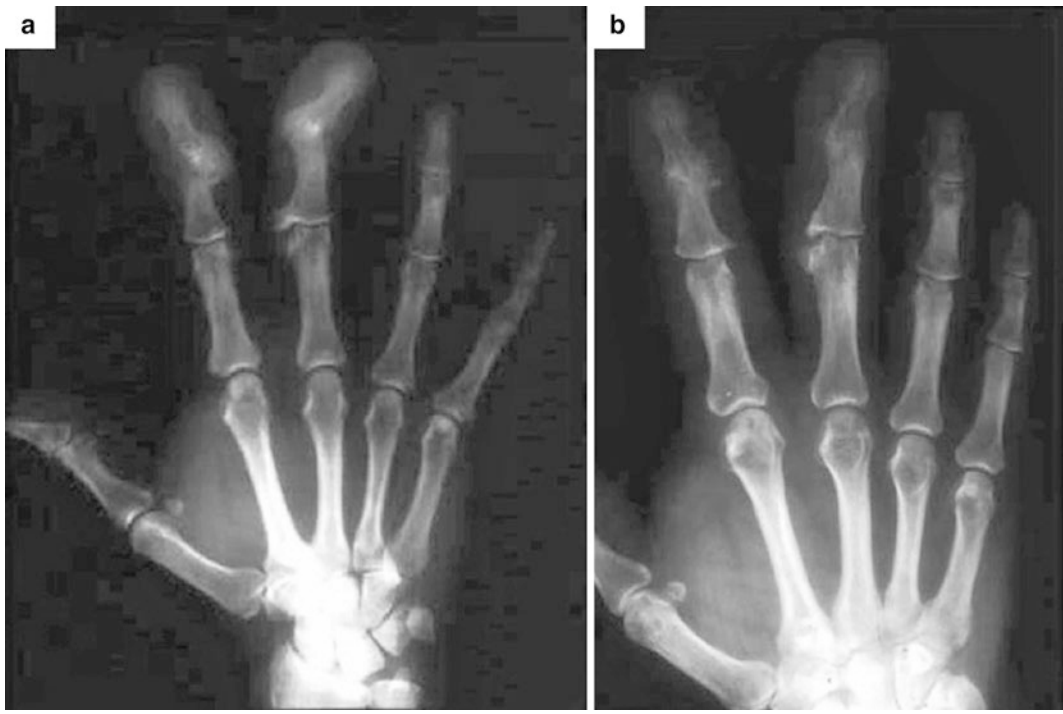

Fig. 22.11 (**a**) Pre- and (**b**) postoperative radiographs showing correction of angulation of the distal interphalangeal joint (DIPJ) of the middle finger, and hyperostosis of the DIPJ of the index finger, in conjunction with soft tissue debulking in an adult patient

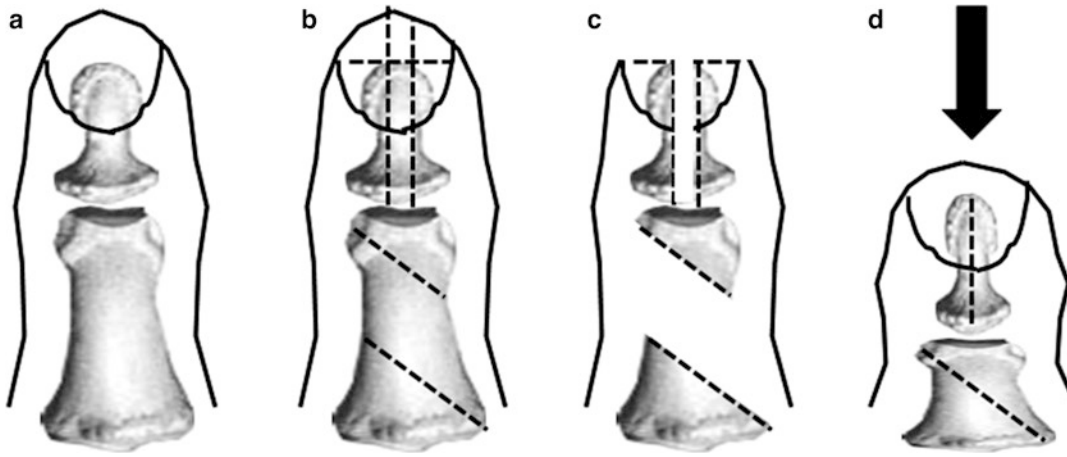

Fig. 22.12 Thumb reduction according to Millesi: (**a**) The enlarged thumb. (**b**) The central section of the distal phalanx and an oblique section of proximal phalanx are incised. (**c**) And removed. (**d**) The proximal and distal phalanges are reconstituted. (Adapted from [154])

Novel Agents

The PI3K/AKT/mTOR pathway has been implicated in non-syndromic polydactyly and Cloves syndrome [101, 113]. More recently, novel agents have been used to modify the effect of the PI3K/AKT/mTOR signaling pathway and cell growth (e.g., rapamycin/sirolimus, NVP-BEZ235, aspirin, and metformin) [155]. Suzuki et al. [155] demonstrated growth inhibition of a mutated PI3K/AKT/mTOR fibroblast cell line harvested from a patient with macrodactyly using NVP-BEZ235, aspirin, and rapamycin [155]. Metformin mildly inhibited fibroblast growth, which may be a good candidate drug for growing children. Parker et al. demonstrated safety and efficacy of low-dose mTOR inhibitor sirolimus in the PIK3CA-related overgrowth spectrum (PROS) in 39 patients [156]. In this 26-week study, sirolimus therapy was associated with a small, but significant reduction in tissue growth at overgrown sites in participants with PROS.

Timing of Surgery

The surgeons' role in the management of this condition is to review and support the child through his growing years and alleviate some of the distress caused by this incurable condition. This requires the development of a close relationship, initially with the parents or guardians of the child, and gradual involvement of the child in the decision-making process with regard to the surgical technique and the timing of interventions. Surgery should be offered to correct problems with function and cosmesis as they arise. As repeated surgery may be necessary, consideration needs to be given to the child's general development and well-being.

Outcomes

In our analysis of macrodactyly affecting the upper and lower limbs, outcomes assessment was performed by postal questionnaire using validated tools, and the opinion of the surgeon [3]. The senior surgeon's outcome verdict was based on an overall combination of function, sensibility, growth arrest, and cosmesis, following discussion with the parents and child. It was interesting to note the difficulty in finding adequately fitting shoes in the cases of lower limb macrodactyly seemed disproportionate to the actual reported difference in shoe size. This is because the length of the toes is only a part of the overall increase in the size of the foot in

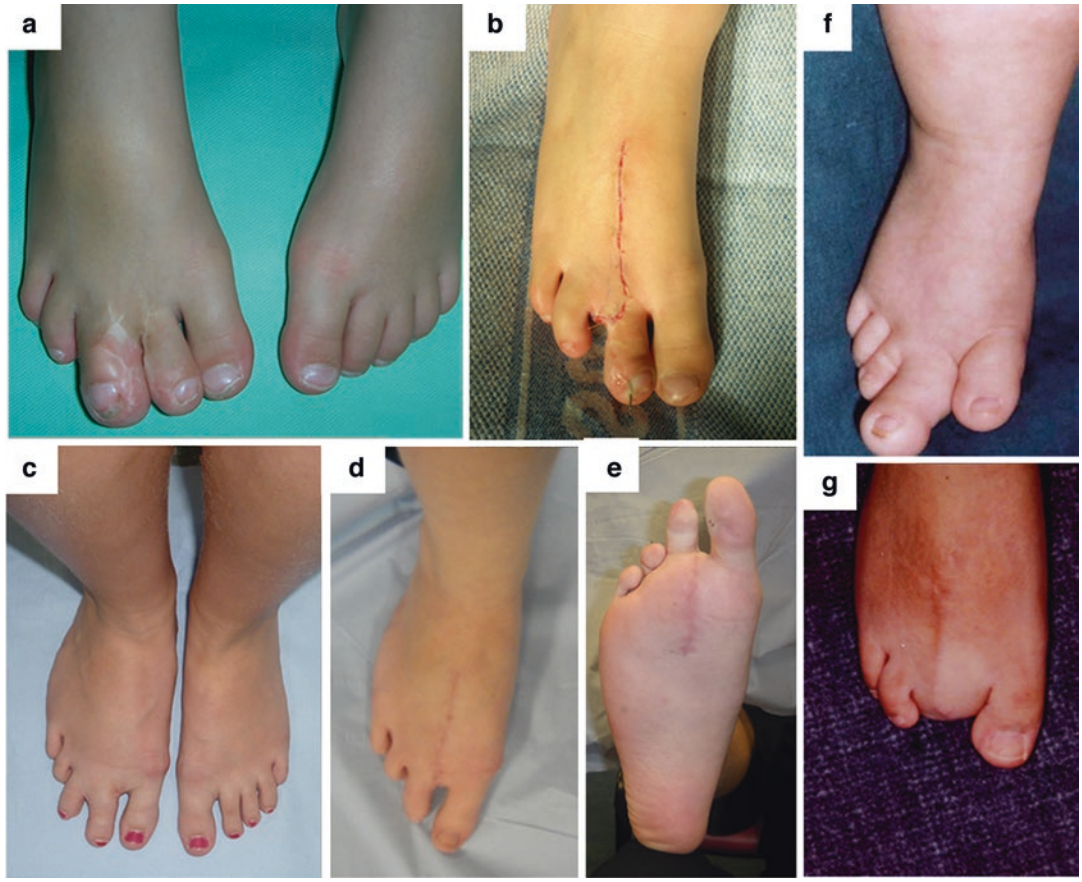

Fig. 22.13 Macrodactyly of the foot: (**a**) Macrodactyly of the right second and third toes. (**b**) Treated by third toe ray amputation and soft tissue debulking of the second toe enabling the reduction of shoe-size discrepancy. (**c**) Macrodactyly of the right second toe leading to widening of the forefoot, which is not resolved by simple amputation of the toe; a full ray amputation is necessary. (**d**) Postoperative dorsal view. (**e**) The plantar scar is well tolerated. (**f**) Macrodactyly of the right second and third toes. (**g**) The forefoot width discrepancy is not resolved by digital amputation alone

that there is nearly always an associated increase in the depth and width of the foot due to the proximal enlargement of the bone and soft tissues of the forefoot (Fig. 22.13). There was a wide range in self-reported outcomes: The better outcomes were related to function and activity participation, which could be assessed by the senior surgeon, while the poorer outcomes were related to happiness and satisfaction, which only were only revealed with self-reporting.

Summary

Macrodactyly represents a heterogenous group of conditions. The parents and child deserve a detailed ongoing personalized assessment and review of their specific situation preferably with the same clinician for as long as possible. Many surgical techniques can be offered to alleviate functional and cosmetic problems. Surgeons managing this condition need to use all their craft skills to improve the quality of life of the child.

References

1. Biesecker LG, Aase JM, Clericuzio C, Gurrieri F, Temple IK, Toriello H. Elements of morphology: standard terminology for the hands and feet. Am J Med Genet A. 2009;149A:93–127.
2. Barsky AJ. Macrodactyly. J Bone Joint Surg Am. 1967;49:1255–66.
3. Hardwicke J, Khan MA, Richards H, Warner RM, Lester R. Macrodactyly - options and outcomes. J Hand Surg Eur Vol. 2013;38:297–303.
4. Cerrato F, Eberlin KR, Waters P, Upton J, Taghinia A, Labow BI. Presentation and treatment of macrodactyly in children. J Hand Surg Am. 2013;38:2112–23.
5. Yaghmai I, Mckowne F, Alizadeh A. Macrodactylia fibrolipomatosis. South Med J. 1976;69:1565–8.
6. Thorne F, Posch J, Mladick R. Megalodactyly. Plast Reconstr Surg. 1968;41:232–9.
7. Flatt AE. The care of congenital hand anomalies. 2nd ed. St. Louis: Quality Medical Publishers; 1994. p. 47–62.
8. Lauschke H, Salminen S. Monstrous congenital macrodactyly with syndactyly of the foot - a case report. Acta Orthop Scand. 1998;69:201–2.
9. Fitoussi F, Ilharreborde B, Jehanno P, Frajman JM, Souchet P, Mazda K, Pennecot GF. Macrodactyly. Chir Main. 2009;28:129–37.
10. Price S, Williams AN. John Locke and a case of macrodactyly. Am J Med Genet A. 2009;149A:1364.
11. Dewhurst K. John Locke, 1632-1704, physician and philosopher; a medical biography with an edition of the medical notes in his journals. London: Wellcome Historical Medical Library; 1963.
12. Polaillon JFB. Chirurgie du doigt. Paris: G. Masson; 1884. p. 143–60.
13. Humphry SG. Macrodactyly, and some other forms of congenital overgrowth, and their relation to tumours. Med Chir Trans. 1891;74:165–80.
14. Swanson AB, Swanson GD, Tada K. A classification for congenital limb malformation. J Hand Surg Am. 1983;8:693–702.
15. Swanson AB. A classification for congenital limb malformations. J Hand Surg Am. 1976;1:8–22.
16. Swanson AB. A classification for congenital malformations of the hand. NJ Bull Acad Med. 1964;10:166–9.
17. Tonkin MA, Tolerton SK, Quick TJ, Harvey I, Lawson RD, Smith NC, Oberg KC. Classification of congenital anomalies of the hand and upper limb: development and assessment of a new system. J Hand Surg Am. 2013;38:1845–53.
18. De Greef A, Pretorius LK. Macrodactyly. A review with a case report. S Afr Med J. 1983;63:939–41.
19. Richardière P. Hypertrophie congénitale de la main. Sem Méd. 1891;11:125.
20. Smith P. Lister's the hand, diagnosis and indications. 4th ed. London: Churchill Livingstone; 2002. p. 502.
21. De Laurenzi V. Macrodattilia del Medico. Gior Med Mil. 1962;12:401–5.
22. Holmes R. The surgical treatment of the diseases of infancy and childhood. Philadelphia: Lindsay and Blaketon; 1869. p. 207–21.
23. Upton J. Failure of differentiation and overgrowth. In: Mathes SJ, editor. Plastic surgery. 2nd ed. Philadelphia: Saunders Elsevier; 2006. p. 265–322.
24. Upton J. Overgrowth (gigantism) in congenital anomalies of the hand and forearm. In: May JW, Littler JW, editors. Plastic surgery. Philadelphia: WB Saunders; 1990.
25. Dell PC. Macrodactyly. Hand Clin. 1985;1:511–24.
26. Kelikian H. Congenital deformities of the hand and forearm. Philadelphia: WB Saunders; 1974. p. 939–75.
27. Wood V. Macrodactyly. J Iowa Med Soc. 1969;59:922–8.
28. Schuind F, Merle M, Dap F, Bour C, Michon J. Hyperostotic macrodactyly. J Hand Surg Am. 1988;13:544–8.
29. Kay SP, McCombe DB, Kozin SH. Deformities of the hands and fingers. In: Wolfe SW, Hotchkiss RN, Pederson WC, Kozin SH, editors. Green's operative hand surgery. 6th ed. Philadelphia: Elsevier; 2011. p. 1359–69.
30. ORDR. Office of Rare Disease Research. http://rarediseases.info.nih.gov/gard/8529/macrodactyly-of-thehand/resources/1. Site accessed 01/11/2013.
31. Leung PC, Chan KM, Cheng JC. Congenital anomalies of the upper limb among the Chinese population in Hong Kong. J Hand Surg Am. 1982;7:563–5.
32. Ekblom AG, Laurell T, Arner M. Epidemiology of congenital upper limb anomalies in 562 children born in 1997 to 2007: a total population study from Stockholm, Sweden. J Hand Surg Am. 2010;35:1742–54.
33. Giele H, Giele C, Bower C, Allison M. The incidence and epidemiology of congenital upper limb anomalies: a total population study. J Hand Surg Am. 2001;26:628–34.
34. Lamb DW, Wynne-Davies R, Soto L. An estimate of the population frequency of congenital malformations of the upper limb. J Hand Surg Am. 1982;7:557–62.
35. Kowtharapu DN, Thawrani D, Kumar SJ. Macrodactyly. In: McCarthy JJ, editor. Drennen's the child's foot and ankle. 2nd ed. Baltimore: Lippincot Williams and Wilkins; 2009. p. 443–9.
36. Padgett EC, Stephenson KL. Reconstructive surgery of the skin and subcutaneous tissues of the extremities. In: Padgett EC, Stephenson KL, editors. Plastic and reconstructive surgery. Springfield: Charles C Thomas; 1948. p. 760.
37. Friedman JM, Riccardi VM. Clinical and epidemiological features. In: Neurofibromatosis: phenotype, natural history, and pathogenesis. 3rd ed. Baltimore: Johns Hopkins University Press; 1999. p. 29–86.
38. Gutmann DH, Aylsworth A, Carey JC, et al. The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. JAMA. 1997;278:51–7.

39. Huson SM, Harper PS, Compston DA. Von Recklinghausen neurofibromatosis: a clinical and population study in Southeast Wales. Brain. 1988;111:1355–81.
40. Consensus Statement NIH. Neurofibromatosis. 1987;6:1–19.
41. Posner MA, McMahon MS, Desai P. Plexiform schwannoma (neurilemmoma) associated with macrodactyly: a case report. J Hand Surg Am. 1996;21:707–10.
42. Tsuge K. Treatment of macrodactyly. J Hand Surg Am. 1985;10:968–9.
43. Tsuge K, Ikuta Y. Macrodatyly and fibrofatty proliferation of the median nerve. Hiroshima J Med Sci. 1973;22:83–100.
44. McCarroll HR. Clinical manifestations of congenital neurofibromatosis. J Bone Joint Surg Am. 1950;32-A:601–17.
45. Riccardi VM. The genetic predisposition to and histogenesis of neurofibromas and neurofibrosarcoma in neurofibromatosis type 1. Neurosurg Focus. 2007;22:E3.
46. D'agostino AN, Soule EH, Miller RH. Sarcomas of the peripheral nerves and somatic soft tissues associated with multiple neurofibromatosis (von Recklinghausen's disease). Cancer. 1963;16:1015–27.
47. Evans DG. Neurofibromatosis type 2 (NF2): a clinical and molecular review. Orphanet J Rare Dis. 2009;4:16.
48. Asthagiri AR, Parry DM, Butman JA, Kim HJ, Tsilou ET, Zhuang Z, Lonser RR. Neurofibromatosis type 2. Lancet. 2009;373:1974–86.
49. Bendon CL, Giele HP. Macrodactyly in the setting of a plexiform schwannoma in neurofibromatosis type 2: case report. J Hand Surg Am. 2013;38:740–4.
50. Albrecht (1904) Quoted by Anderson WAD. Pathology, 6th edn. St. Louis: CV Mosby; 1971. p. 980.
51. Hoey SE, Eastwood D, Monsell F, Kangesu L, Harper JI, Sebire NJ. Histopathological features of Proteus syndrome. Clin Exp Dermatol. 2008;33:234–8.
52. Norman-Taylor F, Mayou BJ. Macrodactyly in tuberous sclerosis. J R Soc Med. 1994;87:419–20.
53. Cohen MM Jr, Hayden PW. A newly recognized hamartomatous syndrome. Birth Defects Orig Artic Ser. 1979;15:291–6.
54. Wiedemann HR, Burgio GR, Aldenhoff P, Kunze J, Kaufmann HJ, Schirg E. The proteus syndrome. Partial gigantism of the hands and/or feet, nevi, hemihypertrophy, subcutaneous tumors, macrocephaly or other skull anomalies and possible accelerated growth and visceral affections. Eur J Pediatr. 1983;140:5–12.
55. Biesecker L. The challenges of Proteus syndrome: diagnosis and management. Eur J Hum Genet. 2006;14:1151–7.
56. Treves F. A case of congenital deformity. Proc Pathol Soc Lond. 1885;36:494–8.
57. Lublin M, Schwartzentruber DJ, Lukish J, Chester C, Biesecker LG, Newman KD. Principles for the surgical management of patients with Proteus syndrome and patients with overgrowth not meeting Proteus criteria. J Pediatr Surg. 2002;37:1013–20.
58. Biesecker LG, Happle R, Mulliken JB, Weksberg R, Graham JM Jr, Viljoen DL, et al. Proteus syndrome: diagnostic criteria, differential diagnosis, and patient evaluation. Am J Med Genet. 1999;84:389–95.
59. Biesecker LG, Peters KF, Darling TN, Choyke P, Hill S, Schimke N, et al. Clinical differentiation between Proteus syndrome and hemihyperplasia: description of a distinct form of hemihyperplasia. Am J Med Genet. 1998;79:311–8.
60. Clark RD, Donnai D, Rogers J, Cooper J, Baraitser M. Proteus syndrome: an expanded phenotype. Am J Med Genet. 1987;27:99–117.
61. Angurana SK, Angurana RS, Panigrahi I, Marwaha RK. Proteus syndrome: clinical profile of six patients and review of literature. Indian J Hum Genet. 2013;19:202–6.
62. Morelli F, Feliciani C, Toto P, De Benedetto A, Tulli A. A minimal form of Proteus syndrome presenting with macrodactyly and hand hyperplasia. Eur J Dermatol. 2003;13:196–8.
63. Miura H, Uchida Y, Ihara K, Sugioka Y. Macrodactyly in Proteus syndrome. J Hand Surg Br. 1993;18:308–9.
64. Barmakian JT, Posner MA, Silver L, Lehman W, Vine DT. Proteus syndrome. J Hand Surg Am. 1992;17:32–4.
65. Desai P, Steiner GC. Pathology of macrodactyly. Bull Hosp Jt Dis Orthop Inst. 1990;50:116–25.
66. Biesecker LG, Sapp JC. Proteus syndrome. In: Pagon RA, Adam MP, Bird TD, Dolan CR, Fong CT, Stephens K, editors. GeneReviews™ [Internet]. Seattle: University of Washington; 1993–2013.
67. Orlova KA, Crino PB. The tuberous sclerosis complex. Ann N Y Acad Sci. 2010;1184:87–105.
68. Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. Lancet. 2008;372:657–68.
69. Ghali FE. Macrodactyly in tuberous sclerosis. Pediatr Dermatol. 2001;18:364–5.
70. Tung HE, Shih SL. Tuberous sclerosis with rare presentation of macrodactyly. Pediatr Radiol. 2009;39:878.
71. Sahoo B, Handa S, Kumar B. Tuberous sclerosis with macrodactyly. Pediatr Dermatol. 2000;17:463–5.
72. Schwartz RA, Fernández G, Kotulska K, Jóźwiak S. Tuberous sclerosis complex: advances in diagnosis, genetics, and management. J Am Acad Dermatol. 2007;57:189–202.
73. Joinson C, O'Callaghan FJ, Osborne JP, Martyn C, Harris T, Bolton PF. Learning disability and epilepsy in an epidemiological sample of individuals with tuberous sclerosis complex. Psychol Med. 2003;33:335–44.
74. Superti-Furga A, Spranger J, Nishimura G. Enchondromatosis revisited: new classification

with molecular basis. Am J Med Genet C Semin Med Genet. 2012;160C:154–64.
75. Pansuriya TC, Kroon HM, Bovée JV. Enchondromatosis: insights on the different subtypes. Int J Clin Exp Pathol. 2010;3:557–69.
76. Kaissi AA, Roetzer K, Klaushofer K, Grill F. Acroform type of enchondromatosis associated with severe vertebral involvement and facial dysmorphism in a boy with a new variant of enchondromatosis type I1 of Spranger: case report and a review of the literature. Cases J. 2008;1:324.
77. Spranger J, Kemperdieck H, Bakowski H, Opitz JM. Two peculiar types of enchondromatosis. Pediatr Radiol. 1978;7:215–9.
78. Al-Qattan MM, Javed K, Pant R. An unusual case of multiple hand enchondromas. J Hand Surg Eur Vol. 2010;35:321–2.
79. Casal D, Mavioso C, Mendes MM, Mouzinho MM. Hand involvement in Ollier disease and Maffucci syndrome: a case series. Acta Reumatol Port. 2010;35:375–8.
80. Silve C, Jüppner H. Ollier disease. Orphanet J Rare Dis. 2006;1:37.
81. Howard FM, Lee RE Jr. The hand in Maffucci syndrome. Arch Surg. 1971;103:752–6.
82. Vigorita V, D'Ambrosio F, Verde R, Kauderer C, Bryk E. Case report 784: fibrous dysplasia of the second pedal digit. Skelet Radiol. 1993;22:441–3.
83. Weksberg R, Shuman C, Beckwith JB. Beckwith-Wiedemann syndrome. Eur J Hum Genet. 2010;18:8–14.
84. Best LG, Hoekstra RE. Wiedemann-Beckwith syndrome: autosomal-dominant inheritance in a family. Am J Med Genet. 1981;9:291–9.
85. Beckwith JB, Wang CI, Donnel GN, et al. Hyperplastic fetal visceromegaly with macroglossia, omphalocele, cytomegaly of adrenal fetal cortex, postnatal somatic gigantism and other abnormalties: newly recognized syndrome (Abst no 41). Proceedings of the American Pediatric Society, Seattle, 1964:16–8.
86. Wiedemann HR. Familial malformation complex with umbilical hernia and macroglossia - a "new syndrome"? J Genet Hum. 1964;13:223–32.
87. Weksberg R, Shuman C, Smith AC. Beckwith-Wiedemann syndrome. Am J Med Genet C Semin Med Genet. 2005;137C:12–23.
88. Cytrynbaum CS, Smith AC, Rubin T, Weksberg R. Advances in overgrowth syndromes: clinical classification to molecular delineation in Sotos syndrome and Beckwith-Wiedemann syndrome. Curr Opin Pediatr. 2005;17:740–6.
89. ISSVA classification. In: Enjolras O, Wassef M, Chapot R, editors. Color atlas of vascular tumors and vascular malformations. New York: Cambridge University Press; 2007. p. 1–11.
90. Enjolras O. Classification and management of the various superficial vascular anomalies: hemangiomas and vascular malformations. J Dermatol. 1997;24:701–10.
91. Klippel M, Trénaunay P. Du naevus variqueux ostéo-hypertrophique. Archives générales de médecine, Paris. 1900;3:641–72.
92. Weber FP. Angioma formation in connexion with hypertrophy of limbs and hemihypertrophy. Br J Derm Syph. 1907;19:231.
93. McGrory BJ, Amadio PC, Dobyns JH, Stickler GB, Unni KK. Anomalies of the fingers and toes associated with Klippel-Trenaunay syndrome. J Bone Joint Surg Am. 1991;73:1537–46.
94. Sapp JC, Turner JT, van de Kamp JM, van Dijk FS, Lowry RB, Biesecker LG. Newly delineated syndrome of congenital lipomatous overgrowth, vascular malformations, and epidermal nevi (CLOVE syndrome) in seven patients. Am J Med Genet A. 2007;143A:2944–58.
95. Alomari AI, Thiex R, Mulliken JB. Hermann Freiberg's case report: an early description of CLOVES syndrome. Clin Genet. 2010;78:342–7.
96. Bloom J, Upton J. CLOVES syndrome. J Hand Surg Am. doi: pii: S0363-5023(13)01188-X. https://doi.org/10.1016/j.jhsa.2013.08.120. [Epub ahead of print].
97. Gucev ZS, Tasic V, Jancevska A, Konstantinova MK, Pop-Jordanova N, Trajkovski Z, et al. CLOVE syndrome (congenital lipomatous overgrowth, vascular malformations, and epidermal nevi): CNS malformations and seizures may be a component of this disorder. Am J Med Genet A. 2008;146A(20):2688–90.
98. OMIM. www.omim.org. Site accessed 01/11/2013.
99. Lau FH, Xia F, Kaplan A, Cerrato F, Greene AK, Taghinia A, et al. Expression analysis of macrodactyly identifies pleiotrophin upregulation. PLoS One. 2012;7:e40423.
100. Miura K, Namba N, Fujiwara M, Ohata Y, Ishida H, et al. An overgrowth disorder associated with excessive production of cGMP due to a gain-of-function mutation of the natriuretic peptide receptor 2 gene. PLoS One. 2012;e42180:7.
101. Rios JJ, Paria N, Burns DK, Israel BA, Cornelia R, Wise CA, et al. Somatic gain-of-function mutations in PIK3CA in patients with macrodactyly. Hum Mol Genet. 2013;22:444–51.
102. Kretschmer PJ, Fairhurst JL, Decker MM, Chan CP, Gluzman Y, Böhlen P, et al. Cloning, characterization and developmental regulation of two members of a novel human gene family of neurite outgrowth-promoting proteins. Growth Factors. 1991;5:99–114.
103. Merenmies J, Rauvala H. Molecular cloning of the 18-kDa growth-associated protein of developing brain. J Biol Chem. 1990;265:16721–4.
104. Rauvala H. An 18-kd heparin-binding protein of developing brain that is distinct from fibroblast growth factors. EMBO J. 1989;8:2933–41.
105. Blondet B, Carpentier G, Lafdil F, Courty J. Pleiotrophin cellular localization in nerve regeneration after peripheral nerve injury. J Histochem Cytochem. 2005;53:971–7.
106. Imai S, Heino TJ, Hienola A, Kurata K, Büki K, et al. Osteocyte-derived HB-GAM (pleiotrophin)

is associated with bone formation and mechanical loading. Bone. 2009;44:785–94.
107. Tare RS, Oreffo ROC, Clarke NMP, Roach HI. Pleiotrophin/Osteoblast-stimulating factor 1: dissecting its diverse functions in bone formation. J Bone Miner Res. 2002;17:2009–20.
108. Azizan A, Gaw JU, Govindraj P, Tapp H, Neame PJ. Chondromodulin I and pleiotrophin gene expression in bovine cartilage and epiphysis. Matrix Biol. 2000;19:521–31.
109. Zhang N, Zhong R, Perez-Pinera P, Herradon G, Ezquerra L, Wang ZY, et al. Identification of the angiogenesis signaling domain in pleiotrophin defines a mechanism of the angiogenic switch. Biochem Biophys Res Commun. 2006;343:653–8.
110. Bocciardi R, Giorda R, Buttgereit J, Gimelli S, Divizia MT, Beri S, et al. Overexpression of the C-type natriuretic peptide (CNP) is associated with overgrowth and bone anomalies in an individual with balanced t(2;7) translocation. Hum Mutat. 2007;28:724–31.
111. Moncla A, Missirian C, Cacciagli P, Balzamo E, Legeai-Mallet L, Jouve JL, et al. A cluster of translocation breakpoints in 2q37 is associated with overexpression of NPPC in patients with a similar overgrowth phenotype. Hum Mutat. 2007;28:1183–8.
112. Bartels CF, Bükülmez H, Padayatti P, Rhee DK, van Ravenswaaij-Arts C, Pauli RM, et al. Mutations in the transmembrane natriuretic peptide receptor NPR-B impair skeletal growth and cause acromesomelic dysplasia, type Maroteaux. Am J Hum Genet. 2004;75:27–34.
113. Kurek KC, Luks VL, Ayturk UM, Alomari AI, Fishman SJ, Spencer SA, et al. Somatic mosaic activating mutations in PIK3CA cause CLOVES syndrome. Am J Hum Genet. 2012;90:1108–15.
114. Rodon J, Dienstmann R, Serra V, Tabernero J. Development of PI3K inhibitors: lessons learned from early clinical trials. Nat Rev Clin Oncol. 2013;10:143–53.
115. Miller TW, Rexer BN, Garrett JT, Arteaga CL. Mutations in the phosphatidylinositol 3-kinase pathway: role in tumor progression and therapeutic implications in breast cancer. Breast Cancer Res. 2011;13:224.
116. Bodine SC. mTOR signaling and the molecular adaptation to resistance exercise. Med Sci Sports Exerc. 2006;38:1950–7.
117. Williams VC, Lucas J, Babcock MA, Gutmann DH, Korf B, Maria BL. Neurofibromatosis type 1 revisited. Pediatrics. 2009;123:124–33.
118. Sabbagh A, Pasmant E, Imbard A, Luscan A, Soares M, Blanché H, et al. NF1 molecular characterization and neurofibromatosis type I genotype-phenotype correlation: the French experience. Hum Mutat. 2013;34:1510–8.
119. Trofatter JA, MacCollin MM, Rutter JL, Murrell JR, Duyao MP, Parry DM, et al. A novel moesin-, ezrin-, radixin-like gene is a candidate for the neurofibromatosis 2 tumor suppressor. Cell. 1993;72:791–800.
120. Zhou L, Ercolano E, Ammoun S, Schmid MC, Barczyk MA, Hanemann CO. Merlin-deficient human tumors show loss of contact inhibition and activation of Wnt/β-catenin signaling linked to the PDGFR/Src and Rac/PAK pathways. Neoplasia. 2011;13:1101–12.
121. Thaxton C, Bott M, Walker B, Sparrow NA, Lambert S, Fernandez-Valle C. Schwannomin/merlin promotes Schwann cell elongation and influences myelin segment length. Mol Cell Neurosci. 2011;47:1–9.
122. Stamenkovic I, Yu Q. Merlin, a "magic" linker between extracellular cues and intracellular signaling pathways that regulate cell motility, proliferation, and survival. Curr Protein Pept Sci. 2010;11:471–84.
123. Gonzalez E, McGraw TE. The Akt kinases: isoform specificity in metabolism and cancer. Cell Cycle. 2009;8:2502–8.
124. Cohen MM Jr. Proteus syndrome review: molecular, clinical, and pathologic features. Clin Genet. 2013;85:111. https://doi.org/10.1111/cge.12266.
125. Eng C. PTEN hamartoma tumor syndrome (PHTS). In: Pagon RA, Adam MP, Bird TD, Dolan CR, Fong CT, Stephens K, editors. GeneReviews™ [Internet]. Seattle: University of Washington; 1993–2013.
126. Hobert JA, Eng C. PTEN hamartoma tumor syndrome: an overview. Genet Med. 2009;11:687–94.
127. Eng C. PTEN: one gene, many syndromes. Hum Mutat. 2003;22:183–98.
128. Caux F, Plauchu H, Chibon F, Faivre L, Fain O, Vabres P, et al. Segmental overgrowth, lipomatosis, arteriovenous malformation and epidermal nevus (SOLAMEN) syndrome is related to mosaic PTEN nullizygosity. Eur J Hum Genet. 2007;15:767–73.
129. Choufani S, Shuman C, Weksberg R. Molecular findings in Beckwith–Wiedemann syndrome. Am J Med Genet Part C Semin Med Genet. 2013;163C:131–40.
130. Keniry A, Oxley D, Monnier P, Kyba M, Dandolo L, Smits G, Reik W. The H19 lincRNA is a developmental reservoir of miR-675 that suppresses growth and Igf1r. Nat Cell Biol. 2012;14:659–65.
131. Maher ER, Reik W. Beckwith-Wiedemann syndrome: imprinting in clusters revisited. J Clin Invest. 2000;37:212–5.
132. Li M, Squire J, Shuman C, Fei YL, Atkin J, Pauli R, et al. Imprinting status of 11p15 genes in Beckwith–Wiedemann syndrome patients with CDKN1C mutations. Genomics. 2001;74:370–6.
133. Ramesar R, Babaya M, Viljoen D. Molecular investigation of familial Beckwith-Wiedemann syndrome: a model for paternal imprinting. Eur J Hum Genet. 1993;1:109–13.
134. Mirzaa G, Conway R, Graham JM Jr, Dobyns WB. PIK3CA-realted segmental overgrowth. In: Pagon RA, Adam MP, Bird TD, Dolan CR, Fong CT, Stephens K, editors. GeneReviews™ [Internet]. Seattle: University of Washington; 1993–2013.

135. Yuksel A, Yagmur H, Kural BS. Prenatal diagnosis of isolated macrodactyly. Ultrasound Obstet Gynecol. 2009;33:360–2.
136. Rypens F, Dubois J, Garel L, Fournet JC, Michaud JL, Grignon A. Obstetric US: watch the fetal hands. Radiographics. 2006;26:811–29.
137. Edgerton MT, Tuerk DB. Macrodactyly (digital gigantism): its nature and treatment. In: Littler JW, Cramer LM, Smith JW, editors. Symposium on reconstructive hand surgery, vol. 9. St. Louis: CV Mosby; 1974.
138. Ishida O, Ikuta Y. Long-term results of surgical treatment for macrodactyly of the hand. Plast Reconstr Surg. 1998;102:1586–90.
139. Kalen V, Burwell DS, Omer GE. Macrodactyly of the hands and feet. J Pediatr Orthop. 1988;8:311–5.
140. Minguella J, Cusi V. Macrodactyly of the hands and feet. Int Orthop. 1992;16:245–9.
141. Meyer BU, Röricht S. Fibrolipomatous hamartoma of the proximal ulnar nerve associated with macrodactyly and macrodystrophia lipomatosa as an unusual case of cubital tunnel syndrome. J Neurol Neurosurg Psychiatry. 1997;63:808–10.
142. Silverman TA, Enzinger FM. Fibrolipomatous hamartoma of nerve. A clinicopathologic analysis of 26 cases. Am J Surg Pathol. 1985;9:7–14.
143. Tahiri Y, Xu L, Kanevsky J, Luc M. Lipofibromatous hamartoma of the median nerve: a comprehensive review and systematic approach to evaluation, diagnosis and treatment. J Hand Surg Am. 2013;38:2055–67.
144. Al-Jabri T, Garg S, Mani GV. Lipofibromatous hamartoma of the median nerve. J Orthop Surg Res. 2010;5:71.
145. Van Meir N, De Smet L. Carpal tunnel syndrome in children. J Pediatr Orthop B. 2005;14:42–5.
146. Lamberti PM, Light TR. Carpal tunnel syndrome in children. Hand Clin. 2002;18:331–7.
147. Nogueira A, Pena C, Martinez MJ, Sarasua JG, Madrigal B. Hyperostotic macrodactyly and lipofibromatous hamartoma of the median nerve associated with carpal tunnel syndrome. Chir Main. 1999;18:261–71.
148. Ulrich D, Ulrich F, Schroeder M, Pallua N. Lipofibromatous hamartoma of the median nerve in patients with macrodactyly: diagnosis and treatment of a rare disease causing carpal tunnel syndrome. Arch Orthop Truama Surg. 2009;129:1219–24.
149. Salon A, Guero S, Glicenstein J. Fibrolipoma of the median nerve. Review of 10 surgically treated cases with a mean recall of 8 years. Ann Chir Main Memb Super. 1995;14:284–95.
150. Frykmann GK, Wood VE. Peripheral nerve hamartoma with macrodactyly in the hand: report of three cases and review of the literature. J Hand Surg Am. 1978;3:307–12.
151. Allende BT. Macrodactyly with enlarged median nerve associated with carpal tunnel syndrome. Plast Resconstr Surg. 1967;39:578–82.
152. Clifford RH. The treatment of macrodactylism: a case report. Plast Reconstr Surg. 1959;23:245–8.
153. Tsuge K. Treatment of macrodactyly. Plast Reconstr Surg. 1967;39:590–9.
154. Millesi H. Macrodactyly: a case study. In: Littler JW, Cramer LM, Smith JW, editors. Symposium on reconstructive hand surgery, vol. 9. St. Louis: CV Mosby; 1974.
155. Suzuki Y, Enokido Y, Yamada K, Inaba M, Kuwata K, Hanada N, Morishita T, Mizuno S, Wakamatsu N. The effect of rapamycin. NVP-BEZ235, aspirin, and metformin on PI3K/AKT/mTOR signaling pathway of PIK3CA- related overgrowth spectrum (PROS). Oncotarget. 2017;8:45470–83.
156. Parker VER, Keppler-Noreuil KM, Faivre L, et al. Safety and efficacy of low-dose sirolimus in the PIK3CA- related overgrowth spectrum. Genet Med. 2019;21:1189–98.

Amniotic Band Syndrome

23

Sarah E. Sasor and Kevin C. Chung

Introduction

Amniotic band syndrome (ABS) is a congenital disorder characterized by constrictive rings that cause deformity or amputation in neonates. The condition is thought to be caused by rupture of the amnion in early pregnancy resulting in loose strands that entangle the fetus. Clinical presentation and severity varies widely. Any body part can be affected; however, the extremities are most at risk. Distal ring constrictions, intrauterine amputations, and acrosyndactyly are frequent upper extremity findings.

ABS-related hand deformities can cause significant disability. Treatment is individualized based on each patient's unique presentation. Multiple reconstructive procedures are often required throughout childhood.

History and Etiology

Hippocrates is credited with the first reference to ABS in 300 B.C. He described a syndrome of encircling fetal membranes resulting in the formation of bands and digital amputations. In 1652, Jan Baptista van Helmont, a Flemish physician, reported intrauterine amputations which he attributed to pregnant mothers having seen injured soldiers. Chaussier (1812) attributed limb amputations to a gangrenous process affecting the extremities in utero [1]. Montgomery (1832) and Simpson (1836) described amniotic band deformities and discussed the differences between agenesis and constriction-induced amputations [2, 3].

The etiology of ABS has been debated for centuries. Different terms are used to describe this disorder including amniotic band syndrome, amnion rupture sequence, constriction band syndrome, constriction ring syndrome, congenital annular constrictions, Streeter dysplasia, and Torpin dysplasia, among others. The number of synonyms for ABS adds to the confusion regarding its etiology. Currently, there are two main theories – intrinsic and extrinsic.

Intrinsic Theory

Intrinsic theory was popularized by Streeter in 1930. He proposed that constriction rings were localized areas of imperfectly formed tissue due to defective areas of germ plasm [1]. Patterson (1961) also believed that developmental error was responsible for the abnormalities seen in ABS [4]. In his thesis, "Congenital ring-constrictions," Patterson performed histologic studies which showed nor-

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mal tissue at the base of constriction rings. This suggests a primary defect of mesenchymal origin (i.e., failure of development of subcutaneous tissue). Other authors believe that vascular compromise or a teratogenic insult could result in the clinical appearance of ABS [5, 6]. Intrinsic theory is supported by the association of external constriction rings and internal abnormalities, such as diaphragmatic defects and ectopic gallbladders.

Extrinsic Theory

Torpin (1965) challenged Streeter's theory and reintroduced the idea of external compression as a cause for ABS [7]. Through the first trimester of pregnancy, the fetal membranes have two distinct layers – the chorion (outer layer) and the amnion (inner layer). Torpin postulated that spontaneous rupture or damage to the amnion during early gestation results in the formation of fibrous strands that can encircle fetal parts. The gestational age at amniotic rupture is critical in determining the type and severity of deformation. Early rupture (before 45 days) leads to craniofacial, central nervous system, visceral defects, or fetal death. Later ruptures more often affect developing limbs [8]. As the fetus grows, the bands become constrictive, resulting in distal deformities, neural dysfunction, vascular compromise, or amputation. If the amniotic bands are swallowed while still attached to the chorion, the tether may lead to bizarre facial clefts and palatal deficiencies that are not along the embryological planes of facial closure [9].

This theory is supported by a growing body of evidence. Fibrous bands are sometimes found entangled around constriction rings at birth [1, 10, 11]. There is documented evidence of delivery and ectopic grafting of amputated fetal parts [7, 12–14]. Distal nerve dysfunction and vascular compromise imply an extrinsic pressure effect.

Epidemiology and Associated Conditions

The incidence of ABS varies from 1/1,200 to 1/15,000 live births depending on the population surveyed and diagnostic criteria [1, 15–17]. Males and females are affected equally. Some studies show racial differences with higher rates in black patients compared to Caucasians, but these findings may be influenced by referral or selection bias rather than a true predisposition [15, 18, 19]. ABS occurs sporadically with no autosomal inheritance pattern.

Up to 60% of ABS cases have an abnormal gestational history [15]. Risk factors include prematurity (<37 weeks), low birth weight (<2500 g), maternal drug exposure, and maternal illness or trauma during pregnancy. Abnormally elevated maternal serum alpha-fetoprotein and beta human chorionic gonadotropin have been associated with ABS [20, 21].

Patients with ABS have an increased frequency of clubfoot deformity, congenital hip dislocation, and Pierre Robin sequence. Oligohydramnios appears to be the common risk factor. Researchers have postulated that early, transient oligohydramnios at the time of amniotic disruption may cause ABS [22]. Other associations include leg length discrepancy, cleft lip, hemangiomas, meningoceles, abdominal wall defects, and skin tags. At least one other disparate anomaly is associated with ABS in up to 70% of cases [15, 19].

Diagnosis

Amniotic band syndrome can sometimes be identified on prenatal imaging. Ultrasound diagnosis is difficult during the first trimester, particularly if bands are limited to the extremities, but becomes easier as the pregnancy progresses. Fibrous bands can sometimes be seen; however, the presence of thin bands alone (without fetal abnormality) is not diagnostic for ABS – they also occur in normal pregnancies [23]. Fetal asymmetry and restricted motion, with or without associated bands, raise suspicion for ABS. Prenatal radiographs may reveal skeletal defects such as absent cranial ossification, spinal deformities, or severe limb deformities. Magnetic resonance (MR) imaging is an adjunctive technique that may provide more detail if the diagnosis is unclear. Amniotic bands appear as wispy, hypo-intense strands on T2-weighted sequences [24].

After birth, deformity, malformation, or amputation is apparent on physical exam. For isolated extremity deformities, important differential diagnoses include symbrachydactyly and transverse deficiency.

Patients with symbrachydactyly typically have a small hand with simple syndactyly. Bilateral cases are rare (<10%), as opposed to ABS where multiple extremities are often involved [25]. The defect in symbrachydactyly is believed to be mesodermal; ectodermal structures, including the finger pulp, nail fold, and nail plate, are unaffected. Symbrachydactyly is associated with Poland syndrome.

Transverse deficiency can appear similar to an intrauterine amputation but is due to an arrest in formation of a limb, rather than constriction of a normal structure. Transverse deficiency, like symbrachydactyly, is more often unilateral. Deficiency may occur at any level but tends to be more proximal than ABS; the most common site for transverse deficiency is the proximal third of the forearm [26, 27]. Rudimentary digits and fingernails are often present at the end of the stump. Transverse deficiency has an autosomal recessive inheritance pattern with variable expression.

Clinical Presentation (Figs. 23.1, 23.2, and 23.3)

No two cases of ABS are the same. Deformities are always present at birth and multiple limbs are often affected. Structures proximal to the con-

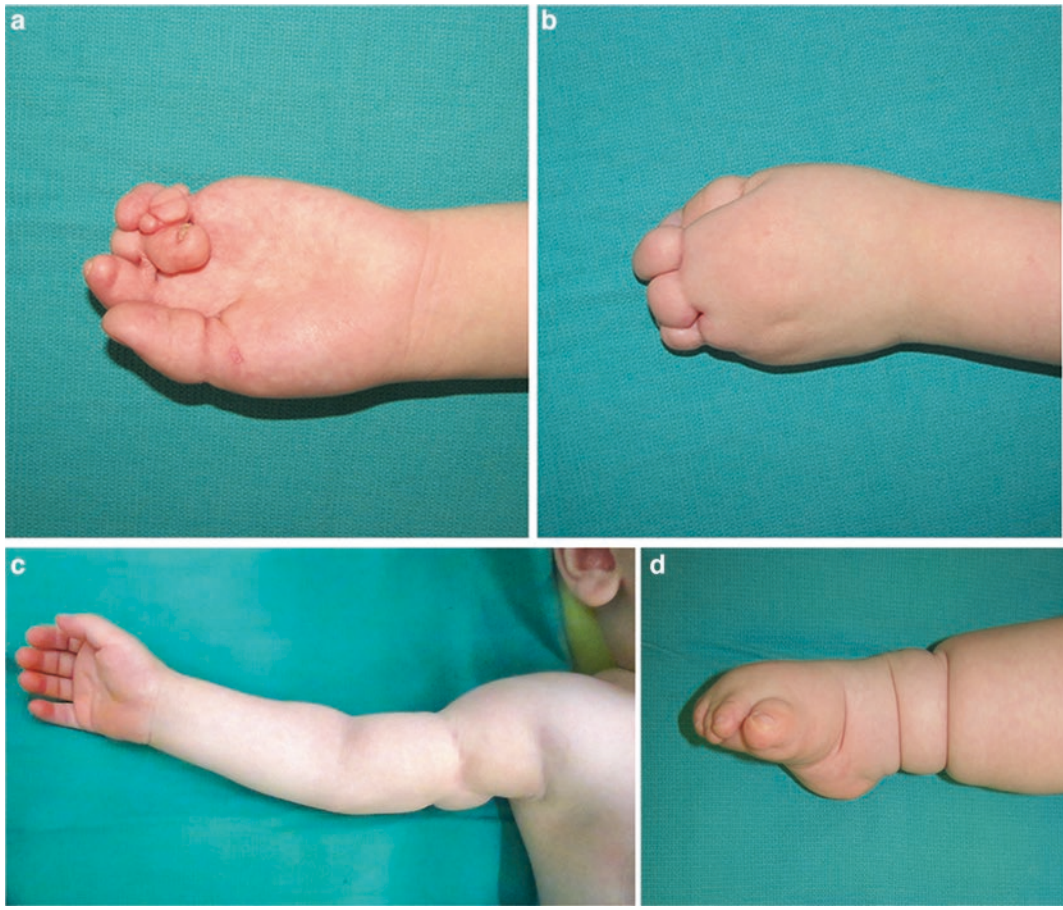

Fig. 23.1 Constriction bands involving the upper and lower extremities. The hand deformity shows constriction bands, lymphedema, acrosyndactyly, and digital amputations (**a**, **b**). Constriction bands of the arm (**c**) and lower extremity (**d**)

striction ring are normal. Many studies show a predilection for the distal parts of the hand [28–30]. Proximal rings do occur but are much less frequent [31]. Middle fingers are most commonly affected, with relative sparing of the thumb – this pattern correlates with fetal positioning with outstretched fingers and protection of a clenched thumb within the palm.

Banding in the upper extremity causes varying degrees of defects, ranging from simple dimpling to complete amputation. Scarring and dense fibrous tissue are often present near constriction bands due to ulceration and healing in utero. Generally, rings tend to be deeper on the dorsal hand and forearm. Volar rings can involve tendons and are associated with joint contractures [32]. Strictures can disrupt nerves, blood vessels, and lymphatics, resulting in nerve palsy, distal anesthesia, vascular compromise, venous congestion, and lymphedema. Skeletal involvement at birth is rare because most auto-amputations occur in utero [11].

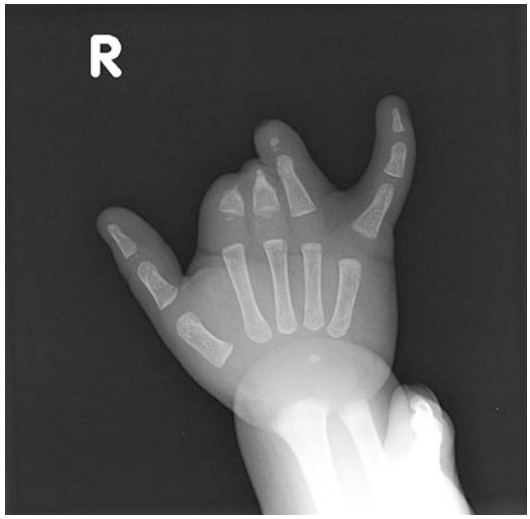

Fig. 23.2 An x-ray with tapering of distal skeletal bones due to constriction bands

ABS can also cause acrosyndactyly, which involves distal fusion of the fingers with proximal interdigital sinus tracts. Interdigital tracts indicate normal digital separation and are remnant web spaces. The synonyms pseudo-syndactyly and fenestrated syndactyly are also used to describe this condition. Acrosyndactyly does not typically involve bone, but fibrous union at constriction sites has been described. The index, middle, and ring fingers are commonly involved with the index finger typically lying most volar; the fused cluster of finger tips is said to resemble a "bunch of grapes" [33].

Most constriction bands reach their final state in utero [34]. Occasionally, rings or amputation stumps appear ulcerated after birth. Distal swelling or ischemia may require urgent band release to prevent worsening of distal necrosis.

Classification

ABS is a complex spectrum of asymmetric congenital anomalies. Several classification systems exist based on the severity and location of the constriction bands, but none are particularly helpful in the clinical setting [9, 31, 32].

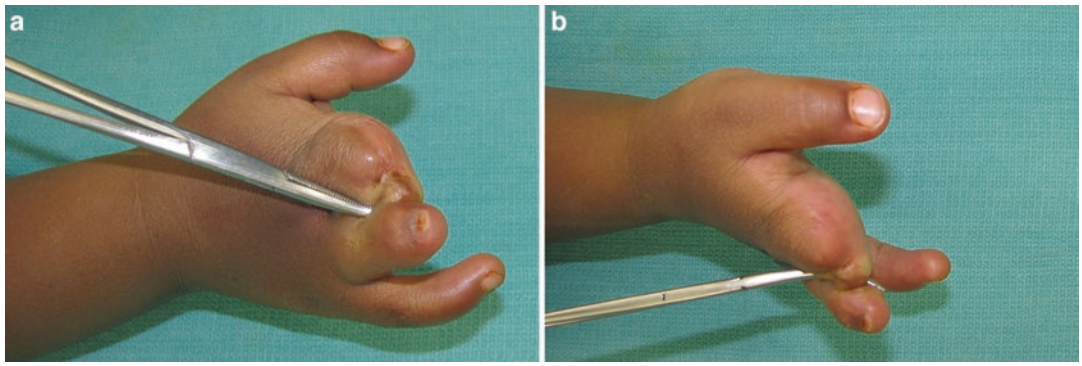

Fig. 23.3 Acrosyndactyly with a probe in the sinus tract - dorsal (**a**), lateral (**b**)

Hall classified constriction bands as mild, moderate, or severe based on whether the rings were deep enough to cause lymphedema or amputations [35]:

- Stage 1: Mild constriction, no lymphedema
- Stage 2: Moderate constriction with lymphedema
- Stage 3: Severe constriction with amputation

Weinzweig added two intermediate stages to Hall's classification system – moderate constriction ring with distal deformity and severe constriction with progressive lymphaticovenous or arterial compromise – and a Stage 4 – intrauterine amputation [34].

Patterson's classification system is the most widely used and clinically relevant [4]:

- Stage 1: Simple constriction rings
- Stage 2: Constriction rings associated with deformity of the distal part with or without lymphedema
- Stage 3: Constriction rings associated with acrosyndactyly
  - Type I: Conjoined fingertips with well-formed webs of the proper depth
  - Type II: The tips of the digits are joined, but web formation is not complete
  - Type III: Joined tips, sinus tracts between digits, and absent webs
- Stage 4: Intrauterine amputations

Treatment

Due to variability in clinical presentation, treatment must be tailored to the individual patient. Prenatal diagnosis serves to monitor progression and treatment planning. Doppler assessment of extremities in utero can identify vascular compromise [36]. Prenatal lysis of amniotic bands can prevent critical limb ischemia but risks preterm labor or causing maternal or fetal injury – risks and benefits must be carefully weighed [37].

Management of constrictive rings in the upper extremity after birth ranges from observation to emergent limb salvage. Superficial rings without distal swelling can be observed or repaired electively to improve appearance. For deep circumferential rings with good distal function, the standard treatment includes Z- or W-plasty. In patients with acrosyndactyly, resurfacing of the web space is required to separate digits and improve finger function. When constrictive bands result in overt ischemia or osteomyelitis, amputation may be required [25, 38]. Complex reconstructive procedures such as toe-to-finger transfer, bone-lengthening, and pollicization may be performed to restore function in cases of digital hypoplasia and amputation.

Nonsurgical Management

Nonoperative management is appropriate for patients without functional deficits. Superficial bands without severe distal edema or neurovascular compromise can be observed. Intervention may become necessary as the child grows or for aesthetic improvement. Patients with amputations must be carefully assessed. Children can easily adapt, and if function is acceptable, no treatment is needed. It is better to modify tools and equipment to fit the child's needs rather than undertake a complex reconstruction with no clear functional benefit.

Surgical Management

Surgery is indicated for acute vascular compromise, severe distal lymphedema, nerve compression, or to improve function. Bands managed nonoperatively should be routinely re-evaluated for changes in distal function such as the onset of cold intolerance or worsening deformity with growth.

Timing

The timing of surgery is driven by disease severity. In some cases, it is possible to see amniotic bands encircling the fingers and toes

of newborns – these can simply be removed. Occasionally, constriction bands cause active vascular compromise or severe distal lymphedema at birth; this requires emergent decompression to prevent ongoing tissue death. Dorsal, hemi-circumferential release typically yields dramatic improvement. The volar portion of the ring and any redundant soft tissue can be managed during a second stage. Division of small, simple soft tissue bridges as the result of acrosyndactyly can be divided under local anesthesia during the neonatal period.

In the absence of critical ischemia, most surgeries for ABS can be performed between 6 and 12 months of age when general anesthesia is safer. Bilateral procedures are possible but are best performed before the child is ambulatory. More complex procedures such as skeletal lengthening or digital transpositions can be delayed to allow for skeletal growth. As with most congenital hand anomalies, the goal is to complete all surgery before the child enters school.

Preoperative Planning

Constriction band surgery is performed under general anesthesia with the patient positioned supine and the affected extremity on a pediatric hand table. Tourniquet control and loupe magnification are mandatory for meticulous dissection. Deep bands with neurovascular compromise may require nerve excision and grafting – a microscope, micro-instruments and suture, fibrin glue, and nerve graft should be available.

Preoperative family counseling with discussion of goals and realistic outcomes is critical. The severity of deformity and functional deficit guides discussion. Very deep rings are harder to correct. Some degree of distal edema will always persist. Patients with preoperative nerve palsies should not expect full muscle recovery. Acrosyndactyly release improves function but the hand will never appear normal. Families are advised that staged or secondary procedures may be necessary as the child grows.

Constriction Band Release (Figs. 23.4, 23.5, and 23.6)

The standard treatment for constriction bands is excision of the constriction ring with adjacent tissue rearrangement. Regardless of the technique used, authors agree that abnormal skin and soft tissue should be completely excised; scarred and fibrotic tissue is immobile and not suitable for use in the reconstruction. Transverse incisions are made on both sides of the constriction ring at the point where the skin begins to invaginate. The intervening band and all abnormal tissue are excised. Deep fascial attachments are released and flaps are fully mobilized both proximally and distally.

Z-plasty around the circumference of the band breaks tension and adds length but does not treat the soft tissue defect; hourglass deformities can persist if the skin and subcutaneous tissue are sutured in a single layer. To improve contour, Upton and Tan describe a technique that involves mobilization of a layer of adipose tissue separate from the dermis with advancement of subcutaneous tissue into the defect. The skin flaps of the Z-plasty are then transposed separately over the adipose tissue [11].

Standard 60-degree Z-plasty with transposition of large skin flaps is recommended to preserve the viability of the skin flaps. Subcutaneous veins are preserved to facilitate venous drainage and reduce postoperative swelling. For deep, circumferential bands, staged release and reconstruction should be considered with an interval of at least 6–12 weeks between stages – this allows scars to soften and restoration of cutaneous blood flow.

Repair of constriction rings around fingers follows the same principles; however, skin incisions are made so that the final scar lies along the mid-lateral line to minimize contracture and visible scarring. When the constriction ring is broad and closure by Z-plasty is not possible, local flaps may be necessary.

Regardless of technique used, sterile, nonconstrictive dressings and a splint are applied. Infants and toddlers are placed in a long-arm cast with the elbow flexed at 90°. The patient is

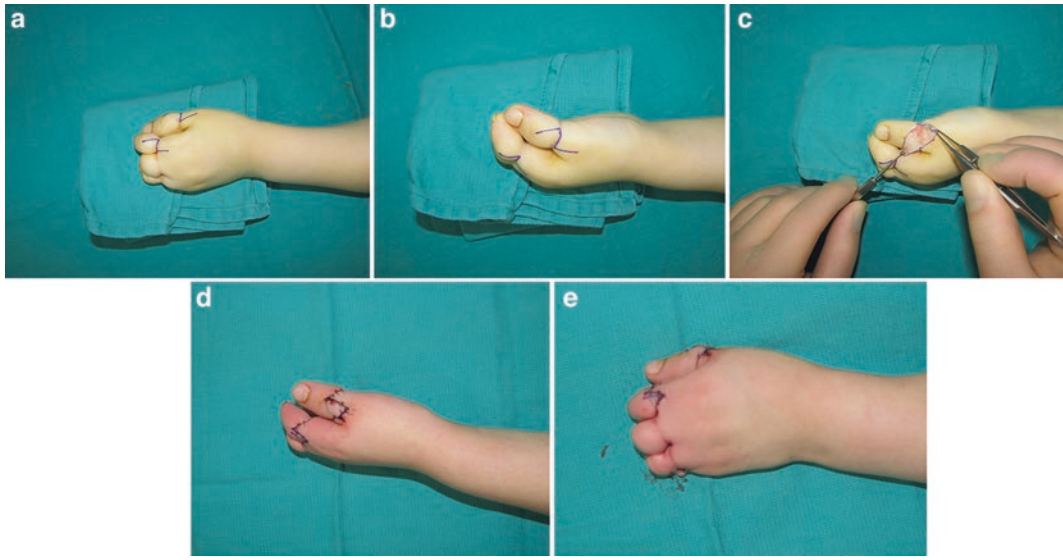

Fig. 23.4 Correction of constriction rings around digits using a Z-plasty. Flap design (a, b), flap elevation (c), flap transposition and inset (d, e)

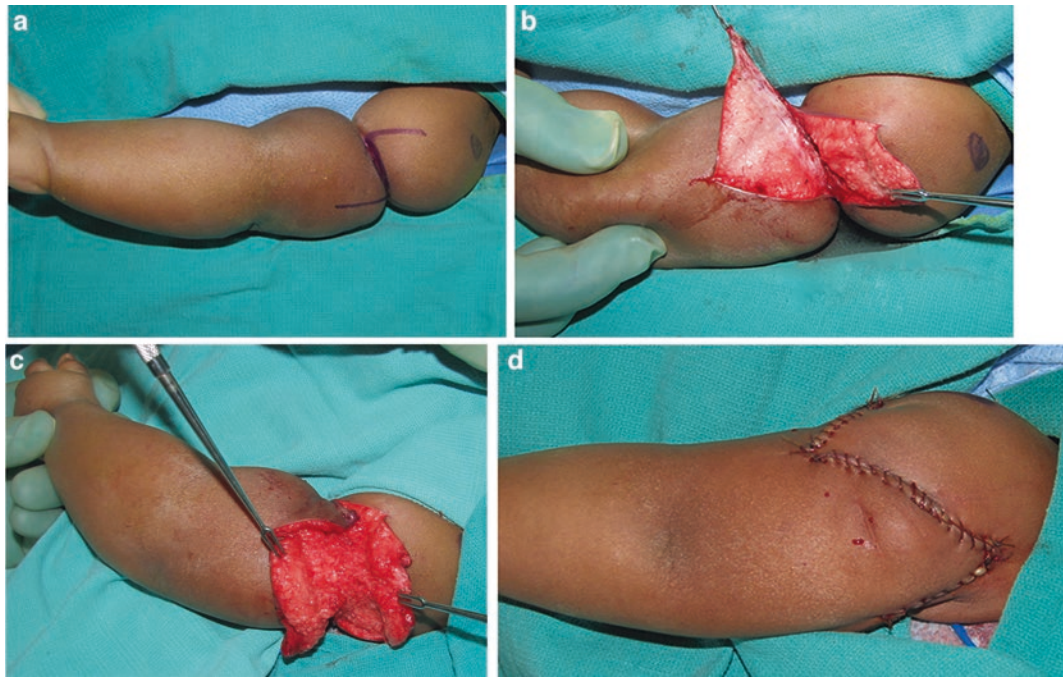

Fig. 23.5 Correction of a circumferential arm constriction band using a Z-plasty. Flap design (**a**), flap elevation (**b**, **c**), flap transposition and inset (**d**)

seen 10–14 days after surgery for cast removal and to begin scar management and edema control. Parents are taught to gently massage the scar with lotion. Silicone sheets are placed over the scar nightly for 3 months and patients are instructed to avoid sun exposure on the scar for 6 months. Compressive wraps or sleeves reduce swelling.

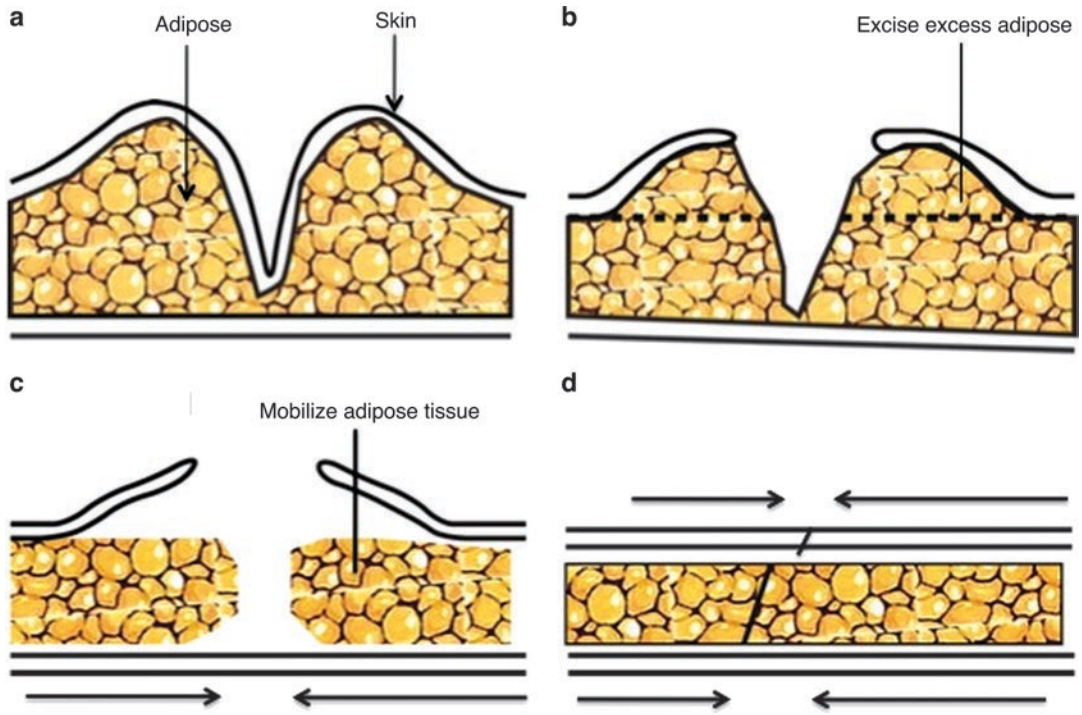

Fig. 23.6 Schematic drawings for release of a constriction band using Upton's technique. (**a**) Excision of all skin in the side walls. (**b**) Debulking of excess adipose tissue. (**c**) Subcutaneous adipose flaps are mobilized as needed to correct the contour deformity. (**d**) Skin and subcutaneous closures are staggered

Acrosyndactyly Repair (Fig. 23.7)

The purpose of acrosyndactyly repair is to improve function. The number of fingers is not as important as their length, bulk, stability, and spacing. The goals in acrosyndactyly surgery are to separate the digits, preserve length, and create a web space deep enough to allow for independent finger use.

Surgical technique depends on the complexity of the deformity. In patients with well-formed fingers and web spaces of proper depth, separation is straightforward and can be done in early infancy. Greater degrees of distal fusion present a challenge. The fingers may be stacked on top of each other in the volar-dorsal direction rather than side-by-side and nonadjacent fingers can be fused. Epithelialized sinus tracts are typically distal to the level of the proper web space and not useful in the reconstruction. It is often difficult to locate the neurovascular bundles and even harder to determine which finger they belong to. Separation of multiple adjacent digits should be performed in a staged fashion to decrease the risk of vascular compromise. Patients with complex acrosyndactyly often require multiple procedures to deepen the web space or lengthen the digits after separation.

Although acrosyndactyly separation can be much more demanding, any standard syndactyly technique can be used. Fingers are separated using interdigitating flaps with care taken to preserve the neurovascular bundles. The epithelialized tract is excised and a dorsal skin flap is raised to resurface the web space. Flaps can be judiciously defatted to aid in tension-free closure. Full-thickness skin grafts are used if needed for skin deficits. Sterile, conforming dressings and a long-arm cast are applied.

The patient is seen in the office 7 days after surgery to assess skin graft take. Once fully healed, patients can resume activity without

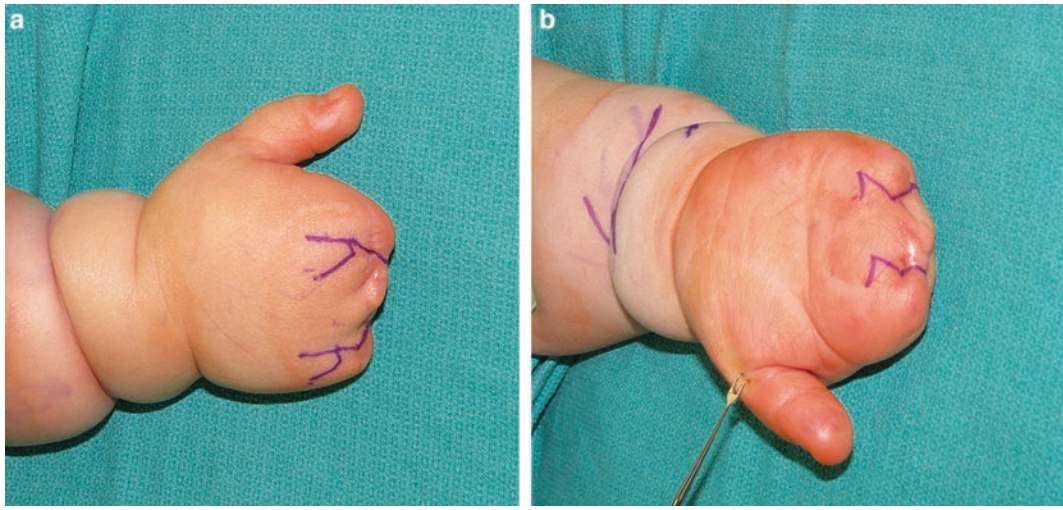

Fig. 23.7 Incision planning with a proximally based dorsal rectangular flap to resurface the web space - dorsal (**a**), volar (**b**)

restriction. Elastomer molds are applied to the web spaces nightly for 3 months postoperatively to prevent web creep.

Reconstruction of Digital Hypoplasia

Reconstruction of digital hypoplasia associated with ABS is indicated to improve function. A basic hand requires a minimum of two digits that are sensate and pain-free. One digit must be mobile for grasp and pinch against a stable post. A third digit facilitates power grasp and tripod pinch [39]. Procedures to consider for digital hypoplasia include web space deepening, bone lengthening, on-top plasty, pollicization, and toe-to-hand transfer.

Web space deepening can increase finger excursion and improve grip. If the surrounding tissue is pliable, this can be accomplished by adjacent tissue rearrangement with a Z-plasty or jumping man flap. When fingers are present but short, distraction osteogenesis can be considered. On-top plasty transposes one finger onto another for lengthening or improved positioning [40]. In cases of complete digital absence, microvascular toe-to-finger transfer is performed. Multiple toes can be transferred to reconstruct the thumb and an ulnar digit. Good range of motion and growth of transferred digits can be expected. Children who undergo toe transfer adapt easily and have excellent functional outcomes [41–44].

Complications

The most worrisome complication after constriction band release or acrosyndactyly reconstruction is vascular compromise. The location of neurovascular bundles are unpredictable; loupe magnification and meticulous surgical dissection is mandatory. Gentle or no exsanguination of the limb prior to tourniquet inflation is helpful to identify small vessels.

Other possible complications are common to most hand procedures – bleeding, infection, delayed wound healing, skin flap necrosis, and skin graft failure. Local flaps such as Z-plasties should be designed wide enough and released proximal enough to transpose without undue tension. It is preferable to leave small areas open to heal by secondary intention rather than close under tension, which may compromise flap blood supply and compress deeper structures. Very deep bands are the hardest to correct and the most prone to complications.

Outcomes

Constriction band excision is successful when all abnormal tissue are excised. Deformities do not recur and patients and families are highly satisfied [15, 19, 29, 38]. Many patients have some level of cold intolerance in affected extremities but chronic pain has not been reported. No studies have looked specifically at functional outcomes.

Patients with preoperative nerve dysfunction have worse overall outcomes. In most cases, band release, nerve decompression, and neurolysis do not improve distal function [45, 46].

Summary

Amniotic band syndrome is a rare congenital disorder that affects the upper extremity. Constriction rings, acrosyndactyly, and intrauterine amputations are common manifestations in the hand. The goals of management are to prevent further tissue damage and improve function. Improvement of appearance is a secondary benefit. Treatment is individualized based on the patient's unique presentation and functional needs.

References

1. Baker CJ, Rudolph AJ. Congenital ring constrictions and intrauterine amputations. Am J Dis Child. 1971;121(5):393–400.
2. Montgomery W. Spontaneous amputation in utero. Dublin J Med Sci. 1832;2(49).
3. Simpson J. Essays on diseases of the placenta. Dublin J Med Sci. 1836;10(220).
4. Patterson TJ. Congenital ring-constrictions. Br J Plast Surg. 1961;14:1–31.
5. Bamforth JS. Amniotic band sequence: Streeter's hypothesis reexamined. Am J Med Genet. 1992;44(3):280–7.
6. Lockwood C, Ghidini A, Romero R, Hobbins JC. Amniotic band syndrome: reevaluation of its pathogenesis. Am J Obstet Gynecol. 1989;160(5 Pt 1):1030–3.
7. Torpin R. Amniochorionic mesoblastic fibrous strings and amnionic bands: associated constricting fetal malformations or fetal death. Am J Obstet Gynecol. 1965;91:65–75.
8. Higginbottom MC, Jones KL, Hall BD, Smith DW. The amniotic band disruption complex: timing of amniotic rupture and variable spectra of consequent defects. J Pediatr. 1979;95(4):544–9.
9. Bouguila J, Ben Khoud N, Ghrissi A, Bellalah Z, Belghith A, Landolsi E, et al. [Amniotic band syndrome and facial malformations]. Rev Stomatol Chir Maxillofac. 2007;108(6):526–9.
10. Light TR, Ogden JA. Congenital constriction band syndrome. Pathophysiology and treatment. Yale J Biol Med. 1993;66(3):143–55.
11. Upton J, Tan C. Correction of constriction rings. J Hand Surg Am. 1991;16(5):947–53.
12. Inoue G, Inagaki Y. Extra digit arising from the forearm. J Hand Surg Am. 1991;16(4):650–2.
13. Rayan GM. Ectopic implantation of constriction band intrauterine digital amputation. Plast Reconstr Surg. 2001;107(4):1000–2.
14. Torpin R, Faulkner A. Intrauterine amputation with the missing member found in the fetal membranes. JAMA. 1966;198(2):185–7.
15. Foulkes GD, Reinker K. Congenital constriction band syndrome: a seventy-year experience. J Pediatr Orthop. 1994;14(2):242–8.
16. Fischer PM, Biddinger P, Drobnes WE. The amniotic band syndrome. Am Fam Physician. 1983;27(2):201–3.
17. Seeds JW, Cefalo RC, Herbert WN. Amniotic band syndrome. Am J Obstet Gynecol. 1982;144(3):243–8.
18. Garza A, Cordero JF, Mulinare J. Epidemiology of the early amnion rupture spectrum of defects. Am J Dis Child. 1988;142(5):541–4.
19. Moses JM, Flatt AE, Cooper RR. Annular constricting bands. J Bone Joint Surg Am. 1979;61(4):562–5.
20. Aitken DA, May HM, Ferguson-Smith MA, Howat R, Kohler HG. Amniotic band disruption syndrome associated with elevated amniotic AFP and normal acetylcholinesterase gel test. Prenat Diagn. 1984;4(6):443–6.
21. Sifakis S, Mantas N, Konstantinidou A, Koukoura O, Avgoustinakis E, Koumantakis E. A stillborn fetus with amniotic band syndrome and elevated levels of alpha-fetoprotein plus beta-human chorionic gonadotropin: a case report. Fetal Diagn Ther. 2008;24(2):111–4.
22. Houben JJ. Immediate and delayed effects of oligohydramnios on limb development in the rat: chronology and specificity. Teratology. 1984;30(3):403–11.
23. Burton DJ, Filly RA. Sonographic diagnosis of the amniotic band syndrome. AJR Am J Roentgenol. 1991;156(3):555–8.
24. Neuman J, Calvo-Garcia MA, Kline-Fath BM, Bitters C, Merrow AC, Guimaraes CV, et al. Prenatal imaging of amniotic band sequence: utility and role of fetal MRI as an adjunct to prenatal US. Pediatr Radiol. 2012;42(5):544–51.
25. Moran SL, Jensen M, Bravo C. Amniotic band syndrome of the upper extremity: diagnosis and management. J Am Acad Orthop Surg. 2007;15(7):397–407.

26. Ogino T, Saitou Y. Congenital constriction band syndrome and transverse deficiency. J Hand Surg Br. 1987;12(3):343–8.
27. Swanson AB, Swanson GD, Tada K. A classification for congenital limb malformation. J Hand Surg Am. 1983;8(5 Pt 2):693–702.
28. Kino Y. Clinical and experimental studies of the congenital constriction band syndrome, with an emphasis on its etiology. J Bone Joint Surg Am. 1975;57(5):636–43.
29. Wiedrich TA. Congenital constriction band syndrome. Hand Clin. 1998;14(1):29–38.
30. Tada K, Yonenobu K, Swanson AB. Congenital constriction band syndrome. J Pediatr Orthop. 1984;4(6):726–30.
31. Browne D. The pathology of congenital ring constrictions. Arch Dis Child. 1957;32(166):517–9.
32. Bernal E, Oeltjen JC. Constriction ring syndrome. J Craniofac Surg. 2009;20(4):1018–20.
33. Flatt AE. The care of congenital hand anomalies. 2nd ed. St. Louis: Quality Medical Publishers; 1994: x, 466.
34. Weinzweig N. Constriction band-induced vascular compromise of the foot: classification and management of the "intermediate" stage of constriction-ring syndrome. Plast Reconstr Surg. 1995;96(4):972–7.
35. Hall EJ, Johnson-Giebink R, Vasconez LO. Management of the ring constriction syndrome: a reappraisal. Plast Reconstr Surg. 1982;69(3):532–6.
36. Sentilhes L, Verspyck E, Eurin D, Ickowicz V, Patrier S, Lechevallier J, et al. Favourable outcome of a tight constriction band secondary to amniotic band syndrome. Prenat Diagn. 2004;24(3):198–201.
37. Ronderos-Dumit D, Briceno F, Navarro H, Sanchez N. Endoscopic release of limb constriction rings in utero. Fetal Diagn Ther. 2006;21(3):255–8.
38. Kawamura K, Chung KC. Constriction band syndrome. Hand Clin. 2009;25(2):257–64.
39. Entin MA. Salvaging the basic hand. Surg Clin North Am. 1968;48(5):1063–81.
40. Ogino T, Kato H, Ishii S, Usui M. Digital lengthening in congenital hand deformities. J Hand Surg Br. 1994;19(1):120–9.
41. Foucher G, Medina J, Navarro R, Nagel D. Toe transfer in congenital hand malformations. J Reconstr Microsurg. 2001;17(1):1–7.
42. Kay SP, Wiberg M, Bellew M, Webb F. Toe to hand transfer in children. Part 2: functional and psychological aspects. J Hand Surg Br. 1996;21(6):735–45.
43. Van Holder C, Giele H, Gilbert A. Double second toe transfer in congenital hand anomalies. J Hand Surg Br. 1999;24(4):471–5.
44. Vilkki SK. Advances in microsurgical reconstruction of the congenitally adactylous hand. Clin Orthop Relat Res. 1995;314:45–58.
45. Uchida Y, Sugioka Y. Peripheral nerve palsy associated with congenital constriction band syndrome. J Hand Surg Br. 1991;16(1):109–12.
46. Jones NF, Smith AD, Hedrick MH. Congenital constriction band syndrome causing ulnar nerve palsy: early diagnosis and surgical release with long-term follow-up. J Hand Surg Am. 2001;26(3):467–73.

Arthrogryposis

24

Emma Levine and Ann E. Van Heest

Introduction

Arthrogryposis is a descriptive term that describes an individual with congenital contractures of three or greater joints. Arthrogryposis is a congenital disorder of formation within the neuromuscular axis. In arthrogryposis, normal limb muscle tissue is replaced by fatty, fibrous tissue [1]. Classification of arthrogryposis can include classic, distal, and syndromic arthrogryposis. Classification helps us understand the extent of the disability.

By definition, arthrogryposis is congenital contractures of three or greater joints in at least two body areas. It is nonprogressive. Its incidence is 1 in 3000–5000 live births. Arthrogryposis is not a specific diagnosis, but rather a clinical finding. It is a characteristic that is seen in over 300 different disorders. An isolated congenital contracture affects only a single area of the body, such as seen in congenital club foot, which occurs in 1 of every 500 live births. This is distinctly different than arthrogryposis, which affects three or more different joints of the body. Treatment is based on functional disabilities and is aimed at improving functional abilities by improving limb position, strength, and mobility. The primary long-term goals of treatment are to improve use of adaptive patterns to allow for walking and independence with activities of daily living.

Classification

As shown in Fig. 24.1, congenital contractures can be divided into *isolated* congenital contractures, such as club foot, or *multiple* congenital contractures which are termed arthrogryposis [2]. Hall has classified arthrogryposis as limb only, limb and viscera, or limb and CNS [3]. Clinically, this presents as three distinct types: classic (amyoplasia), distal, and syndromic.

Classic arthrogryposis is also known as amyoplasia, or arthrogryposis multiplex congenital (AMC). This is a distinct form of arthrogryposis with characteristic clinical findings. Amyoplasia refers to *a* = no, *myo* = muscle, *plasia* = growth. In this condition, the shoulders are usually internally rotated and adducted, the elbows are extended, the wrists are flexed and ulnarly deviated, the fingers are stiff, and the thumbs are in the palm (Fig. 24.2). If there is lower extremity involvement, the hips may be dislocated, the knees are extended, and the feet often have severe equinovarus contractures. Many patients have a midfacial hemangioma. Associated conditions can exist. In one series, 10% of children had

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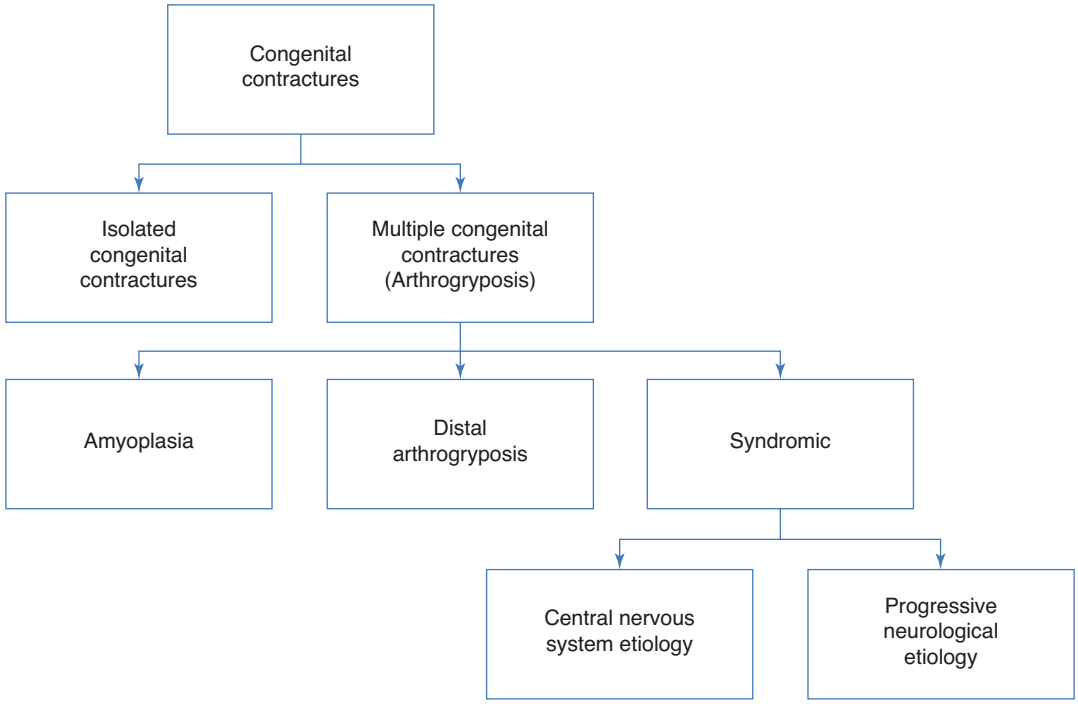

Fig. 24.1 Classification of types of arthrogryposis [2]

gastroschisis or bowel atresia [3]. In most clinical series, symmetrical involvement of the upper and lower extremities occurs. Other variations include upper extremity only, lower extremity only, or asymmetric involvement. In Hall's original description of 135 patients with amyoplasia, all cases were sporadic; however, there was an increased prevalence in twins and it occurred more commonly in conditions that would lead to decreased intrauterine limb movement, such as a bicornuate uterus, oligohydramnios, or intrauterine crowding [4].

Distal arthrogryposis includes ten distinct types as seen in Table 24.1. As described in the Online Mendelian Inheritance in Man® (OMIM®) [5], distal arthrogryposis includes what was previously called Freeman–Sheldon syndrome, Sheldon–Hall syndrome, Gordon syndrome, and multiple pterygium syndrome. Specific diagnostic criteria are necessary to make a diagnosis of a distal arthrogryposis. In the upper limb, major diagnostic criteria include camptodactyly, hypoplastic or absent flexion creases, overriding fingers, and ulnar deviation of the wrist (Fig. 24.3). This is commonly referred to as "the windblown hand." For the lower limb, major diagnostic criteria include talipes equinovarus, calcaneovalgus deformities, congenital vertical talus, and/or metatarsus adductus. To be affected, an individual must exhibit two or more major criteria; however, when a first-degree family member meets diagnostic criteria, other family members only need one major criterion to be affected.

Syndromic arthrogryposis includes multiple CNS disorders or neuromuscular diseases, which include multiple congenital contractures. Developmental abnormalities that affect the forebrain, such as microcephaly, are sometimes associated with arthrogryposis. Genetic peripheral neuropathies with an onset during fetal life are rare causes of arthrogryposis. Neuromuscular junction blockade in fetuses carried by mothers with myasthenia gravis or autoantibodies against fetal acetylcholine receptors can result in arthrogryposis [6].

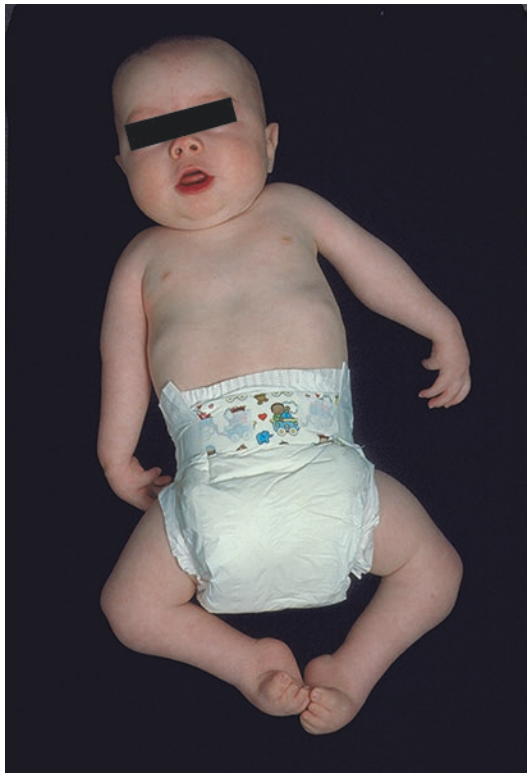

Fig. 24.2 A baby with classic arthrogryposis shows the typical features of internally rotated shoulders, extended elbows, flexed and ulnarly deviated wrists, stiff fingers, and the thumbs are in the palm. Additionally, her hips are dislocated, her knees are extended, and her feet have severe equinovarus contractures

Table 24.1 Distal arthrogryposis syndromes

Syndrome	New Label	OMIM[a] Number
Distal arthrogryposis type 1	DA1	108120
Distal arthrogryposis type 2A (Freeman–Sheldon syndrome)	DA2A	193700
Distal arthrogryposis type 2B (Sheldon–Hall syndrome)	DA2B	601680
Distal arthrogryposis type 3 (Gordon syndrome)	DA3	114300
Distal arthrogryposis type 4 (scoliosis)	DA4	609128
Distal arthrogryposis type 5 (opthalmoplegia, ptosis)	DA5	108145
Distal arthrogryposis type 6 (sensorineural hearing loss)	DA6	108200
Distal arthrogryposis type 7 (trismus pseudo-camptodactyly)	DA7	158300
Distal arthrogryposis type 8 (autosomal dominant multiple pterygium syndrome)	DA8	178110
Distal arthrogryposis type 9 (congenital contractural arachnodactyly)	DA9	121050
Distal arthrogryposis type 10 (congenital plantar contractures)	DA10	187370

[a]Online Mendelian Inheritance in Man® (OMIM®)

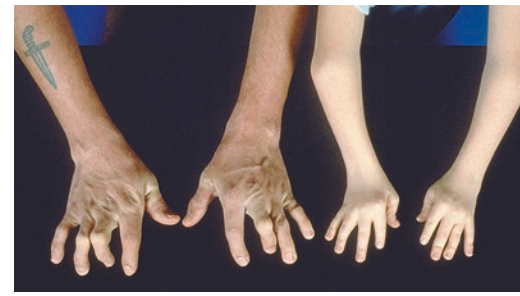

Fig. 24.3 Clinical features of distal arthrogryposis are seen in this father and son. The autosomal dominant disorder shows camptodactyly in the digits, with mild ulnar deviation of the wrists. Dislocated radial heads are noted by the prominence in the lateral elbow for the son

Etiology

Multiple congenital contractures appear to have a final common pathway. In the normal fetus, joint formation occurs by cavitation between 26 and 52 days postfertilization. In order for normal joint development to occur, there must be adequate space, nerve supply, and muscle activity to promote normal joint formation. A disruption in any of these elements will lead to loss of normal joint movement, causing congenital contracture [2, 6]. Restricted movement can occur through fetal crowding with multiparous births, or uterine abnormalities such as a bicornuate uterus. Maternal illness can cause restricted movement, such as myasthenia gravis. Abnormal muscle or nerve development additionally leads to congenital contractures. Oligohydramnios has a known association with multiple congenital contractures. Since anything that decreases fetal movement can lead to multiple contractures, this is something that can be diagnosed in utero as earlier as 16 weeks if the fetus has extended elbows. This diagnosis is missed 75% of the time (insert citation). Fetuses with arthrogryposis are often breech or need to be delivered via C-section because of abnormal fetus positioning. Ten percent of fetuses will have perinatal long bone fractures [1]. Arthrogryposis can be inherited in several ways: autosomal dominant, autosomal

recessive, X-linked, and maternal inheritance of some mitochondrial disorders [7]. Further, there is an equal male to female ratio in those presenting with arthrogryposis [7].

Classic arthrogryposis (amyplasia) is not known to have a specific genetic cause and has a range of severity. Discordant monozygotic twins have an increased rate of amyplasia (6.6% of affected individuals have an unaffected monozygotic twin) [1]. Amyplasia is associated with several other anomalies attributed to vascular compromise: 9% have gastroschisis, bowel atresia, or both, 2.7% have trunk muscle deficiencies, 12% have digit compromise, and 4.3% have constriction bands of limbs or digits. Further, 3–5% have intellectual disabilities [1].

Distal arthrogryposes are a group of autosomal dominant disorders that mainly involve the distal aspects of the limbs, characterized by primary hand and foot involvement, limited involvement of proximal joints, and variable expressivity [8]. Mutations most frequently occur in sarcomere muscle proteins such as troponin, tropomyosin, and myosin [1]. Mutations in at least five genes (TNN12, TNNT3, TPM2, MYH3, and MYH8) that encode components of the fast twitch contractile myofibers have been associated with distal arthrogryposis [9–11]. For example, in approximately 90% of cases of distal arthrogryposis type 2, mutations are found in MYH3 (this gene is expressed only during fetal life from 16 to 24 weeks), a gene that encodes embryonic myosin. Distal arthrogryposes may also be from a multigene background rather than a mutation in a single gene [1]. Mechanisms by which altered contractility leads to congenital contracture are not known.

Syndromic arthrogryposis is commonly most severe and includes many CNS and muscular diseases [2]. CNS malformations that are associated with diminished corticospinal activation of spinal cord motor neurons, such as hydranencephaly or microcephaly, most likely contribute to fetal hypomobility and development of congenital contractures [12]. Congenital neuropathies, myopathies, and muscular dystrophies may similarly lead to multiple congenital contractures due to lack of normal fetal movement.

Historical Perspective

Adolph Wilhelm Otto first described an infant with multiple congenital contractures noted at autopsy in 1841. He described this as “a monster with inwardly curved extremities.” This has been credited as the first written description of arthrogryposis.

Clinical Manifestations of Arthrogryposis

The most common presentation to the hand surgeon includes classic arthrogryposis and distal arthrogryposis. Many children with syndromic arthrogryposis that includes limb and viscera are not surgical candidates. Patients with limb and CNS involvement have a lethal presentation as stillborn.

Classic Arthrogryposis (Amyoplasia)

Patients with classic arthrogryposis (amyoplasia) most commonly have lack of formation of normal musculature. In most cases, it is affects joints symmetrically and affects all four limbs [1]. The lack of normal muscles leads to multiple congenital joint contractures in the upper extremity. The most common pattern of deformity in the upper extremity is internal rotation of the shoulder with weak or absent shoulder girdle muscles; extension contracture of the elbow with weak or absent biceps and brachialis muscles; pronated, flexed, and ulnarly deviated wrists, with weak or absent wrist extension; hands have partially flex fingers; and rigid digits with thumb and palm deformity. In 15% of cases, there is hip dislocation; knees may be fixed in extension or flexion; feet are almost always in severe equinovarus position. The jaw and trunk are normally spared [1]. The degree of stiffness and weakness ranges from mild to severe and is not progressive.

The goal of treatment for children with arthrogryposis is to improve their quality of life by facilitating functional independence. At birth, nonoperative measures are initiated, with range

Table 24.2 Surgical treatment options in amyoplasia

Shoulder	Derotational humeral osteotomy
Elbow	Elbow capsular release
	Elbow tendon transfers
	Radial head excision
Wrist	Dorsal carpal wedge osteotomy
	Tendon transfer
Digits	Syndactyly release
Thumb	Tendon transfer
	First web release
	Thumb adductor release

of motion exercises, muscle and joint stretching, and splinting of specific joints to improve passive range of motion. Treatment to improve the function of the upper limb requires comprehensive planning with simultaneous assessment of shoulder, elbow, wrist, forearm, and hand function.

Nonoperative management is initiated at birth, and most commonly carried out for at least 12 months. Improvement of joint mobility is common, particularly at the elbow and wrist. The elbow is most critical in terms of achieving passive mobility to gain hand-to-mouth function. If after nonoperative treatment functional independence is still not possible, consideration for surgical treatment is explored [13]. Possible surgical treatment options are shown in Table 24.2.

Clinical Features of Amyoplasia

The joints of the upper and lower extremities are stiff in varying degrees. The skin is smooth over the joints, with reduced or absent skin creases. Oftentimes at large joints, particularly the shoulders, skin dimples are seen. Reduced mass of the muscles is visualized, and palpation shows an increase of firm tissue with an increase in fibrous tissue. A similarity in facial appearance is notable; intellectual development is usually normal.

Treatment of the Shoulder

In most patients, shoulder internal rotation is an integral part of their ability to perform bi-manual skills, as the shoulder internal rotation helps bring their hands to midline and cross over to assist with grasp, as shown in Fig. 24.4. However, in some children, if the internal rotation contracture is severe and actually interferes with function, an external rotational osteotomy of the proximal humerus can be performed to improve function.

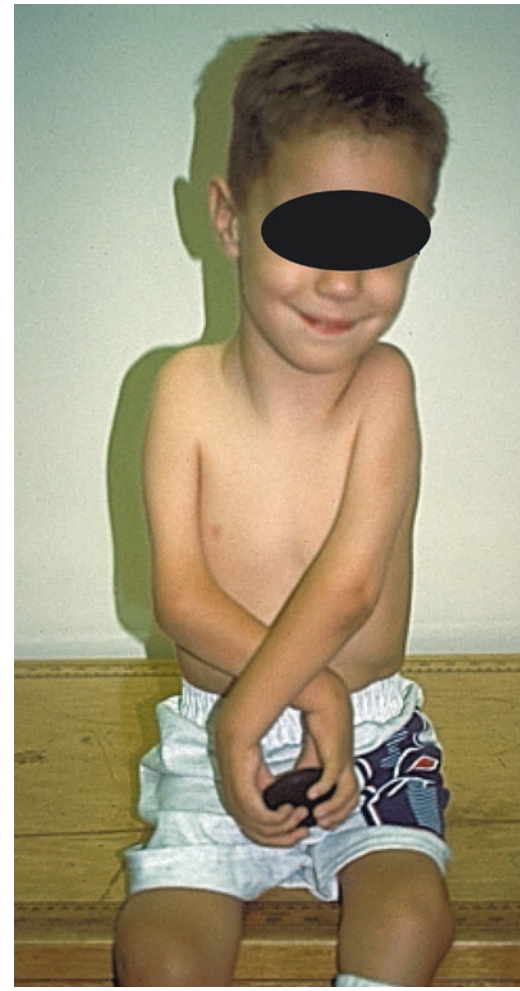

Fig. 24.4 De-rotation osteotomy of the shoulder can be indicated for severe internal rotation positioning of the limb causing significant dysfunction. Care must be taken with judicious use of this operation as most children with amyoplasia use the shoulder internal rotation to assist with bimanual hand use as shown in this figure

Treatment of the Elbow

Nonoperative management is initiated at birth, and most commonly carried out for at least

12 months. Improvement of joint mobility is common, particularly at the elbow and wrist. The elbow is most critical in terms of achieving passive mobility to gain hand-to-mouth function. If after nonoperative treatment elbow flexion is insufficient to allow passive mobility of hand to mouth, surgical treatment would be indicated. Specifically, if less than 90° of flexion is achieved and the hand cannot be brought to the mouth passively, a posterior elbow capsulotomy with triceps lengthening would be indicated [13]. Indications for surgery are less than 90° of passive elbow flexion and an inability to reach the hand to the mouth.

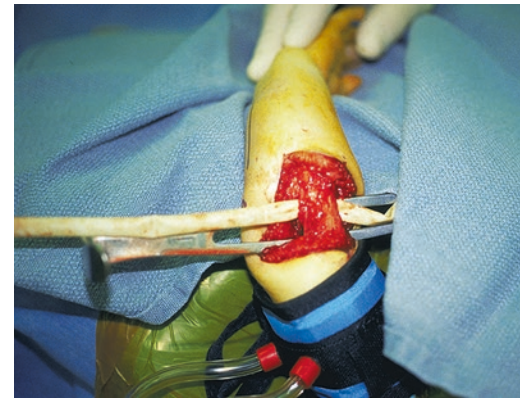

Fig. 24.5 Posterior elbow capsular release with triceps lengthening is performed through a posterior incision. The triceps is isolated, as shown here, and is subsequently lengthened using a Z-lengthening technique

Surgical Technique

Posterior elbow capsulotomy with triceps lengthening is performed with the patient in a lateral decubitus position. A sterile tourniquet is used, at least through initial dissect to allow identification and protection of the ulnar nerve. The posterior aspect of the elbow is identified by palpation. Caution should be taken that oftentimes the limb is so internally rotated that the medial epicondyle can be mistaken for the olecranon. A curvilinear incision is made down the posterior aspect of the elbow. In arthrogryposis, significance of cutaneous tissue with minimal tissue planes is a common pathological finding. The ulnar nerve is identified as it passes through the inner muscular septum and through the cubital tunnel. Osborne's fascia is released, and the ulnar nerve is protected with a vessel loop. The sterile tourniquet then can be removed to allow greater proximal dissection and triceps mobilization once the ulnar nerve has been identified and protected, particularly in the small child. The triceps is isolated on its insertion at the olecranon. Dissection is carried out medially and laterally, isolating the triceps tendon back to the level of the musculotendinous junction as shown in Fig. 24.5. A Z-lengthening or V-Y advancement is performed; at least doubling the length of the tendon will be necessary to provide appropriate elbow flexion.

The posterior aspect of the capsule is then incised, exposing the joint surface. The arthrotomy is extended medially and laterally to allow maximum elbow flexion with gentle passive stretch. It is important to be careful about increasing the joint mobility, as physeal fractures can occur if excessive force is used. Dissection most commonly needs to be carried out at least to the mid-axial line and may include the posterior aspects of the medial and lateral ligaments. Full flexion of the elbow is the goal of the posterior capsular release. The triceps is then repaired in an elongated position with use of a nonabsorbable or reinforced suture. The skin is closed, and a light dressing applied. The limb is then placed in a hinged elbow brace or a long-arm cast in at least 90° of flexion. Passive range of motion to allow joint mobility is initiated as soon as tolerated by the patient. Therapy is advanced to include hand-to-mouth activities with passive flexion. During the first month, this is limited to 90° to protect the triceps lengthening, and advanced thereafter to full passive flexion. Use of a splint to maximize flexion during the day is possible with a hinged splint and use of rubber bands anteriorly as shown in Fig. 24.6. If an elbow flexion contracture ensues, alternative nighttime flexion splinting alternated with extension splinting can be initiated.

Surgical Outcomes

Several series examining results of posterior capsular release with triceps lengthening report excellent results. For example, Van Heest et al. [13] reported on a study group of 23 children treated between 7 months and 13 years of age with an average follow-up of 5.4 years. Prior to the surgery, the average arc of passive motion was 32°, with an average of 38° of flexion. An arc of at least 90° of passive flexion was achieved in all children intraoperatively. At an average follow-up of 5.4 years, 22 of the 23 children were able to feed themselves with the hand on the operated side. Twenty-one of the children with less than grade three elbow flexion strength required the use of passive assistance. No further muscle transfers were performed in these children, as adaptive mechanisms, as shown in Fig. 24.7, allowed independent activities of daily living.

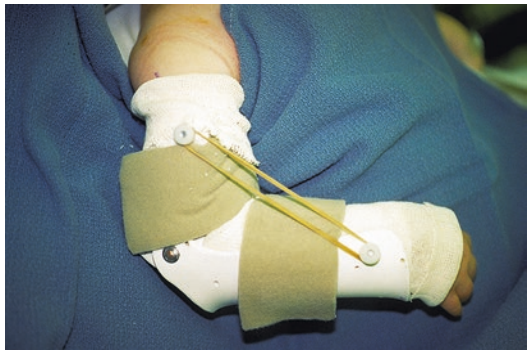

Fig. 24.6 Use of a splint to maximize flexion during the day is possible with a hinged splint and use of rubber bands anteriorly as shown. During the first month, this is limited to 90° to protect the triceps lengthening, and advanced thereafter to full passive flexion

Operative Outcomes with Muscle Transfer

Several options exist for muscle transfers. First, if passive range of motion has been achieved either operatively or nonoperatively, passive adaptive maneuvers can be performed by the child for functional use of the elbow. Such is described by Van Heest et al. [13]. Nonoperative intervention for active elbow flexion requires the use of passive elbow flexion, and adaptive maneuvers such as tabletop push (Fig. 24.7a), swinging of the arms (Fig. 24.7b), or contralateral arm use (Fig. 24.7c, d) to bring the hand to the mouth. Many children are quite creative in being able to passively achieve hand-to-mouth function.

Operative measures to improve active elbow flexion include transfer of the flexor pronator origin (Steindler) [14, 15]; transfer of the pectoralis muscle; transfer of the triceps muscle; free muscle transfer of the grascilis; or, most recently, transfer of a single head of the triceps on its separate neurovascular pedicle. One review of the results of surgical treatment of arthrogryposis with tendon transfer surgery examined 18 tendon transfers in 14 children with an average follow-up of 4 years [16]. Using functional outcome cri-

Fig. 24.7 Nonoperative intervention for active elbow flexion requires the use of passive elbow flexion, and adaptive maneuvers such as tabletop push (**a**), swinging of the arms (**b**), or contralateral arm use (**c**, **d**) to bring the hand to the mouth. Many children are quite creative in being able to passively achieve hand-to-mouth function, so that operative treatment with muscle transfer is not necessary

teria, six of nine transfers provided good function, one provided fair, and two provided poor. The most common reason for downgrading was development of an elbow flexion contracture, which precluded active and passive elbow extension after triceps transfer. Subsequent studies have similarly shown severe elbow flexion contractures and, most commonly, triceps to biceps tendon transfer is no longer recommended [17]. The pectoralis transfer can be used as a unipolar [18], partial bipolar [19], or complete bipolar transfer [20]. The advantage of the pectoralis transfer is that additional muscle mass is added to the hypoplastic limb. The disadvantage is the extensive dissection necessary. It may also be contraindicated for use in females because of the chest wall deformity; lack of predictability of strength is common as well. The third available option for transfer is the latissimus dorsi muscle. Muscle mass is added from the chest wall to the hypoplastic limb without significant loss of function. However, in many children with arthrogryposis, the latissimus dorsi muscle is underdeveloped and insufficient for transfer. Several authors have recommended preoperative evaluation by MRI scan or intraoperative assessment of muscle quality prior to transfer. Additionally, due to its shape as a long muscle, extension is difficult to assess. The Steindler transfer, as described by Goldfarb et al. [14], is a less invasive elbow flexion transfer. The medial epicondyle origin of the flexor pronator muscle is divided and transferred to the anterior portion of the humerus. This transfer has been shown to improve initiation of elbow flexion, but has difficulty with achieving the full arc of elbow flexion for hand-to-mouth function. Additionally, critics have been concerned about enhancing the Steindler effect in requiring simultaneous wrist and elbow flexion in children who already have a wrist flexion contracture. Lastly, transfer of a single head of the triceps has recently been described by Ezaki [21]. Isolation of a single head of the triceps would allow transfer of one head while maintaining the other two heads as an antagonist elbow extensor. Theoretically, this would avoid the elbow flexion contractures seen after triceps to biceps transfer. The difficulty with the muscle transfers described above is that most children with amyoplasia have weak muscles, and transferring a weak muscle does not provide significant strength; thus, most of the outcomes of muscle transfer surgery are only good, not excellent.

Radial Head Dislocations

Some children with arthrogryposis will present with radial head dislocations. On physical examination, prominence of the radial head may be seen or palpated (Fig. 24.8); radiographs will reveal a radial head dislocation. If this occurs, assessment of the effect of loss of range of motion must be conducted. For example, an anteriorly dislocated radial head can block terminal flexion. Resection of the radial head can, in some cases, restore or improve function [22].

Treatment of the Wrist

Nonoperative management of the wrist includes passive range of motion and splinting. Most commonly, a wrist hand orthosis is worn at night to improve passive extension of the wrist and fin-

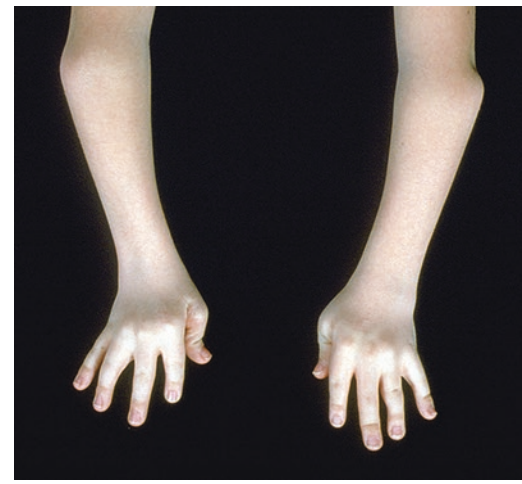

Fig. 24.8 A dislocated radial head can be diagnosed on physical examination by prominence of the radial head at the lateral head as seen here. Motion of the radial head can be palpated during pronation and supination

gers (Fig. 24.9). During the day, wrist splints are avoided because movement of the wrist is already limited in these stiff joints, and further splinting most commonly does not enhance function.

The most common treatment of the wrist is dorsal carpal wedge osteotomy. Dorsal carpal wedge osteotomy was first described by Ezaki in 1993 [21]. Surgical indications for dorsal carpal wedge osteotomy include excessive wrist flexion contracture deformity which limits upper extremity function, having failed nonoperative treatment. Of particular note is that some children with severely stiff upper limbs do use their wrist flexion posturing in order to achieve hand-to-mouth function or to assist in crawling and standing up (Fig. 24.10). If this is the case for a child, straightening the wrist would worsen their abilities. Only in children with adequate elbow flexion should wrist extension osteotomies be performed.

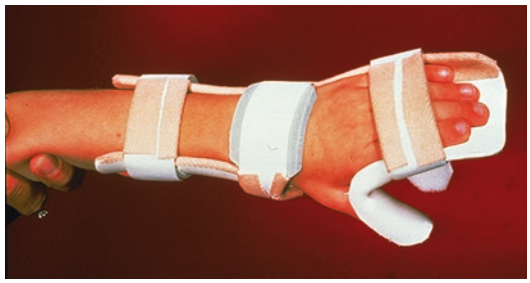

Fig. 24.9 Wrist hand orthosis worn at night to improve passive extension of the wrist and fingers. During the day, wrist splints are avoided because movement of the wrist is already limited in these stiff joints, and further splinting most commonly does not enhance function

Surgical Technique

Dorsal carpal wedge osteotomy is performed using a dorsal approach to the wrist; the digital and wrist extensor tendons are isolated and protected. A dorsal capsulotomy is then performed. At the level of the midcarpus (Fig. 24.11), a dorsal wedge osteotomy is made sufficient to correct the wrist flexion deformity to at least a neutral position, taking care that noteworthy finger flexor tightness is not produced by tenodesis. If ulnar deviation correction is required as well, the dorsal carpal wedge can resect more bone on the radial side to provide biplanar deformity correction. This position is held in place with two cross K-wires. In addition, tendon transfer of the extensor carpi ulnaris (ECU) to the extensor carpi radialis brevis may be performed to correct the ulnar

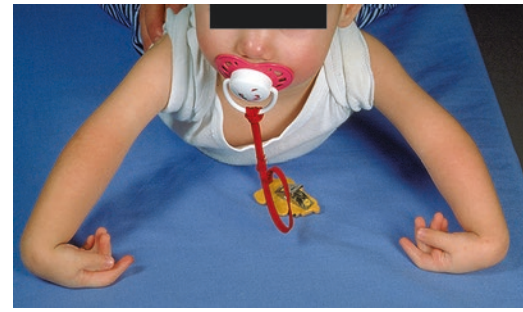

Fig. 24.10 Some children with arthrogryposis have severely stiff upper limbs and they use their wrist flexion posturing in order to achieve hand-to-mouth function or to assist in crawling and standing up, as shown here. If this is the case for a child, straightening the wrist would worsen their abilities. Only in children with adequate elbow flexion should wrist extension osteotomies be performed

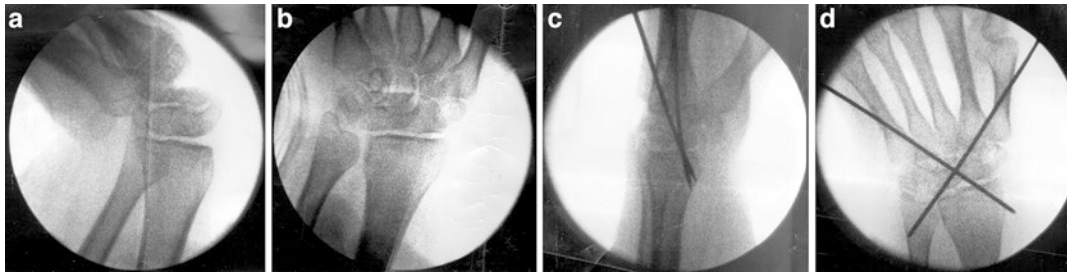

Fig. 24.11 Dorsal carpal wedge osteotomy is performed using a transverse dorsal incision and dorsal capsulotomy. A dorsal wedge of carpus is excised through the midcarpal joint (**a**, **b**), which is often synostostotic. Preservation of the radiocarpal joint is essential to maintain the limited arc of motion present. Pinning in a position of extension (**c**, **d**) with cast for 4–6 weeks to allow for bone healing is recommended. Concomitant centralization of the ECU tendon can improve long-term results for maintaining wrist extension

deviation deformity or wrist extension weakness, or both, if the ECU tendon is noted to have sufficient excursion intraoperatively. After the procedure, the patient is placed in a cast for 1 month. If radiographs show healing of the osteotomy, the cast is removed and the K-wires are pulled. The patient is given a wrist splint for protection and begins to participate in occupational therapy activities for wrist range of motion, particularly wrist extension, and hand function. Removable night splints are indicated on a case-by-case basis if needed for further improvement of wrist extension.

Surgical Outcomes

An evaluation of 20 wrists in 13 children with an average 4 years follow-up revealed a mean improvement of 43° of wrist extension with a loss of 35° of wrist flexion [23]. No significant change in the arc of motion was seen; however, extension was relocated into a more functional extended position. In one review [23], children older than 7 years of age at the time of surgery had significantly greater extension improvement than those less than 7 years of age. Additionally, patients who had a concomitant ECU tendon transfer at the time of dorsal carpal wedge osteotomy had a greater improvement in wrist extension. Dorsal carpal wedge osteotomy can significantly improve wrist extension while at the same time preserving the arc of motion (Fig. 24.12).

Treatment of the Hand

Syndactyly releases are most commonly a partial syndactyly and can be performed using local flaps with or without skin graft. The patterns in the hand with amyoplasia are similar to those with distal arthrogryposis and will be discussed together.

Distal Arthrogryposis

The second type of arthrogryposis commonly seen by hand surgeons is distal arthrogryposis. Features shared by all distal arthrogryposes include a consistent pattern of hand and foot involvement, limited proximal joint involvement, and variable expressivity. Ten different types of distal arthrogryposes have been described to date (see Table 24.1). Most commonly in these types of arthrogryposis the "windblown hand" is seen. The windblown hand includes ulnar deviation of the digits through the metacarpophalangeal (MCP) joint, stiff digits, and thumb-in-palm. The digits can be stiff in flexion, such as seen in camptodactyly, or stiff in extension, with side-to-side intrinsic grasp patterns. The thumb is typically flexed across the palm with adduction of the ray through the carpometacarpal joint, as well as flexion of the MCP joint. Simple incomplete syndactyly is common (Fig. 24.13).

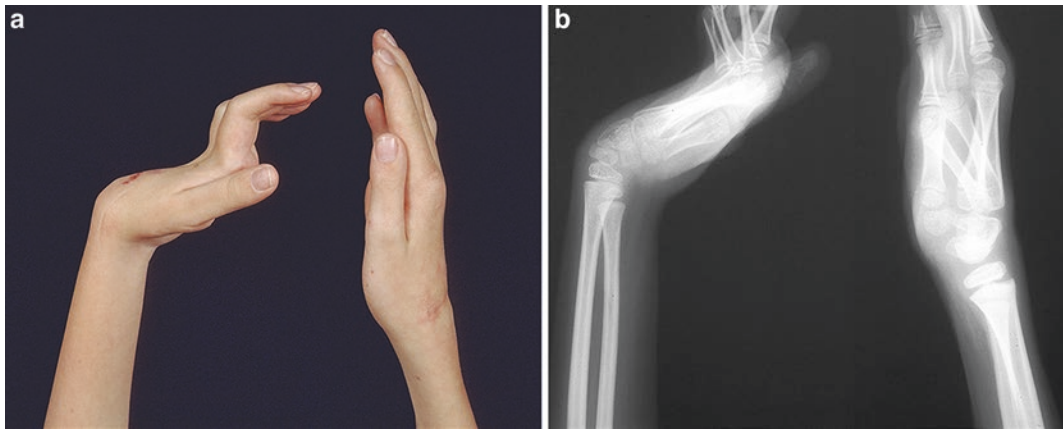

Fig. 24.12 This patient presents after a left wrist dorsal carpal wedge osteotomy (DCWO) requesting that the right wrist be treated. Part (**a**) shows a clinical picture of the post-op DCWO on the left wrist and a pre-op DCWO on the right wrist. Part (**b**) shows the lateral radiograph of the post-op DCWO on the left wrist and a pre-op DCWO on the right wrist. Prior to the surgery, the left wrist had similar deformity to the right wrist

Treatment of the Hand

The mainstay of treatment for the windblown hand is nonoperative management with splints for improved positioning and passive range of motion of the joint, starting as an infant when the diagnosis is first made. In the early school-age child, if positioning has not improved, then surgical management can be considered.

Surgical management in the windblown hand would include release of contractures. Release of camptodactyly has been disappointing, so that stiff digits are most commonly treated nonoperatively.

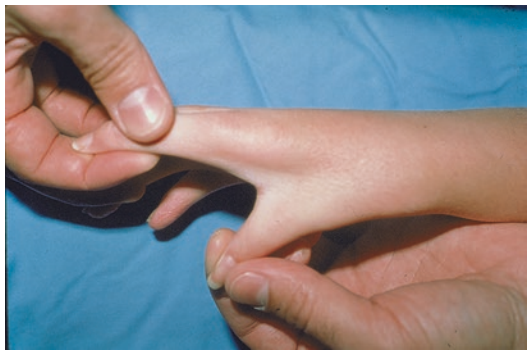

Fig. 24.13 Simple incomplete syndactyly is common in arthrogryposis and can be treated with local flaps or full thickness skin grafts if functionally limiting finger or thumb use

Treatment of the Thumb-in-Palm Deformity

Treatment of thumb-in-palm deformity involves repositioning of the thumb through osteotomies, fusions, or tendon transfers. Release of the first web can include a dorsal rotation flap, a Z-plasty, or volar skin grafting. Release of the thumb adductor is performed as described by Matev [24], with release of the origin of the thumb adductor from the third metacarpal, thus preserving its pinch power through preserving its nerve supply. This is important in children who are already weak when maximum thumb pinch strength needs to be preserved. If posturing across the palm is severe, consideration of an MCP fusion to position the thumb MCP joint in greater extension can be considered in the older child. In the younger child, release of the volar capsule and augmentation of the dorsal capsule with pinning for 4–6 weeks to allow healing can be considered. Augmentation of the extensor pollicus brevis tendon through transfer from the extensor indicis proprius has been used as shown in Fig. 24.14. Transfer of the extensor carpi radialis longus tendon, if present, to the first ray can improve abduction of the ray itself. Large series are not available for either of these surgical techniques. Adduction of the first metacarpal with contracture of the first web and volar skin is often

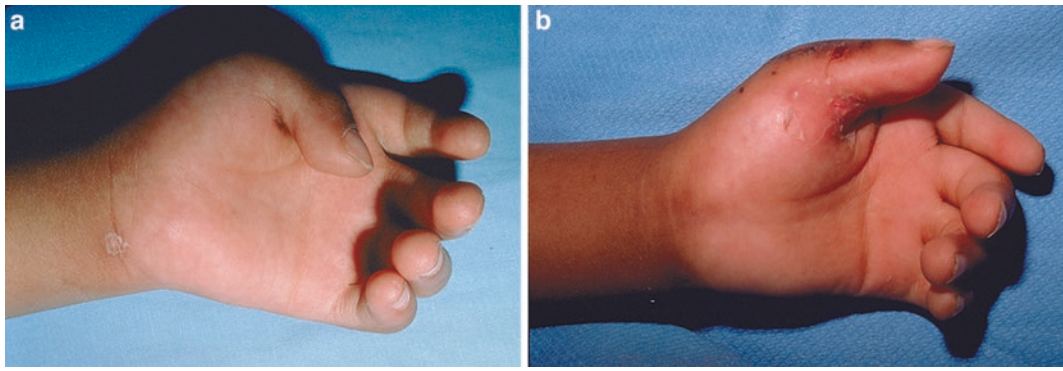

Fig. 24.14 Thumb-in-palm deformity is a common feature of both amyoplasia and many types of distal arthrogryposes (**a**). Surgical treatment with Z-plasty of the contracted volar skin, MP dorsal capsulodesis, and augmentation of thumb extension with transfer of the EIP tendon to EPB can improve thumb position and function (**b**)

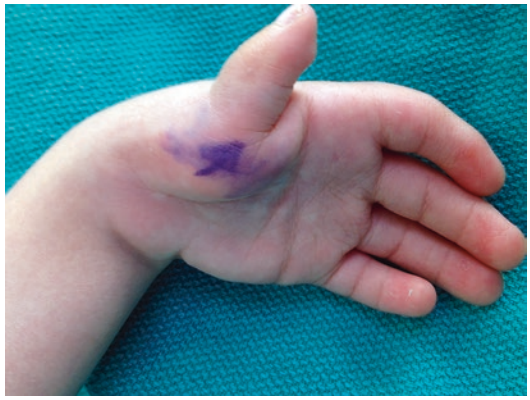

Fig. 24.15 Thumb-in-palm can on occasion cause adduction of the first ray with secondary hyperextension of the MCP joint. In cases such as these, volar capsulodesis would be necessary as part of surgical treatment. In the older child, MCP joint fusion may be an option

accompanied by contracture of the thumb adductor and deficient thumb extension. Thus, a thumb reconstruction would include release of the first web, with possible skin grafting on its volar aspect.

In some cases, children with arthrogryposis will present with hyperextension deformity through the MCP joint as shown in Fig. 24.15. Most likely this will be due to adduction of the first metacarpal across the palm, with secondary stretching of the volar capsule in hyperextension, which can lead to dislocation of the MCP. Release of the first ray using the Matev procedure [17] with a volar capsulotomy as described by Tonkin et al. [25] has been conducted. Surgical operations for the windblown hand reviewed by Wood [26] concluded that the most common procedure was Z-plasty of the thumb, followed by release of the thumb adductor, extensor indices proprius transfer to extensor pollicis longus or extensor pollicis brevis, with dorsal rotation flap or skin grafting. In three cases, lengthening of the flexor pollicis longus tendon was necessary.

Summary

In summary, arthrogryposis is a disorder of joint formation of the neuromuscular axis leading to multiple congenital contractures. Classification as classic arthrogryposis (amyoplasia), distal arthrogryposis, and syndromic arthrogryposis helps us understand the extent of disability and its treatment. Amyoplasia is the most common arthrogryposis that is treated surgically. Elbow capsular release with triceps lengthening, dorsal carpal wedge osteotomies, and thumb-in-palm correction are the most common surgical procedures. Treatment is based on functional positioning and use of the limb. The goal of management of the child with arthrogryposis is to increase independence by improving joint position and mobility.

References

1. Hall JG, Kimber EP, Van Bosse H. Genetics and classifications. J Pediatr Orthop. 2017;37 Suppl 1(5):S4–8.
2. Bamshad M, Van Heest AE, Pleasure D. Arthrogryposis: a review and update. J Bone Joint Surg Am. 2009;91 Suppl 4:40–6. PubMed PMID: 19571066.
3. Hall JG, Reed SD, McGillivray BC, Herrmann J, Partington MW, Schinzel A, et al. Part II. Amyoplasia: twinning in amyoplasia—a specific type of arthrogryposis with an apparent excess of discordantly affected identical twins. Am J Med Genet. 1983;15(4):591–9.
4. Hall JG, Reed SD, Driscoll EP, Part I. Amyoplasia: a common, sporadic condition with congenital contractures. Am J Med Genet. 1983;15(4):571–90.
5. OMIM® Online Mendelian Inheritance in Man® [Database]. Johns Hopkins University; 1966 [updated 6 December 2013 8 December 2013]. An Online Catalog of Human Genes and Genetic Disorders]. http://omim.org/.
6. Polizzi A, Huson SM, Vincent A. Teratogen update: maternal myasthenia gravis as a cause of congenital arthrogryposis. Teratology. 2000;62(5):332–41. PubMed PMID: 11029151.
7. Ma L, Yu X. Arthrogryposis multiplex congenita: classification, diagnosis, perioperative care, and anesthesia. Front Med. 2017;11(1):48–52. Web.
8. Bamshad M, Jorde LB, Carey JC. A revised and extended classification of the distal arthrogryposes. Am J Med Genet. 1996;65(4):277–81.
9. Sung SS, Brassington AM, Grannatt K, Rutherford A, Whitby FG, Krakowiak PA, et al. Mutations in genes encoding fast-twitch contractile proteins cause distal arthrogryposis syndromes. Am J Hum Genet. 2003;72(3):681–90. PubMed PMID: 12592607.
10. Sung SS, Brassington AM, Krakowiak PA, Carey JC, Jorde LB, Bamshad M. Mutations in TNNT3 cause multiple congenital contractures: a second locus for

distal arthrogryposis type 2B. Am J Hum Genet. 2003;73(1):212–4. PubMed PMID: 12865991.
11. Toydemir RM, Rutherford A, Whitby FG, Jorde LB, Carey JC, Bamshad MJ. Mutations in embryonic myosin heavy chain (MYH3) cause Freeman-Sheldon syndrome and Sheldon-Hall syndrome. Nat Genet. 2006;38(5):561–5. PubMed PMID: 16642020.
12. Pakkasjarvi N, Ritvanen A, Herva R, Peltonen L, Kestila M, Ignatius J. Lethal congenital contracture syndrome (LCCS) and other lethal arthrogryposes in Finland—an epidemiological study. Am J Med Genet A. 2006;140A(17):1834–9. PubMed PMID: 16892327.
13. Van Heest A, James MA, Lewica A, Anderson KA. Posterior elbow capsulotomy with triceps lengthening for treatment of elbow extension contracture in children with arthrogryposis. J Bone Joint Surg. 2008;90A(7):1517–23. PubMed PMID: 18594101.
14. Goldfarb CA, Burke MS, Strecker WB, Manske PR. The Steindler flexorplasty for the arthrogrypotic elbow. J Hand Surg Am. 2004;29(3):462–9.
15. Steindler A. Tendon transplantation in the upper extremity. Am J Surg. 1939;44(1):260–71.
16. Van Heest A, Waters PM, Simmons BP. Surgical treatment of arthrogryposis of the elbow. J Hand Surg Am. 1998;23(6):1063–70.
17. Doyle JR, James PM, Larsen LJ, Ashley RK. Restoration of elbow flexion in arthrogryposis multiplex congenita. J Hand Surg Am. 1980;5(2):149–52.
18. Clark JM. Reconstruction of biceps brachii by pectoral muscle transplantation. Br J Surg. 1946;34(134):180. PubMed PMID: 20278126. Epub 1946/10/01. Eng.
19. Schottstaedt ER, Larsen LJ, Bost FC. Complete muscle transposition. J Bone Joint Surg Am. 1955;37-A(5):897–918; discussion, 918–9. PubMed PMID: 13263337. Epub 1955/10/01.eng.
20. Atkins RM, Bell MJ, Sharrard WJ. Pectoralis major transfer for paralysis of elbow flexion in children. J Bone Joint Surg Br. 1985;67(4):640–4.
21. Ezaki M. Treatment of the upper limb in the child with arthrogryposis. Hand Clin. 2000;16(4):703–11.
22. Campbell CC, Waters PM, Emans JB. Excision of the radial head for congenital dislocation. J Bone Joint Surg Am. 1992;74(5):726–33. PubMed PMID: 1624487.eng.
23. Van Heest AE, Rodriguez R. Dorsal carpal wedge osteotomy in the arthrogrypotic wrist. J Hand Surg Am. 2013;38(2):265–70. PubMed PMID: 23267756. Epub 2012/12/27. Eng.
24. Matev I. Surgery of the spastic thumb-in-palm deformity. J Hand Surg Br. 1991;16(2):127–32. PubMed PMID: 2061648. Epub 1991/05/01. Eng.
25. Tonkin MA, Beard AJ, Kemp SJ, Eakins DF. Sesamoid arthrodesis for hyperextension of the thumb metacarpophalangeal joint. J Hand Surg Am. 1995;20(2):334–8.
26. Wood VE. Another look at the causes of the windblown hand. J Hand Surg Br. 1994;19(6):679–82. PubMed PMID: 7706863. Epub 1994/12/01. Eng.

Madelung's Deformity

25

M. Claire Manske, Michelle A. James, and H. Relton McCarroll

Introduction

Madelung's deformity is an uncommon congenital wrist condition characterized by premature closure of the volar-ulnar aspect of the distal radius physis, volar carpal subluxation, and distal ulna prominence (Fig. 25.1). It is classified as a malformation of the radio-ulnar axis involving the entire upper limb, according to the Oberg-Manske-Tonkin Classification [1]. It accounts for less than 2% of congenital upper extremity differences [2]. Madelung's deformity is most commonly idiopathic, but a Madelung-like deformity may result from trauma, infection, multiple hereditary exostoses (MHE), and Ollier's disease. Additionally, it is associated with skeletal dysplasias involving mutations of the short stature homeobox (SHOX) gene. Madelung's deformity predominantly affects females and becomes clinically apparent during adolescence. Affected individuals may present with wrist pain, restricted range of motion of the wrist and forearm, decreased grip strength, and function difficulties, as well as aesthetic concerns. Several surgical options have been described for children with Madelung's deformity, depending on their age and degree of deformity, and include physiolysis, soft tissue release, and osteotomies, with promising outcomes.

History

The first description of Madelung's deformity is attributed to Dupuytren in 1834. Although not the first to identify the wrist deformity that now bears his name, the German surgeon Otto Madelung was the first to provide a comprehensive clinical description of "manus valga," as well as its proposed etiology and treatment options [3–5]. At the Congress of the German Society for Surgery in Berlin in 1878 and in subsequent publications, Madelung presented a case series of patients in whom "the distal end of the ulna juts out clearly. The styloid process and articular surface are recognizable and become apparent by feel. The hand, for itself alone regarded, is normal, but it has dropped forward. The widest diameter of the wrist is increased by almost double…The whole lower epiphysis of the radius of the deformed side is also angulated volarwards" [6, 7]. Madelung described this condition as commonly bilateral and predominantly affecting females who usually presented in early adolescence [7]. Although his clinical observations predated the availability of radiographs, Madelung's descrip-

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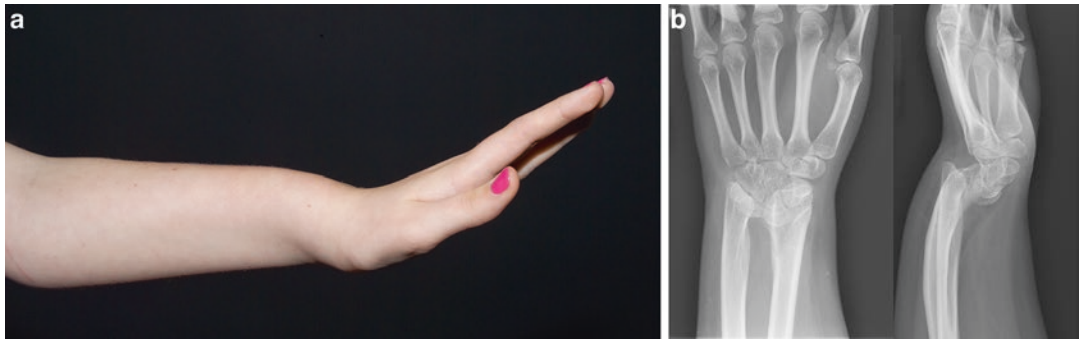

Fig. 25.1 (**a**) Clinical photograph and (**b**) AP and lateral wrist radiographs of patient with Madelung deformity. (Copyright Shriners Hospitals for Children—Northern California)

tion remains accurate today and is supported by subsequent radiographic and epidemiologic studies.

Anatomy and Etiology

The etiology of Madelung's deformity is unknown. The pathologic finding characteristic of Madelung's deformity is premature arrest of the volar-ulnar aspect of the distal radius physis, but the mechanism by which this physeal arrest occurs is incompletely understood. Both ligamentous and osseous abnormalities have been identified, but it has yet to be demonstrated which is the primary pathoanatomy and which occur secondarily. In 1992, Vickers and Nielsen described an aberrant ligament between the lunate and the volar aspect of the distal radius observed in 91% of individuals with Madelung's deformity [8, 9]. Although histologically normal, this ligament is abnormally thick and originates on the radial metaphysis, rather than the epiphysis. The authors proposed that this ligament, known as "Vickers ligament," tethers the lunate in a proximal position between the radius and ulna which in turn causes compression of the volar-ulnar epiphysis and physis of the distal radius and inhibits longitudinal growth. Munns et al. evaluated the histopathology of the distal radius physis in patients with Madelung's deformity and identified disordered physeal anatomy of the distal radius, including disruption of the normal columnar arrangement of mature chondrocytes, expansion of the hypertrophic layer, reduction of the proliferative zone, and presence of hypertrophic osteoid in the metaphysis, suggesting impaired endochondral ossification [10, 11].

Although the genetic basis of Madelung's deformity is not clear, pedigree studies suggest an autosomal dominant inheritance pattern with variable expressivity and penetrance [12]. Moreover, the presence of Madelung's deformity in syndromes related to deficiency of the short stature homeobox (SHOX) gene syndromes, including Leri-Weill dyschondrosteosis [13], Turner's syndrome [13, 14], and Langer mesomelic dysplasia [15], provides potential insight into the pathogenesis. The SHOX gene, located on the pseudo-autosomal region of the sex chromosomes, is expressed in both males and females and is thought to play a role in bone growth and development [13, 16]. Haploinsufficiency of the SHOX gene results in Leri-Weill dyschondrosteosis (LWD), a dominantly inherited skeletal dysplasia presenting with short stature and mesomelic limb shortening; Madelung deformity is observed in 74% of individuals with LWD [13]. Madelung's deformity is also seen in association with Langer mesomelic dysplasia (LMD), which results from a homozygous or compound heterozygous mutation of the SHOX gene and is characterized by severe short stature and both rhizomelic and mesomelic shortening; Madelung's deformity is seen less commonly with LMD than LWD. Turner's syndrome, a mesomelic skeletal dys-

plasia resulting from the combination of SHOX haploinsufficiency and a 45 X,O karyotype, is characterized by short stature, ovarian failure, and a variety of somatic features, including webbed neck, lymphedema, cardiac and renal abnormalities, and skeletal defects; Madelung's deformity is observed in 7% of those with Turner's syndrome [13, 16]. The variable prevalence of Madelung deformity in these SHOX deficiency syndromes is not entirely understood but may result from the interaction of SHOX mutations and estrogen [17]. This interaction with sex steroids may also explain the female predilection and presentation during the adolescent growth spurt. Madelung's deformity has also been reported in association with pseudohypoparathyroidism types 1a and 1b resulting from GNAS gene mutations [18, 19] and nail-patella syndrome [20], which highlights the complexity of the genetic basis of Madelung's. Further research is needed to delineate the genetic mutations associated with Madelung's deformity.

Madelung-like deformities due to post-traumatic distal radius physeal arrest (Fig. 25.2), post-infection, sickle cell disease, or gymnast wrist (physeal arrest due to repetitive axial loading of the wrist) are distinguished by patient history. Other skeletal dysplasias such as multiple hereditary exostoses and Ollier's disease may also result in a Madelung-like deformity, but these are differentiated by the presence of systemic bone changes. A reverse Madelung's deformity may also present with wrist deformity, pain, and limited forearm motion. Wrist and forearm radiographs will distinguish this diagnosis, in which the distal radial articular surface is angulated dorsally, dorsal subluxation of the carpus, volar displacement of the distal ulna, and dorsal bowing of the radial shaft (Fig. 25.3). It is not clear that this rare deformity is related to Madelung's deformity.

Diagnosis

The diagnosis of Madelung's deformity is made based on clinical and radiographic findings.

Clinical Presentation

Individuals with Madelung's deformity are commonly female (4:1 female-to-male ratio) and present in their pre-teen or adolescent years [21]. Typically, the chief complaint relates to the appearance of the wrist, which may have been initially subtle but has worsened with skeletal growth. This deformity is characterized by a volar-ulnar tilt of the radius due to the abnormalities of the distal radial physis. Because the ulna is unaffected, it grows normally, often longer than the radius and assumes a dorsally subluxated position. Additional concerns include wrist pain, stiffness, and difficulties with activities of daily living or recreational activities. Family history may be remarkable for other affected family members (especially females), and younger sib-

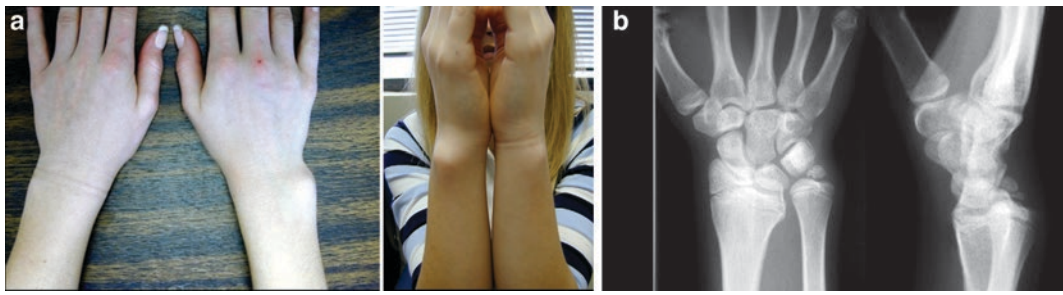

Fig. 25.2 (**a**) Clinical photographs and (**b**) PA and lateral wrist radiographs of a patient with post-traumatic Madelung's deformity from a traumatic injury to the volar ulnar physis of the distal radius. (Copyright Shriners Hospitals for Children—Northern California)

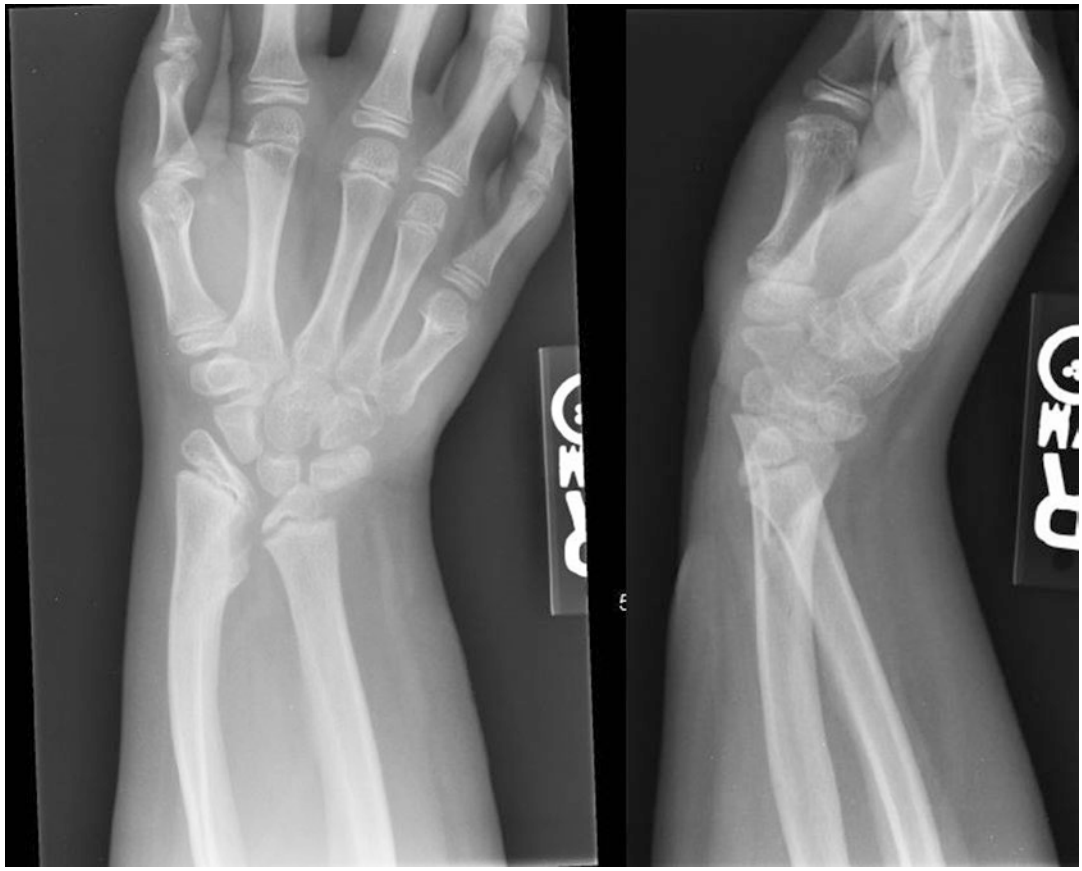

Fig. 25.3 PA and lateral radiographs of a reverse Madelung's deformity with dorsal angulation of the distal radius physis, dorsal subluxation of the carpus, and volar displacement of the distal ulna. (Copyright Shriners Hospitals for Children—Northern California)

lings should be examined (including wrist radiographs) to identify subtle abnormalities prior to the onset of symptomatic deformity.

Physical examination is notable for a prominent distal ulna with volar subluxation of the carpus relative to the forearm (volar sag) and forearm shortening and palmar curvature (see Fig. 25.1). Affected individuals may have limited range of motion (particularly in forearm supination and wrist extension), reduced grip strength, and DRUJ instability. Typically hand and finger function is unaffected, although attritional rupture of the extensor tendons has been reported due to the dorsal prominence of the ulna in long-standing deformity [22–24]. Seventy-four percent of affected individuals have bilateral deformity which may be asymmetric [20]. Children should also be evaluated for short stature, neck webbing, short metacarpals, and other clinical findings associated with SHOX deficiency and referred for genetic assessment if present.

Radiographs of the wrist and forearm confirm the diagnosis of Madelung's deformity. Wrist x-rays demonstrate physeal closure of the volar-ulnar aspect of the distal radius, lunate subsidence ("carpal pyramidalization"), volar bowing of the radial shaft, and dorsal subluxation of the distal ulna. Numerous radiographic measurements have been described to quantify Madelung's deformity. Although initial parameters were based

on the radius, the radiographic criteria based on the ulna have been shown to be more reliable given the anatomic variability of the radius. McCarroll et al. evaluated five radiographic parameters to quantify Madelung's deformity and found that ulnar tilt, lunate subsidence, and palmar carpal displacement most reliably and reproducibly quantify the severity of Madelung's deformity [25] (Fig. 25.4). In a subsequent study, McCarroll et al. established threshold values for these radiographic findings to diagnose Madelung's deformity: ulnar tilt ≥33°, lunate fossa angle ≥40 °, lunate subsidence ≥4 mm, or palmar carpal displacement of ≥20 mm [26]. Zebala et al. recognized that up to one-third of individuals with Madelung's demonstrate proximal forearm deformity in addition to the wrist deformity; this includes increased sagittal bow of the radial diaphysis, decreased radial length, and increased radial head-capitellum distance [27]. Recognition of proximal deformity on full-length forearm x-rays is important as proximal involvement influences treatment and outcomes.

Magnetic resonance imaging (MRI) and computed tomography (CT) are typically not required to diagnose Madelung's deformity, although they may be useful for treatment planning in early or complex cases. MRI may be useful to evaluate to assess the location and extent of physeal disease and identify Vickers ligament in young children with mild deformity in whom physiolysis and Vickers ligament excision is being considered. With advances in three-dimensional modeling for surgical planning, CT scans may become increasingly useful to delineate the complex three-dimensional deformity of Madelung's deformity and reveal previously unidentified anatomic findings. Paymani et al. [28] reported the anatomic findings on three-dimensional CTs in 28 wrists with Madelung's deformity and identified abnormalities of the lunate fossa and difference in intracarpal angles compared to unaffected wrists, in addition to confirming radiographic findings (increased ulnar tilt, lunate subsidence, lunate fossa angle, and palmar carpal displacement) associated with Madelung's. Moreover, three-dimensional modeling using CT scans is in the early phases of development for surgical planning in the correction of complex deformity.

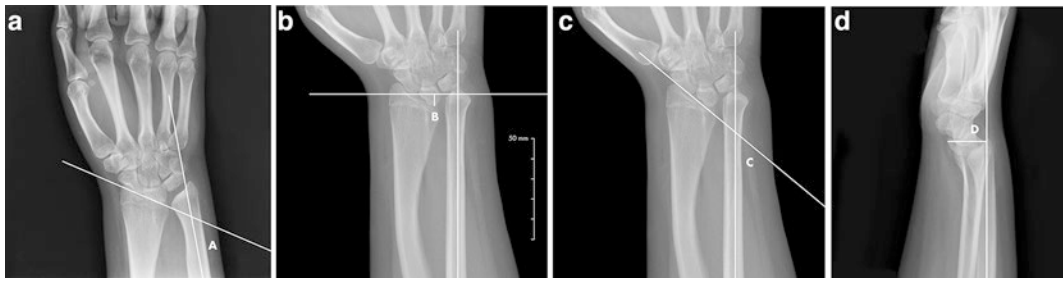

Fig. 25.4 Radiographic parameters of Madelung deformity. (**a**) (Ulnar tilt): Ulnar tilt is defined on the PA x-ray as the complement (90°-angle A) of the acute angle (angle A) between the longitudinal axis of the ulna and a line tangential to the proximal surfaces of the scaphoid and lunate. (**b**) (Lunate subsidence): Lunate subsidence on a PA x-ray is defined as the distance in millimeters (distance B) between the most proximal point of the lunate and a line perpendicular to the longitudinal axis of the ulna and through its distal articular surface. The measurement is positive if the ulna extends distal to the proximal surface of the lunate. (**c**) (Lunate fossa angle): Lunate fossa angle on a PA x-ray is defined as the complement (90°-angle C) of the acute angle (angle C) between the longitudinal axis of the ulna and a line across the lunate fossa of the radius. (**d**) (Palmar carpal displacement): Palmar carpal displacement on a lateral x-ray is defined as the distance in millimeters (distance D) between the longitudinal axis of the ulna and the most palmar point on the surface of the lunate or capitate. Copyright Shriners Hospitals for Children—Northern California

Treatment

The optimal treatment of Madelung's deformity remains controversial. Factors influencing treatment decisions include skeletal age, deformity severity, and symptoms. Nonoperative treatment is indicated in children with asymptomatic deformity or mild intermittent symptoms. These children may be monitored with serial radiographs at 6- to 12-month intervals. This is often appropriate for younger siblings of affected individuals who are identified prior to the onset of symptoms or substantial deformity. However, those with mild deformity at a young age may be indicated for surgery to prevent deformity progression. Other indications for operative intervention include pain, functional limitations, or progressive or unacceptable deformity.

Surgical treatment of Madelung deformity can be divided into three categories: early prevention, late correction, and salvage procedures in adulthood. Early prevention is indicated in young, skeletally immature children and consists of physiolysis and Vickers ligament release. Late correction, consisting of radius and ulna osteotomies to correct established deformity, may be considered in older children and adolescents with limited growth remaining. Lastly, salvage procedures, including partial or complete wrist arthrodesis, resection arthroplasty, or staged osteotomy with implant arthroplasty, may be considered in the setting of radiocarpal or DRUJ arthritis [17]. This chapter will focus on the early prevention and late correction procedures performed in childhood and adolescents.

Physiolysis and Vickers Ligament Release

Physiolysis and Vickers ligament release are indicated in young patients with minimal deformity and substantial growth remaining. The goal of the procedure is to restore radial growth and carpal alignment. The procedure was originally described using a transverse wrist incision [8], but modifications of this procedure utilize a longitudinal incision [29, 30].

The procedure is performed under tourniquet control and with a regional nerve block of the extremity. A traditional Henry approach to the volar distal radius along the flexor carpi radialis (FCR) is utilized. Vickers ligament is identified deep to the pronator quadratus on the distal ulnar border of the volar radius, elevated from proximal to distal, and excised to release the soft tissue tether. The bone bridge on the volar-ulnar aspect of the distal radial physis is identified, using preoperative imaging, intraoperative fluoroscopy, and direct inspection. A curette, rongeur, or burr is used to resect the bone bridge until the normal appearing physeal cartilage (blue coloration) is identified; care must be taken to avoid injury to the adjacent healthy physis. Fat or pronator quadratus muscle is interposed into the bone defect to decrease the risk of physeal bar recurrence. The pronator is then repaired and the skin closed in layers. The wrist is immobilized in a short arm cast for 2 weeks (Fig. 25.5). Formal therapy is not typically needed to regain wrist range of motion. Postoperatively, wrist radiographs are obtained at 6-month intervals to monitor for restoration of radial growth. If the ulna appears to be overgrowing, epiphysiodesis should be considered.

In their original description of the surgical technique, Vickers and Nielsen reported the outcomes of ligament release and physiolysis in 11 skeletally immature patients (15 wrists) [8]. All patients reported improvement in wrist pain, four of whom had complete resolution. No patients had progression of their wrist deformity, and slight improvement was observed in most cases. Forearm supination improved by a mean of 23°, but this improvement was not sustained at long-term follow-up. More recently, Otte et al. reported the outcomes of this procedure in 6 skeletally immature females (12 wrists) at a mean age of 7.5 years [31]. At final follow-up (minimum 17 months), the radial physeal angle improved in 10 of the 12 wrists (mean of 7.5 degrees of improvement), and metaphyseal growth was observed in 11 of the 12 wrists. All patients had postoperative resolution of their pain postoperatively, but two reported intermittent pain at final follow-up. All were able to return to their

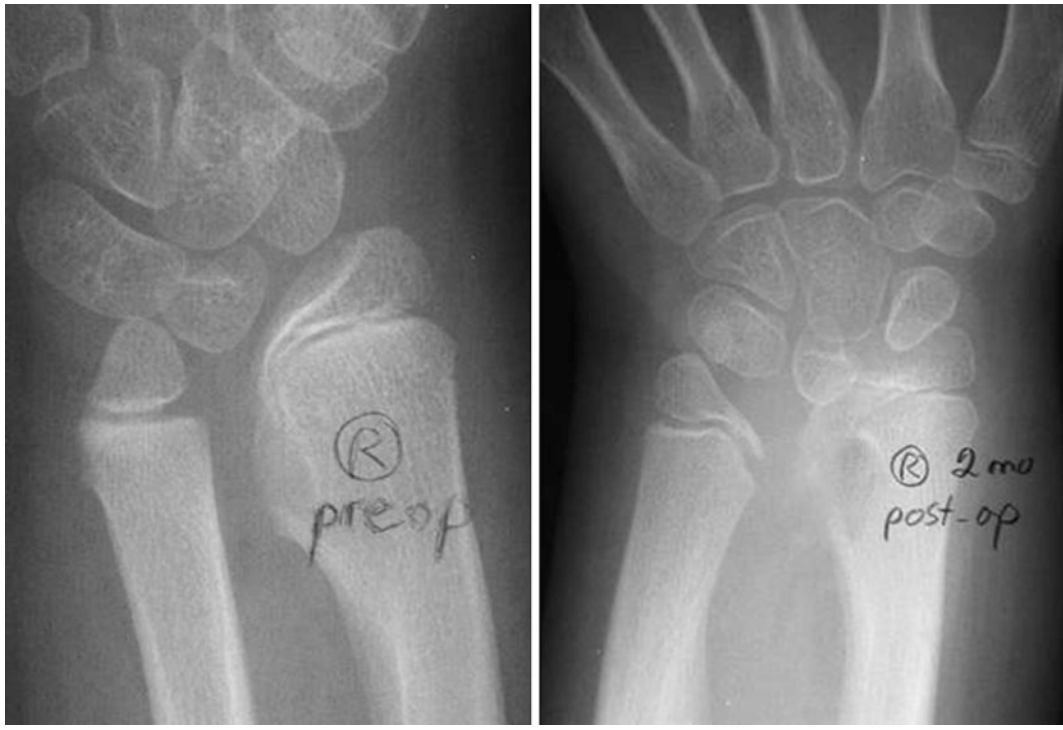

Fig. 25.5 AP wrist radiograph before and 2 months after Vickers ligament release and physiolysis. (Copyright Shriners Hospitals for Children—Northern California)

preoperative level of activity. Del Core and colleagues [32] reported the long-term outcomes of this procedure into young adulthood. At a mean 10 years follow-up, six of the eight wrists were completely pain free, and forearm and wrist range of motion at long-term follow-up were similar to preoperative values. Radiographically, ulnar tilt and palmar carpal displacement did not change substantially compared to preoperative values, but lunate subsidence progressed. Based on these studies, it appears that this procedure results in pain relief in most patients, preservation of motion, and possible restoration of longitudinal growth. Whether it prevents deformity progression has not been clearly demonstrated.

Radial Dome Osteotomy

In older children with limited growth potential, established deformity, and pain or functional limitations, boney procedures are indicated. A dome osteotomy of the radius corrects the deformity in both the sagittal and coronal plane and is often performed concomitantly with a distal ulna epiphysiodesis or ulnar shortening osteotomy, discussed subsequently.

Under general anesthesia with an upper extremity tourniquet, a standard Henry approach to the distal radius is performed. Vickers ligament may be released as described above. The metaphyseal-diaphyseal junction is identified, and the periosteum is elevated circumferentially and retracted with small Hohmann retractors in preparation for the osteotomy. A small stab incision is made at the tip of the radial styloid, and the dorsal sensory branch of the radial nerve is protected. Two parallel or divergent 0.062 inch K-wires are placed on the styloid and driven retrograde into the distal radius, short of the osteotomy site. Because the distal fragment will be rotated, the K-wires should be placed nearly longitudinally to ensure that they will capture the proximal fragment after the correction. Under fluoroscopic

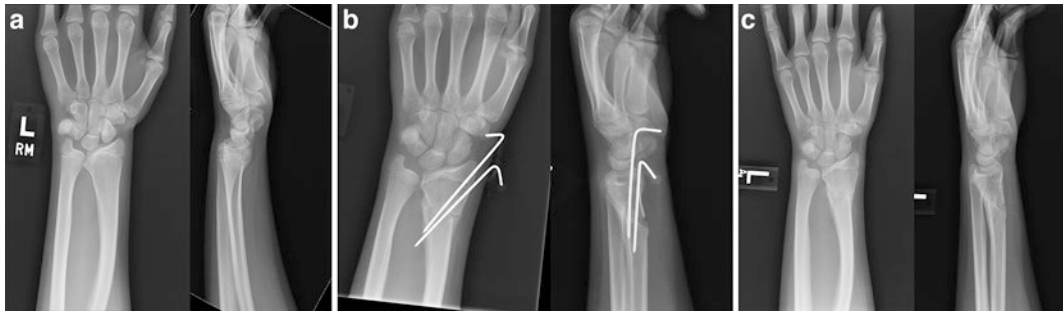

Fig. 25.6 Correction of Madelung deformity via distal radius dome osteotomy. (**a**) Preoperative radiographs. (**b**) Postoperative radiographic appearance, immediately before pin removal. (**c**) Final radiographic appearance at 3 months after surgery. (Copyright Shriners Hospitals for Children—Northern California)

guidance and direct visualization, a dome-shaped osteotomy is performed at the level of the metaphysis, proximal enough to avoid injury to the DRUJ and, if open, the distal radius physis. The osteotomy may be performed with a Domesaw® (Matric Orthopaedics, Inc., Twin Falls, ID) or by using a K-wire to perforate the volar and dorsal cortex several times in a crescent shape and connecting the perforations with an osteotome. The osteotomy should be concave in both the coronal and sagittal planes to allow multiplanar deformity correction. It is the authors' preference to perform the osteotomy with the concave portion of the dome distal (i.e., a smile, not a frown), as a convex osteotomy creates a prominent metaphyseal spike on the distal fragment that limits radial deviation and extension. Longitudinal traction and manual manipulation are used to radially deviate, extend, and dorsally translate the distal fragment to correct the deformity. If necessary to achieve the desired correction, a spike of bone may be removed from the proximal volar cortex, which may be used as a bone graft in the osteotomy site. The previously placed K-wires are then driven across the osteotomy site into the proximal fragment with bicortical purchase (see Fig. 25.5). The pins are cut and bent outside the skin. In children with a large degree of correction or prolonged tourniquet time, we recommend performing a fasciotomy of the volar forearm. The skin is closed in layers, and a well-padded long-arm splint or bivalved cast is applied. The pins are removed in clinic when radiographic healing is evident, typically between 4 and 8 weeks. Range of motion exercises is initiated when the pins are removed, and a removable wrist splint is worn for activity and weaned over 2 weeks as comfort allows (Fig. 25.6).

Reported outcomes of the dome osteotomy are encouraging. Harley et al. [33] reported that children treated with dome osteotomy and volar ligament release reported improved wrist pain and appearance and increased forearm supination and wrist extension, without loss of pronation or wrist flexion at a mean 2-year follow-up. Additional ulnar-sided surgeries, either performed simultaneously or in a staged fashion, were common. Long-term studies of this procedure indicate sustained outcomes. The same cohort of children in the Harley study was evaluated in early adulthood at a mean of 11 years following surgery [34]. The authors note preservation of radial inclination but slight progression of lunate subsidence (2 mm). They observed no loss of wrist extension and forearm supination. Many patients had additional procedures following the dome osteotomy, most commonly ulnar shortening osteotomy; other procedures included revision dome osteotomy, Darrach resection, and Sauve-Kapandji procedure. Importantly, the authors identified an association between whole bone involvement as described by Zebala [27] and arthritic changes, as well as an association between arthritic changes and increasing (worse) disabilities of the arm, shoulder, and hand (DASH) scores, confirming that those with whole bone involvement have poorer radiographic and functional outcomes.

Distal Ulna Epiphysiodesis

A distal ulna epiphysiodesis is often performed in conjunction with the radial osteotomy in young patients who are at risk of worsening deformity due to continued ulnar growth. The distal ulnar physis is localized under fluoroscopy using a 25-gauge hypodermic needle. A small longitudinal incision on the ulnar border of the distal forearm is centered over the physis. Subperiosteal dissection is performed, and curettes or a small drill is introduced into the physis. The physis is ablated under fluoroscopic guidance. Because the distal ulnar physis tends to be robust, it can be difficult to ablate, and we are aggressive in removing all of the physeal cartilage. The skin is closed in layers with dissolvable suture, and a long arm cast is applied as above.

Ulnar Shortening Osteotomy

In children with limited growth remaining and positive ulnar variance in addition to the radius deformity, an ulnar shortening osteotomy is often performed in conjunction with the radius osteotomy. It should also be considered in skeletally mature individuals with Madelung's deformity and ulnar-sided wrist pain due to ulnocarpal abutment [35].

A longitudinal incision is made over the ulnar border of the mid and distal forearm with care to protect the dorsal sensory branch of the ulnar nerve. The interval between the extensor carpi ulnaris (ECU) and flexor carpi ulnaris (FCU) is developed in the mid forearm to expose the ulnar shaft. Subperiosteal exposure of the ulnar shaft is performed, and an appropriately size plate that will accommodate the osteotomy is selected; we usually use a 2.7-mm LCDC plate (DePuy Synthes, West Chester, PA), but 3.5-mm plates can be used for larger patients or stacked 1/3 tubular plates for smaller patients, as described by Waters and Bae [21]. The distal holes are drilled with partial placement of the screws. The osteotomy site is marked, as well as a longitudinal line along the plate to guide against malrotation. Two parallel oblique passes are made with a sagittal saw to correspond with the desired amount of shortening. In the authors' experience, it is difficult to shorten more than about 6 mm and still achieve bony apposition. The ring of bone is removed and the plate and screws reapplied. The osteotomy is reduced, and proximal fixation is achieved with the screw applied in compression. Fluoroscopic imaging and direct visualization are used to confirm the position of the implants and good bone contact. Fluoroscopic images of the wrist with the forearm in neutral rotation view are used to assess the ulnar variance after correction. The skin is closed in layers with dissolving suture. The arm is immobilized as needed for the radius osteotomy.

Very Distal Radius Osteotomy

The dome osteotomy of the radius is effective at addressing the radial bow and palmar tilt but is less effective at correcting the ulnar tilt. In cases in which the ulnar tilt is a major component of the deformity, a very distal dome osteotomy allows correction of the ulnar tilt as well as the radial bow and palmar tilt. Additionally, when there is substantial radial bow, the very distal radius osteotomy can be combined with a proximal radial shaft osteotomy.

The very distal osteotomy was described by McCarroll and James [36] (see Fig. 25.6). In this procedure, the ulna is prepared for a shortening osteotomy first. The ulna is approached, and a plate is provisionally attached distal to the osteotomy site as described previously. A transverse osteotomy is made with a sagittal saw, and the ends of the ulna are allowed to overlap. The mobility of the ulnar ends is necessary to allow the radius to mobilize freely. The distal radius is then approached dorsally from the carpometacarpal (CMC) joints to the outcropper muscles in the forearm. The third dorsal compartment is opened, the EPL liberated, and the extensor compartments elevated and retracted. The distal radius is exposed through a longitudinal incision in the periosteum, followed by a small capsulotomy made in the dorsal wrist capsule to assess the palmar tilt of the articular surface. A K-wire is placed, blunt end

first, in the joint to estimate the palmar tilt of the distal radius. A second K-wire is placed in the radial styloid transversely across in radius, just proximal to the dorsal joint surface. A T-plate is selected for the planned osteotomy; an outline of the plate is marked on the dorsal radial cortex with a surgical marking pen. We use a stainless steel buttress T-plate with three or four proximal holes for 3.5-mm screws. This plate is malleable and able to bend to the new contour of the radius. A guideline is then drawn across the dorsal radius parallel to the radius articular surface, which is placed as distally as possible but with sufficient space to place the T-plate. A second mark is drawn from the proximal margin of the DRUJ perpendicular to the axis of the radius. This is the location of the second osteotomy cut for the very distal osteotomy. A third line is drawn between the first two guidelines but at half the angle to the perpendicular line; this is the line of the first cut for the very distal osteotomy and will correct the ulnar tilt of the articular surface by 50%. The ulnar extent of the osteotomy must be proximal to the DRUJ. The osteotomy is made with a sagittal saw following the central guide mark in a radial-ulnar direction and parallel to the vertical joystick and the K-wire across the articular surface of the radius in a dorsal to palmar direction. The K-wires are then used as joysticks to correct the palmar and ulnar tilt of the distal fragment.

At this point, the hand, carpus, and distal radius are a separate, mobile fragment, which often cannot be positioned on the radial metaphysis without shortening the radius. A segment of the radius is resected from the proximal end of the osteotomy and is used to shorten the radius and allow the distal radius to be placed on radial metaphysis in the corrected alignment. If the distal osteotomy is acceptably aligned, only a transverse osteotomy of the radial shaft is needed; however, if addition correction is needed, the proximal osteotomy can be altered to achieve the desired correction. The end of the proximal radius fragment often has a very sharp dorsal point that provides poor support to the distal fragment, and sufficient bone must be removed to shorten the radial shaft appropriately and provide a flat stable surface to support the distal fragment. The osteotomy is provisionally fixed with K-wires.

Attention is turned back to the distal radius, and the final T-plate is selected. The plate is contoured to the shape of the corrected distal radius, and the plate is fixed to the distal radius with care to avoid penetration of the radiocarpal joint or DRUJ. The proximal screws of the T-plate are positioned proximal to the more proximal of the two osteotomies to achieve fixation of both osteotomies.

Attention returns to the ulnar shortening osteotomy. The previously selected ulnar plate is attached to the distal ulna via the previously drilled screw holes. Manual traction is applied to the distal ulna, and the overlap between the distal and proximal ulna is marked. A segment of ulna is removed from the end proximal to the osteotomy site to remove the overlap between the bone ends. The fragments are then aligned and the plate secured to the proximal fragment. The skin is closed with dissolvable suture in a layered fashion and the upper extremity placed in a well-padded, bivalved short arm cast. The cast is overwrapped at 1 week and removed at 6 weeks. Radiographs are obtained at 6 weeks, and the patient is transitioned to a removable wrist splint if there is clinical and radiographic evidence of healing. Serial x-rays are obtained at 4- to 6-week intervals until solid union is observed. The patient may then wean from the splint and increase upper extremity use and activities as tolerated (Fig. 25.7).

Short-term follow-up of 17 wrists treated with this procedure demonstrate reliable bony union in 6 weeks to 3 months and high patient satisfaction with the appearance of the wrist and resolution of pain. No patients developed infections or neurovascular compromise. The authors report that the procedure preserved DRUJ function while correcting the deformity. Larger and long-term follow-up studies are needed to further evaluate these outcomes.

Multiple Osteotomies Using Three-Dimensional Modeling

Historically, surgical planning for correction of Madelung's deformity was based on radiographs, which provides a two-dimensional representation of a complex three-dimensional deformity.

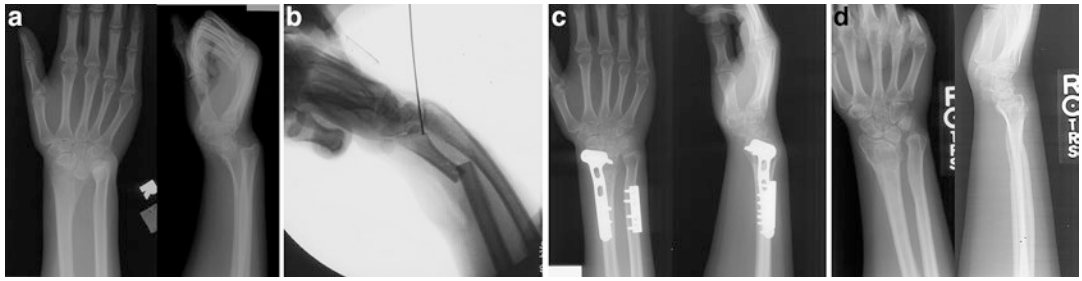

Fig. 25.7 Correction of Madelung deformity via very distal radius osteotomy. (**a**) Preoperative radiographs. (**b**) Intraoperative fluoroscopic image. The ulna has been cut and allowed to move into bayonet apposition. A K-wire has been inserted across the radiocarpal joint. (**c**) Postoperative radiographs at 6 months after surgery demonstrating healed osteotomies with hardware still in place. (**d**) Final postoperative radiographs 2 years after initial surgery, hardware has been removed. (Copyright Shriners Hospitals for Children—Northern California)

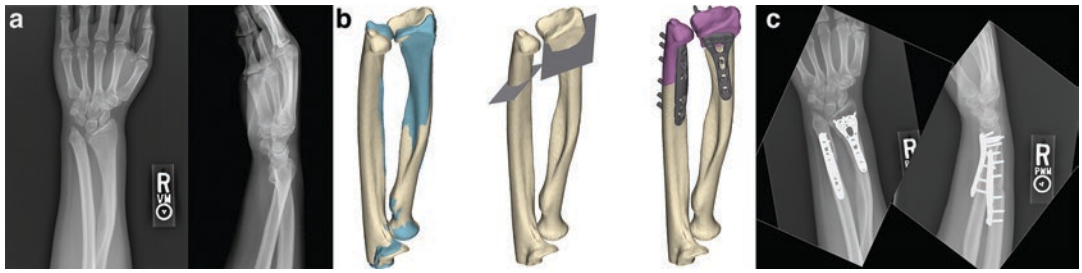

Fig. 25.8 Correction of Madelung deformity via multiple osteotomies using three-dimensional modeling. (**a**) Preoperative wrist radiographs. (**b**) Preoperative plan. The first image shows the preoperative state (in *white*) superimposed on a mirror image of the contralateral side (in *green*). Next, the planned osteotomy sites are indicated. Lastly, the planned outcome with hardware in place; corrected distal fragments in *purple*. (**c**) Final radiographic appearance at 4 months after surgery. (Copyright Shriners Hospitals for Children—Northern California)

Technological advances in CT imaging and computer programming now allow a more comprehensive three-dimensional understanding of Madelung's deformity and enable comparison to the contralateral extremity or to an age-matched normal limb. Additionally, this technology assists the surgeon in accurately planning and performing three-dimensional osteotomies using three-dimensional printed, customized surgical guides.

To plan a corrective osteotomy, three-dimensional imaging is required, which is most easily obtained with a CT scan with three-dimensional reconstruction. The specific protocol for the CT scan is dictated by the computer software used to plan the osteotomies. The use of computer simulation is often facilitated by an engineer familiar with three-dimensional modeling and surgical planning. Typically, a CT scan is obtained of the bilateral upper extremities, including the joints above and below the deformity, and the images of the unaffected arm superimposed on the affected arm to guide correction. Because the bilateral upper extremities are often affected in Madelung's, the contralateral limb may not provide an acceptable comparison; an age matched normal upper extremity or a more mildly affected extremity may be used for comparison in such cases. Based on this comparative data, osteotomies can be planned that can correct the affected extremity to the normal alignment (Fig. 25.8). Additionally, bone models before and after deformity correction, along with customized guides to assist with the osteotomy and implant placement, can be printed using three-dimensional printing technology and sterilized for use in the operating room.

Corrective osteotomies using three-dimensional modeling are in the early stages of

development and principally have been used to correct post-traumatic deformity. The few case series detailing the use of this technology in Madelung's are promising [37, 38].

Summary

Madelung's deformity is an uncommon congenital condition of the wrist and forearm predominantly presenting bilaterally in adolescent females and may be associated with SHOX deficiency syndromes. Its etiology is incompletely understood. Due to the rarity of this condition, its natural history and the outcomes of surgical treatment are difficult to determine. Surgical intervention appears to improve pain, motion, and the appearance of the wrist, but whether these techniques result in sustained improvements in radiographic alignment is unknown. The risk of recurrence is particularly high in younger children. Moreover, no studies have reported patient reported outcomes to assess the effect of this condition of health-related quality of life or the outcomes of operative management. Future long-term prospective, multicenter studies will improve our ability to care for children with Madelung's deformity.

References

1. Goldfarb CA, Ezaki M, Wall LB, Lam WL, Oberg KC. The Oberg-Manske-Tonkin (OMT) classification of congenital upper extremities: update for 2020. J Hand Surg. 2020;45(6):542–7.
2. Flatt A. The care of congenital hand anomalies. St. Louis: Mosby; 1994.
3. Lecon GD. Leçons Orales De Clinique Chirurgicale: Faites A L'hotel-dieu De Paris, Germer Baillière; 1839, vol. 4; 1834. p. 197.
4. Mostofi SB. Who's who in orthopedics. London: Springer; 2005. p. 89–92, 214, 217–219.
5. Malgaigne JF, Baillière JB. Traité des fractures et des luxations. Paris: chez JB. Baillière; 1855, Vol. 2. Paris; 1855. p. 259–76.
6. Madelung O. Die Spontane Subluxation de Hand Nach Vorne. Verh Dtsch Ges Chir. 1878;7:259–76.
7. Arora AS, Chung KC. Otto W. Madelung and the recognition of Madelung's deformity. J Hand Surg. 2006;31(2):177–82.
8. Vickers D, Nielsen G. Madelung deformity: surgical prophylaxis (physiolysis) during the late growth period by resection of the dyschondrosteosis lesion. J Hand Surg Edinb Scotl. 1992;17(4):401–7.
9. Nielsen JB. Madelung's deformity. A follow-up study of 26 cases and a review of the literature. Acta Orthop Scand. 1977;48(4):379–84.
10. Munns CF, Glass IA, LaBrom R, Hayes M, Flanagan S, Berry M, et al. Histopathological analysis of Leri-Weill dyschondrosteosis: disordered growth plate. Hand Surg Int J Devoted Hand Up Limb Surg Relat Res J Asia-Pac Fed Soc Surg Hand. 2001;6(1):13–23.
11. Seki A, Jinno T, Suzuki E, Takayama S, Ogata T, Fukami M. Skeletal deformity associated with SHOX deficiency. Clin Pediatr Endocrinol. 2014;23(3):65–72.
12. Dawe C, Wynne-Davies R, Fulford GE. Clinical variation in dyschondrosteosis. A report on 13 individuals in 8 families. J Bone Joint Surg Br. 1982;64(3):377–81.
13. Ross JL, Scott Jr C, Marttila P, Kowal K, Nass A, Papenhausen P, et al. Phenotypes associated with SHOX deficiency. J Clin Endocrinol Metab. 2001;86(12):5674–80.
14. Lippe B. Turner Syndrome. Endocrinol Metab Clin N Am. 1991;20(1):121–52.
15. Zinn AR, Wei F, Zhang L, Elder FF, Scott CI, Marttila P, et al. Complete SHOX deficiency causes Langer mesomelic dysplasia. Am J Med Genet. 2002;110(2):158–63.
16. Clement-Jones M, Schiller S, Rao E, Blaschke RJ, Zuniga A, Zeller R, et al. The short stature homeobox gene SHOX is involved in skeletal abnormalities in turner syndrome. Hum Mol Genet. 2000;9(5):695–702.
17. Ghatan AC, Hanel DP. Madelung deformity. J Am Acad Orthop Surg. 2013;21(6):372–82.
18. Rump P, Jongbloed JDH, Sikkema-Raddatz B, Mundlos S, Klopocki E, van der Luijt RB. Madelung deformity in a girl with a novel and de novo mutation in the GNAS gene. Am J Med Genet A. 2011;155A(10):2566–70.
19. Ioan DM, Maximilian C, Fryns JP. Madelung deformity as a pathognomonic feature of the onychoosteodysplasia syndrome. Genet Couns Geneva Switz. 1992;3(1):25–9.
20. Anton JI, Reitz GB, Spiegel MB. Madelung's deformity. Ann Surg. 1938;108(3):411–39.
21. Waters PM, Bae DS. Pediatric hand and upper limb surgery: a practical guide. Philadelphia: Wolters Kluwer Health; 2012.
22. Ducloyer P, Leclercq C, Lisfranc R, Saffar P. Spontaneous ruptures of the extensor tendons of the fingers in Madelung's deformity. J Hand Surg Edinb Scotl. 1991;16(3):329–33.
23. Jebson PJ, Blair WF. Bilateral spontaneous extensor tendon ruptures in Madelung's deformity. J Hand Surg. 1992;17(2):277–80.
24. Shahcheraghi GH, Peyman M, Mozafarian K. Madelung deformity and extensor tendon rupture. Am J Orthop Belle Mead NJ. 2015;44(7):E242–4.

25. McCarroll HR, James MA, Newmeyer WL, Molitor F, Manske PR. Madelung's deformity: quantitative assessment of x-ray deformity. J Hand Surg. 2005;30(6):1211–20.
26. McCarroll HR, James MA, Newmeyer WL, Manske PR. Madelung's deformity: diagnostic thresholds of radiographic measurements. J Hand Surg. 2010;35(5):807–12.
27. Zebala LP, Manske PR, Goldfarb CA. Madelung's deformity: a spectrum of presentation. J Hand Surg. 2007;32(9):1393–401.
28. Peymani A, Dobbe JGG, Streekstra GJ, McCarroll HR, Strackee SD. Quantitative three-dimensional assessment of Madelung deformity. J Hand Surg Eur Vol. 2019;44(10):1041–8.
29. Oishi S, Wheeler L, Ezaki M. Madelung's deformity. In: The pediatric upper extremity. 1st ed. New York: Springer Reference Abzug JM, Kozin S, Zlotolow DA eds. 2015;1763–72.
30. Kozin SH, Zlotolow DA. Madelung Deformity. J Hand Surg. Abzug JM, Kozin S, Zlotolow DA eds. 2015;40(10):2090–8.
31. Otte JE, Popp JE, Samora JB. Treatment of Madelung deformity with Vicker ligament release and radial physiolyses: a case series. J Hand Surg. 2019;44(2):158.e1–9.
32. Del Core M, Beckwith T, Phillips L, Ezaki M, Stutz C, Oishi SN. Long-term outcomes following Vickers ligament release and growth modulation for the treatment of Madelung deformity. J Pediatr Orthop. 2020;40(4):e306–11.
33. Harley BJ, Brown C, Cummings K, Carter PR, Ezaki M. Volar ligament release and distal radius dome osteotomy for correction of Madelung's deformity. J Hand Surg. 2006;31(9):1499–506.
34. Steinman S, Oishi S, Mills J, Bush P, Wheeler L, Ezaki M. Volar ligament release and distal radial dome osteotomy for the correction of Madelung deformity: long-term follow-up. J Bone Joint Surg Am. 2013;95(13):1198–204.
35. Bruno RJ, Blank JE, Ruby LK, Cassidy C, Cohen G, Bergfield TG. Treatment of Madelung's deformity in adults by ulna reduction osteotomy. J Hand Surg. 2003;28(3):421–6.
36. McCarroll HR, James MA. Very distal radial osteotomy for Madelung's deformity. Tech Hand Up Extrem Surg. 2010;14(2):85–93.
37. Bauer AS, Storelli DAR, Sibbel SE, McCarroll HR, Lattanza LL. Preoperative computer simulation and patient-specific guides are safe and effective to correct forearm deformity in children. J Pediatr Orthop. 2017;37(7):504–10.
38. Imai Y, Miyake J, Okada K, Murase T, Yoshikawa H, Moritomo H. Cylindrical corrective osteotomy for Madelung deformity using a computer simulation: case report. J Hand Surg. 2013 Oct;38(10):1925–32.

Epidermolysis Bullosa

26

Roberto Diaz, Jennifer Chan, and Amy L. Ladd

Background

Epidermolysis bullosa (EB) is a rare genetic connective tissue disorder of the skin that leads to blister formation following minimal mechanical trauma. Gene mutations result in the production of abnormal structural proteins whose primary function is anchoring of the epidermis to the dermis, making the skin vulnerable to injury with trivial mechanical trauma. In the United States, the prevalence of EB was estimated at approximately eight cases per one million population in 1990 based on the National EB Registry [1]. The incidence was estimated as 19 cases per one million between 1986 and 1990 [1].

The severity of the disease can vary from mild to severe and appears to be related to the degree of protein abnormality and quantities present [2]. EB can manifest in many areas of the body including extra-cutaneous sites such as the eyes, gastrointestinal tract, and genitourinary tracts. Severity and location will vary based on subtype of EB. Currently, there is no cure for EB, and treatment is aimed at minimizing blister formation, preventing infection, optimizing nutrition, managing pain, and maintaining function. One of the most disabling aspects of EB is the formation of pseudosyndactyly of the hands (Fig. 26.1), leading

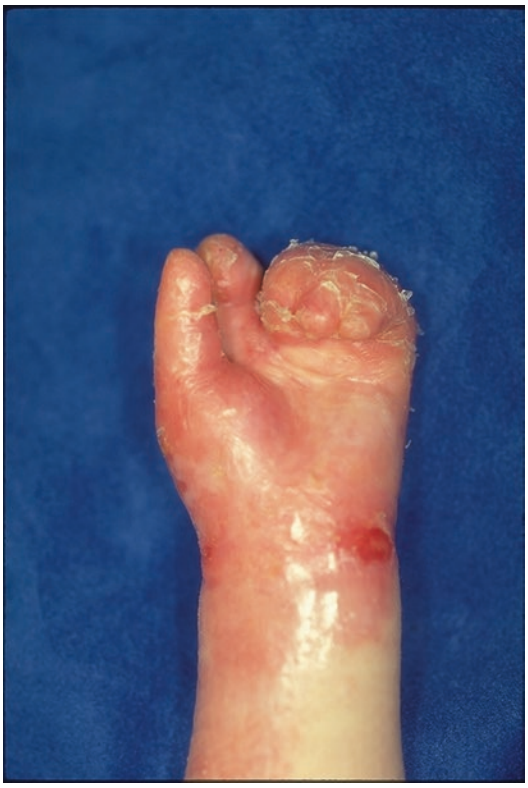

Fig. 26.1 Example of pseudosyndactyly

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to progressive loss of hand function [3]. Hand involvement is most frequently observed in the recessive dystrophic epidermolysis bullosa subtype [4]. The hands are particularly vulnerable to blister formation as they frequently experience sheer forces during various activities of daily living. Surgical treatment of the hand is aimed at improving hand function by restoring independent finger mobility, pinch, and grasp function. This chapter will focus on the treatment of hand deformities caused by EB, specifically those in children with recessive dystrophic epidermolysis bullosa as seen at our institution.

History

EB was first described by Austrian dermatologist Von Hebra in 1870 [5]. In 1879, Tilbury Fox, a British dermatologist, described the inheritance of EB in two cases involving a 6-year-old girl who presented with hand blisters and her sister, a 2-year-old with blisters on multiple areas and ulcerations on the tongue [6]. In 1886, this condition was named epidermolysis bullosa by Heinrich Koebner.

EB Types

There are four major types of EB [4]. EB is classified according to the level at which skin cleavage occurs: (1) EB simplex (intraepidermal separation), (2) junctional EB (intra-lamina lucida separation), (3) dystrophic EB (sub-basal lamina separation), and (4) Kindler syndrome (mixed cleavage points).

EB simplex (EBS) is the most common type that follows an autosomal dominant inheritance pattern with several subtypes having an autosomal recessive pattern of inheritance. It is characterized by localized or widespread blisters depending on subtype and typically presents at birth or early infancy. Blister formation occurs within the epidermis, and blisters heal without scar formation. Most patients with the localized subtype will have a normal life expectancy [2, 7]. Nail dystrophy, milia, and mucosal involvement are rare in all types of EBS compared to the other major types [1].

Junctional EB (JEB) is inherited in an autosomal recessive fashion and can vary from mild to severe disease. Cleavage occurs at the dermal-epidermal junction within the lamina lucida. The hallmark clinical feature of all forms of JEB is enamel hypoplasia that has an appearance of pitting on tooth surfaces [1]. There are two general subtypes of JEB, which include the JEB Herlitz or generalized severe [4] and the more common generalized atrophic benign EB [1, 2]. The junctional EB Herlitz variant is the most severe form that is present at birth and carries a high risk of death within the first 2 years of life. Blisters heal with atrophic scars. Manifestations can occur in the eyes and gastrointestinal and genitourinary systems. Death is related to complications from malnutrition, infection, and respiratory failure [2, 7]. In the milder form, generalized atrophic benign EB, patients can have a normal lifespan. They may have scalp involvement, which can lead to hair loss.

Dystrophic EB is characterized by cleavage below the basal lamina and has both autosomal dominant and recessive inheritance patterns [1, 2, 7]. The autosomal dominate subtype (DDEB) has a milder presentation with blistering occurring primarily in the upper and lower extremities. In contrast, the recessive type (RDEB) manifests with widespread blistering with involvement of the eyes, gastrointestinal tract, genitourinary tract, kidney, and heart. Blisters heal with severe scar formation that can result in nail dystrophy, joint flexion contractures, and pseudosyndactyly of the fingers and toes. This ongoing process of blister and scar formation can result in significant hand dysfunction. There is also an increased risk of the development of squamous cell carcinoma in areas of chronic non-healing ulcers. Because there is mucosal involvement, scar formation and erosions can occur in the esophagus, cornea, and genitourinary and gastrointestinal tracts. Death typically ensues in early adult life secondary to malnutrition, infection, and cutaneous carcinomas.

Kindler syndrome is an autosomal recessive form of EB with cleavage occurring at multiple

sites including intraepidermal, junctional, and sublamina densa [1, 2]. Blistering presents at birth and typically occurs in acral locations. Blister healing occurs with atrophic scar. Patients generally have a normal life span with blister formation decreasing with time. This form EB is associated with photosensitivity, skin atrophy, and dyspigmentation and can also have mucosal involvement [2].

Diagnosis

EB commonly presents at birth with skin blisters that must be distinguished from other skin lesions occurring during the neonatal period. The diagnosis of EB begins with a thorough history and physical examination including a family history to rule out inheritable causes of skin blisters and erosions [8]. The differential diagnosis of a newborn with skin blisters is quite extensive as described by Nischler et al. Some notable conditions include inheritable causes, traumatic blisters, and infectious causes such as herpes simplex, staphylococcal scalded skin syndrome, bullous impetigo, and immunobullous disorders including bullous pemphigoid and epidermolysis bullosa acquisita [8]. If there is a high suspicion for EB, a skin biopsy of a blister is required for a definitive diagnosis. Immunofluorescence mapping (IFM) of a skin biopsy is the primary diagnostic tool used in the diagnosis of EB and can identify the EB subtype in addition to the level of skin separation. If IFM is inconclusive, transmission electron microscopy and genetic testing can be performed to aid in the diagnosis [2, 4, 7].

Hand Contractures

Hand deformities can occur with all major types of EB; however, they more commonly occur with recessive dystrophic EB subtypes [4]. Le Touze et al. described four characteristic lesions seen in EB affecting the hand: (1) complete loss of nails, (2) flexion contracture of fingers and palm, (3) thumb adduction contracture, and (4) pseudosyndactyly. Deformities develop from repeated blister healing that forms dense scar tissue causing partial fusion between digital web spaces. As this process continues, fusion of entire digits can result, and scar tissue can eventually encase the entire hand, a condition referred to as a mitten hand (Fig. 26.2). This mitten hand restricts movement of fingers, causing finger contractures, adduction contracture of the thumb and proximal muscle atrophy, and even joint destruction in cases with severe long-standing deformities [9]. This renders the hand non-functional, making it difficult for patients to carry out even simple tasks. Fine et al. reviewed the National Epidermolysis Bullosa Registry to determine the frequency and risk of developing hand and foot deformities in the major and subtypes of EB. This database contains information on 3280 patients with EB that enrolled between the period of 1986 and 2002. There were 2,748 patients identified who had sufficient data to allow classification into 10 different subtypes of EB. The authors concluded that mitten hand deformities occur less commonly in EBS, JEB, and DDEB than in RDEB. The frequency of mitten hand deformities observed in EBS and JEB ranged from 0.0 to 4.39% and 0.53 to 6.82% depending on subtype. This is in comparison with 41.18% and 51.13% seen with non-Hallopeau-Siemens RDEB and RDEB-inversa, respectively. The highest frequency was observed in the Hallopeau-Siemens RDEB subtype at 95%. The frequency of mitten hand deformities was only 2.35% in the DDEB subtype.

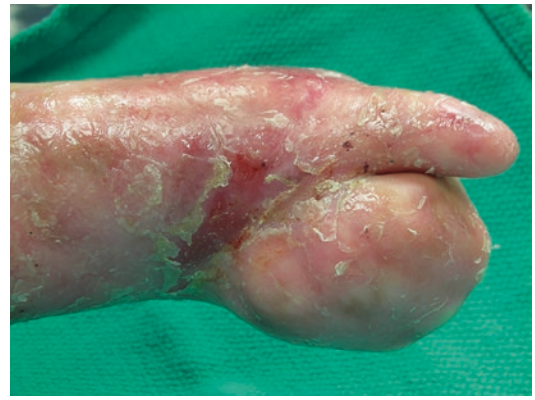

Fig. 26.2 Mitten hand

Management

Nonoperative

Treatment of persons with EB is best delivered in a multidisciplinary fashion with involvement of the patient's family, primary care physician, dermatologist, dentist, nutritionist, and physical and occupational therapists. Involvement of subspecialty services such as gastroenterology, urology, ophthalmology, pain management, plastic surgery, and hand surgery is determined based on need. There is currently no cure available for EB. Nonoperative treatment is aimed at maximizing function, preventing blister formation by minimizing skin trauma, providing adequate nutrition and wound care, and preventing infection [2].

Patients with the greatest risk of developing hand deformities such as pseudosyndactyly should receive an assessment of their hands preferably with an OT with experience working with persons with EB or a hand therapist. This should occur within the first 1–2 years of life with regular monitoring into adulthood [10, 11]. The therapist can provide assessment of finger ROM, web space length, and hand function. An assessment form has been developed by a panel of OTs with expertise in working with persons with EB [11]. There are various methods of measuring web length including using the wrist to floor of the web spaces [12], residual finger length, and a hand tracing. One of the most important measurements to monitor is the opening of the first web space and the preservation of a functional pinch [11].

The literature describes various methods for the provision of downward pressure to the finger web spaces in an effort to minimize web creep. These include interdigital hand wrapping, orthosis intervention, and use of off-the-shelf or custom gloves [2, 10, 11, 13, 14] (Fig. 26.3).

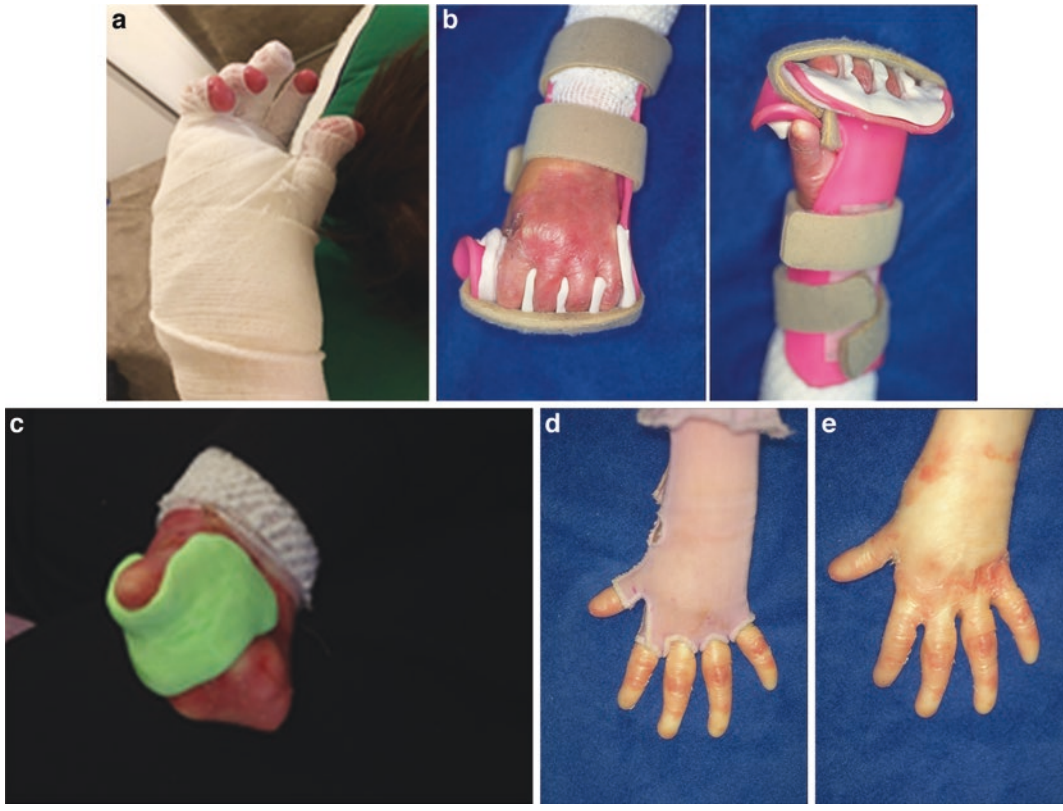

Fig. 26.3 (**a**) Interdigital hand wrapping. (**b**) Thermoplastic orthosis with silicon putty partitions. (**c**) Silicon putty orthosis. (**d**) Elastic compressive custom-made glove worn at daytime. (**e**) Same hand with glove removed demonstrating maintenance of web spaces

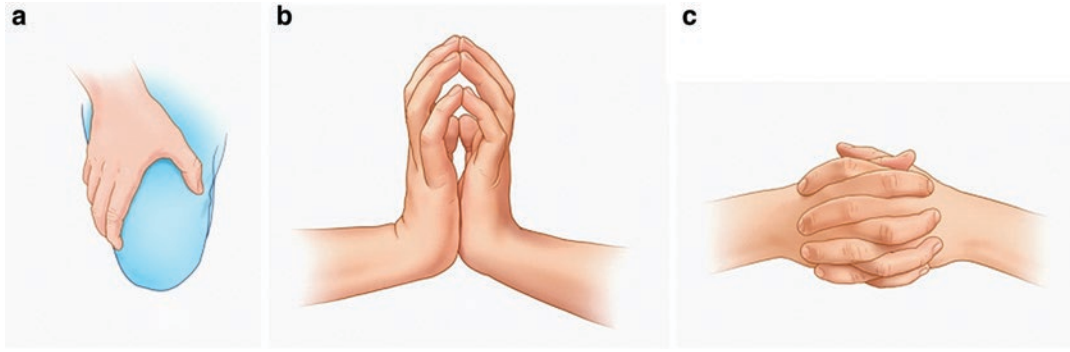

Fig. 26.4 (**a**) Thumb CMC stretching exercise. (**b**) Wrist stretching exercise. (**c**) Interdigital finger web space stretching exercise

Gentle hand range of motion exercises may be beneficial in maintaining finger and thumb ROM and function [10, 11]. Figure 26.4 illustrates examples of exercises appropriate for patients with EB including thumb CMC abduction stretching, wrist stretching, and stretches to interdigital web spaces. It is recommended to encourage patients that are able to participate in their home program to provide their own stretches within their tolerance and ability.

Operative Treatment Indications

The indications for operative treatment of the hand in patients with EB include progressive loss of hand function as demonstrated by decreased grasp or pinch, formation of pseudosyndactyly, loss of finger independence, flexion contractures, and formation of a mitten hand. The goals of surgery are to improve overall hand function by reestablishing pinch and grasp function and to delay recurrence [2, 10, 11]. The timing of surgery will depend on surgeon preference, patient's goals, and the willingness and ability of the patient and their caregivers to participate in, often painful, postoperative dressing changes and therapy [3, 11]. Although some patients will present with severe contractures and a mitten hand deformity, we prefer early surgical intervention when patients maintain some hand function with only mild to moderate contractures. Early surgical intervention is advocated in order to avoid interruptions in a developing child [3, 15].

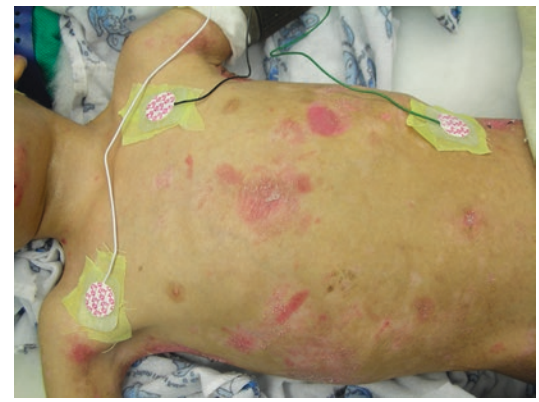

Fig. 26.5 Electrocardiographic leads placed over non-adhesive dressings

Preoperative Considerations

It is important to recognize that EB can affect many areas of the body, and extreme care must be exercised when treating the patient. An air mattress should be utilized when possible. All bony prominences should be well-padded, and sequential compression devices are preferentially not utilized as they can further damage fragile skin. No rubbing of skin should be allowed, and the use of adhesive tape is contraindicated. A blood pressure cuff should only be applied to a well-padded extremity [15]. Electrocardiographic leads are placed over petroleum non-adhesive dressing as shown in Fig. 26.5 [1]. An intravenous line is placed after the patient has been adequately sedated and is sutured into place and secured with a cotton wrap and Coban (3 M

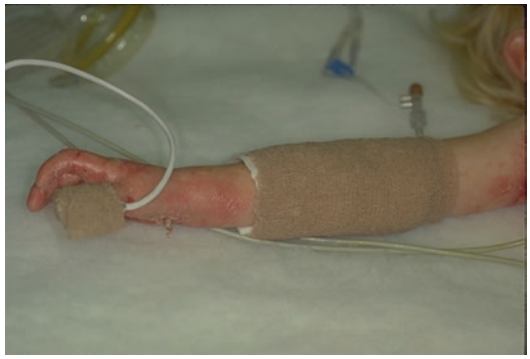

Fig. 26.6 Intravenous line secured with Coban

Corp., St. Paul, MN) (Fig. 26.6). It is important that all members participating in the care of the patient are aware of these precautions.

Surgical Technique

The operative technique performed by the senior author is similar to that described by several other surgeons [3, 12, 15–17]. However, our technique differs such that no tourniquet is used, full-thickness skin grafts are used instead of split thickness, and pinning of the thumb is not performed after release of its adduction contracture [18]. After carrying out the preoperative precautions described previously, the patient is placed on synthetic sheepskin overlying the operative table. Although some surgeons prefer the use of tourniquet [12, 15–17], we elect not to use a tourniquet to avoid skin trauma at the site of tourniquet placement. The patient is given one dose of appropriately dosed cefazolin intraoperatively if there are no allergic contraindications. Bleeding generally consists of slow ooze that can be controlled with hemostatic collagen (Avitene, Alcon Puerto Rico Inc., Humacao, Puerto Rico) or thrombin-soaked cellulose. There is also a constant serous ooze from the surgical sites that must be monitored carefully in order to adequately provide fluid resuscitation intraoperatively. A median nerve wrist block of dose appropriate 0.25% bupivacaine with epinephrine 1:200,000 is administered. This block decreases anesthetic requirements and also helps with postoperative pain (Fig. 26.7). The abdomen and extremity are prepped without mechanical scrubbing, pouring dilute chlorhexidine soap over the proposed operative sites.

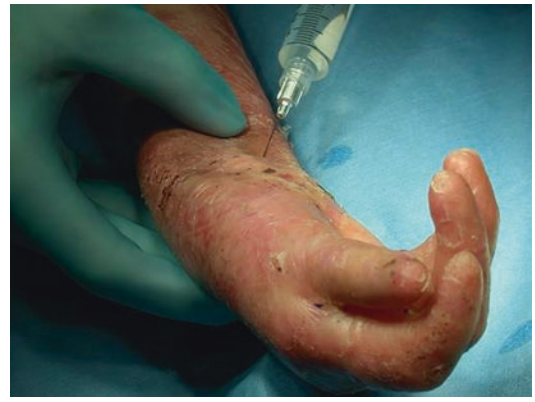

Fig. 26.7 Median nerve block

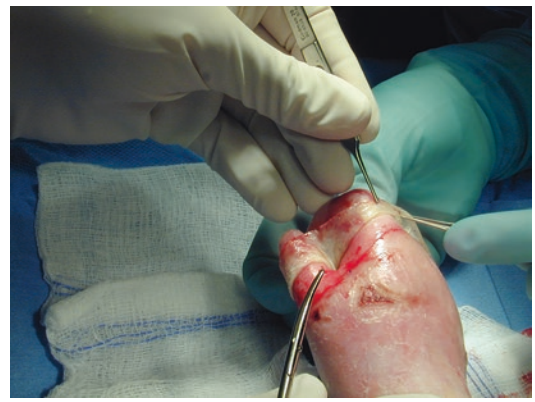

Fig. 26.8 Surgical "degloving" of hand

Surgery begins with epidermal degloving of the hand by scoring only the epidermis with a scalpel and then gently teasing away the epidermal cocoon using fine forceps, a Freer elevator, and selective separation with Littler scissors (Figs. 26.8 and 26.9). The pseudosyndactyly that forms between the fingers is released with the elevator, advanced with selective cuts, and gently separated with opposing traction on the digits. When applying traction, a single layer of gauze padding over each digit absorbs the ooze, which can create slippery surfaces. Degloving alone has proven to be ineffective and is associated with early recurrence [19]. The first web space con-

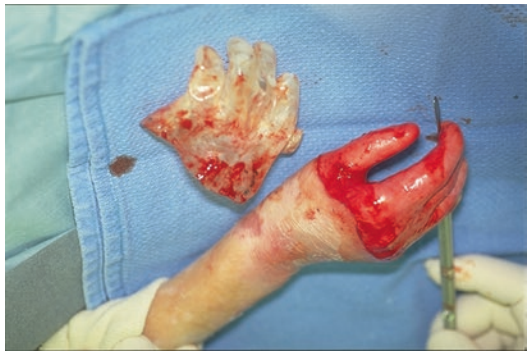

Fig. 26.9 Intraoperative image demonstrating the epidermal cocoon after degloving the hand

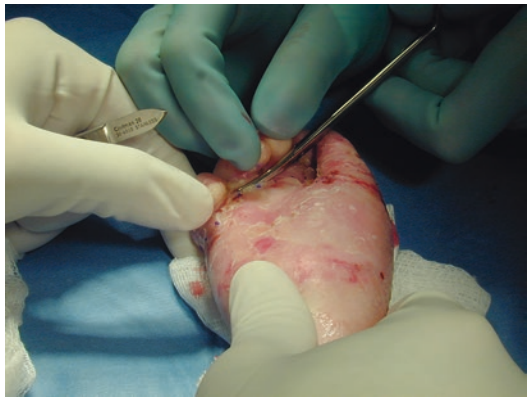

Fig. 26.10 Contracture release

tracture usually requires release of the adductor fascia and only occasionally full-thickness skin grafting. A four-flap z-plasty is not used to release the first web space contracture as the skin non-pliable.

Joint contractures are released by identifying areas of tension, using gentle passive extension forces. Sites of tension are released sharply along with gentle manipulation (Fig. 26.10). Care must be taken to prevent injury to the neurovascular structures. Complete contracture releases are often not possible; limitations to release include vulnerability of the neurovascular bundle and size of the subcutaneous defect. Fine K-wires are placed across the interphalangeal joints of the fingers to maintain the correction of the contractures achieved in surgery (Fig. 26.11). Full-thickness skin grafts are applied to areas of skin deficits that are greater than 1 cm (see Fig. 26.11).

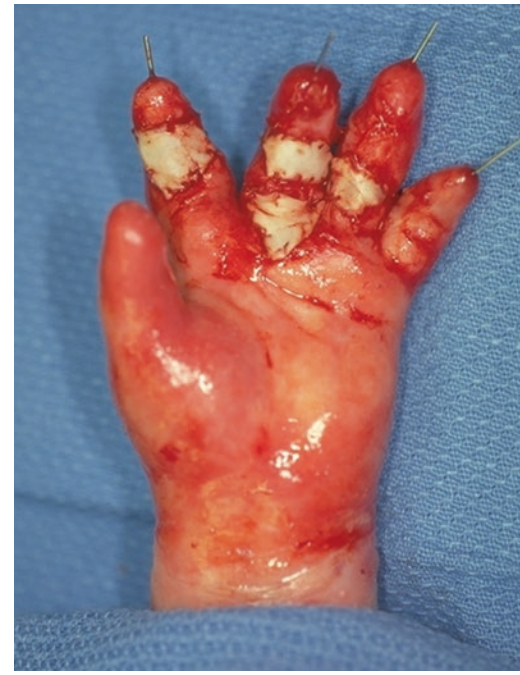

Fig. 26.11 Hand demonstrating finger pinning and full-thickness skin grafts

Skin grafts are harvested from areas void of blisters, with the abdomen most preferred. It typically has areas free of blisters. Obtaining skin graft in patients with EB is more technically challenging than from harvesting from the normal skin, especially since these children have little subcutaneous fat and have noncompliant skin and variable location of clothing—underwear and waistband—can irritate the wound. Templates are recommended to plan precise areas of skin grafts, given the non-compliance of EB skin. We prefer to use full-thickness skin grafts in contrast to other surgeons [12, 20, 15, 16, 19]. The epidermis readily sloughs off during the handling of the skin graft creating a dermal graft; however, we found that this does not affect graft acceptance or healing. The donor site is closed with absorbable subcuticular and interrupted epidermal sutures. Nonabsorbable sutures should be avoided as they can become buried in the healing scar. We prefer the use of 6-0 ophthalmic suture because the spatula needle and suture coating allow easy gliding through the sticky tissues. The graft incision is covered with non-adhesive dressings followed

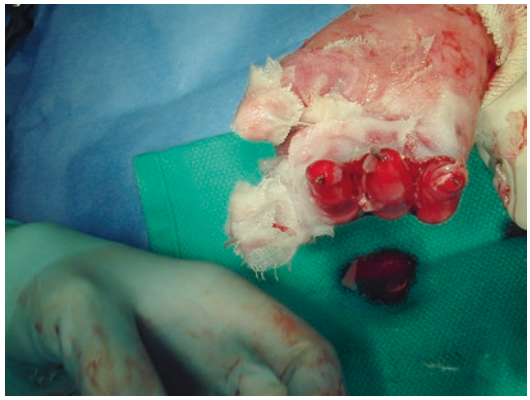

Fig. 26.12 Postoperative dressings demonstrating the use of antibiotic ointment and petrolatum gauze

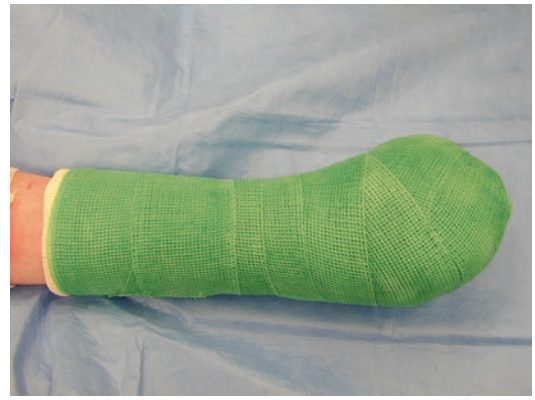

Fig. 26.13 Well-padded postoperative cast

by gauze and flexible tubular fishnet bandage. The skin grafts are then sutured into the skin-deficient areas of the hand with running nonabsorbable sutures.

In recent years, we have moved away from skin grafting when possible, given the rapid epithelialization in these patients and to avoid donor-site morbidity. Liberal use of antibiotic ointment is then applied to the hand wounds followed by petroleum gauze (Fig. 26.12). Mupirocin (Bactroban, GlaxoSmithKline) is preferred, providing coverage against the common contaminant, *Pseudomonas*. The web spaces are maintained open by placing bulky mineral oil-soaked cotton in between the digits over the non-adherent gauze. No K-wire is used for the thumb. Instead, the thumb is maintained in the abducted position by placing a 2″ roll bandage as a spacer. The extremity is then placed in a well-padded cast completely covering the hand; in young children, we use a long arm cast (Fig. 26.13). Patients are typically discharged home on the day of surgery.

Cast Removal

The second-stage procedure is performed at 10 to 14 days under anesthesia (IV sedation or brief intubation). This includes cast and pin removal, wound dressing change, and splint orthosis fabrication with the therapists. One dose of prophylactic antibiotics is given. The cast is carefully removed with a cast saw, and the dressings are soaked with normal saline and dilute peroxide to aid in careful dressing removal. The wounds are inspected and debrided; although the cast padding and dressings are typically replete with colored drainage and foul smell suggestive of pseudomonas, we have never encountered a deep infection. The wounds are then covered with dressings coated with a mixture of antibiotic ointment and an emollient cream (e.g., Aquaphor, Beiersdorf, Inc.) followed by non-adhesive petroleum gauze and dry gauze for drainage absorption. An orthosis is fabricated to maintain gains in range of motion. Figure 26.14 is an example of a pattern and hand orthosis that is used postoperatively over the bandages. If there is copious drainage, the orthosis can be secured with gauze bandage or tubular gauze versus soft straps for hygiene purposes. Use of padded, absorbent dressings inside the orthosis is an option that can be replaced with

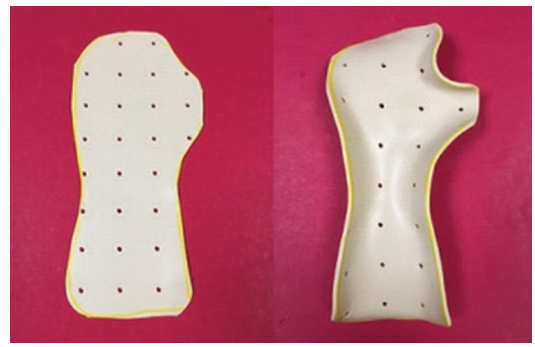

Fig. 26.14 Postoperative splint pattern and orthosis

each dressing change and provides a padded surface over the thermoplastic as the wounds heal and the padding provided by bandages decreases. The family is instructed in wound care and dressing changes to continue at home every 2 to 3 days. Adequate analgesics are required for dressing changes, which may be guided by the pain management service if available.

Rehabilitation

Postoperative hand therapy serves a very important role in the management of EB. Therapy typically begins 2 to 3 days after cast removal. Therapy goals are to guide wound care and healing, improve/maintain finger range of motion, improve hand function, and prevent recurrence of contractures and web creep [13]. The patient may have limited available joint motion due to finger and thumb deformities. For instance, movement may only be available at the MP joints or PIP joints. Despite these limitations, the patient can have a functional grasp and pinch that need to be maintained and strengthened. Initially the patient will experience significant pain with movement, but finger, thumb, and wrist range of motion exercises are important during the early postoperative period as patients can develop stiffness from pin placement and immobilization of the fingers. Generally, active-assisted range of motion is used with the patient directing the pressure used to stretch the fingers into flexion and extension and the thumb into flexion, extension, and abduction. Care is taken to minimize skin trauma. Initially, exercises need to occur multiple times each day with wound dressings on. Exercises should also be performed during dressing changes as patients can achieve greater ranges of motion with dressings removed. The patient's home program can include hand use for various daily functional tasks that require finger movement. Static positions such as sitting with arms resting with wrists and fingers in extension are encouraged over wrist flexion.

Postoperatively patients typically wear a thermoplastic orthosis full time for 2 to 4 weeks depending on the healing phase and remove it for daily exercises and dressing changes every 2 to 3 days. With progressive healing, range of motion and abilities to use functional grasp and pinch will also improve. Patients are then transitioned from full-time orthosis use to a glove or interdigital gauze bandage wrapping of the hands to be worn during the day and use of an orthosis at night indefinitely. As the use of wound dressings decreases, the orthosis may be more tolerable with the use of silicon putty inserts with partitions to maintain web spaces (see Fig. 26.3b). Several physicians believe that splinting and the use of compressive gloves can help delay recurrences [18–16].

Complications

Most complications occurring during the management of a patient with EB are related to skin fragility and mucosal involvement. Skin trauma resulting in blister formation can occur during the handling of the patient during any stage of treatment. Mask ventilation can result in skin blistering, and intubation can result in mucosal injury. Poorly padded extremities during placement of blood pressure cuff cans cause severe blistering as can the use of adhesives such as placement of electrocardiographic leads directly on the skin. Patients with EB have a higher incidence of gastroesophageal reflux and are at increased risk for aspiration [21]. Increased fluid losses can occur and should be monitored closely especially in patient with poor nutrition to prevent dehydration. Patients with EB are also at increased risk for thermal losses because of skin blisters and low body mass index [21]. EB patients are also at an increased risk of infection. However, we routinely only give prophylactic antibiotics intraoperatively and have not observed any postoperative infections using this protocol.

Outcomes

In 1982, Greider and Flatt published their results on the surgical treatment of nine hands in five patients with RDEB. Average patient age was 6 years at the time of surgery. There were no complications in this series. One patient had a marked recurrence on one hand and a moderate recurrence on the other hand. Two patients had a slow or slight recurrence at their 8- and 10-year follow-up, respectively. At a 4-year follow-up, a fourth patient had a recurrence of their thumb adduction contracture. One patient died within a year from surgery secondary to pneumonia and sepsis.

Le Touze et al. described their experience in four patients with hand deformities secondary to EB. They reported good immediate postoperative results with respect to finger independence, finger flexion and extension, and thumb opposition. They were to able maintain good hand function for 18 to 24 months with therapy but report a recurrence between 4 and 6 years requiring repeat surgery.

Ladd et al. reported their results on nine hands in seven EB patients treated operatively with an average follow-up period of 17 months. There were no infections or wound complications. All patients had persistent or recurrent contractures measuring 15 to 30° at the interphalangeal joints and some form of metacarpal phalangeal joint extension contracture limiting flexion. Recurrence developed to a mild degree in two patients and moderate degree in three patients. Five patients who were compliant with the postoperative treatment regimen were observed to have good functional results demonstrated by grasp and pinch function (Fig. 26.15). Our experience over two decades suggests that recurrence is variable depending on severity of disease, compliance with splinting or wrapping, and medical attention. We have operated on some children several times. Most patients and families prefer the simple wrapping to maintain the webs compared to splinting, given its ease of use and freedom of the fingers. Although in our experience this provides excellent web maintenance, it leaves no check for the digital contracture in the anteroposterior plane.

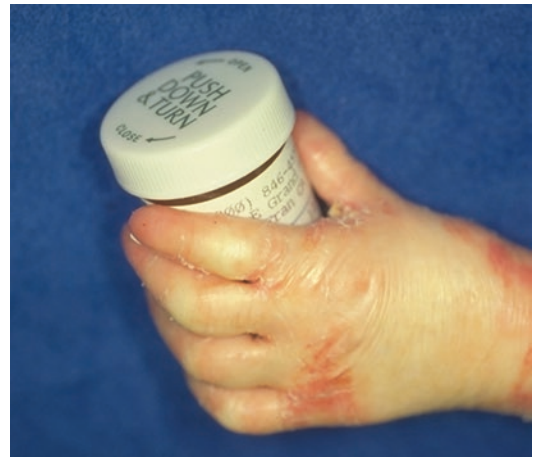

Fig. 26.15 Postoperative patient demonstrating ability to grasp objects

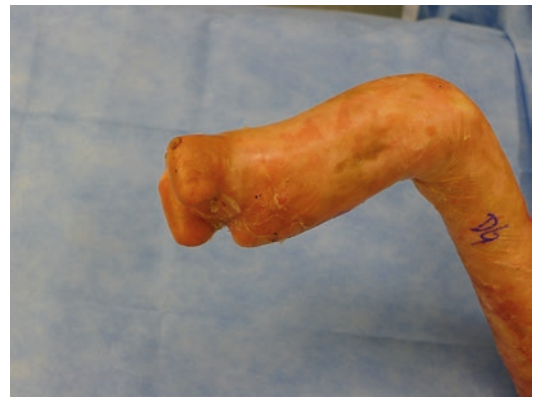

Fig. 26.16 Preoperative image of 25-year-old male who has undergone multiple surgeries for recurrence. He now reports difficulty with grasping objects

Since there is no cure for EB, recurrence of hand deformities will likely occur despite surgical treatment [3, 16]. Surgery can provide significant improvement in hand function allowing patients to perform activities of daily living and continue psychomotor development. However, it is important to inform patients and parents that a second surgery will likely be needed as surgery does not change the underlying disease [3]. The following case illustrates hand deformities that may develop with long-standing recurrent blistering and scarring in patients with EB. The patient whose hand is shown in Fig. 26.16 has undergone multiple surgeries as a child begin-

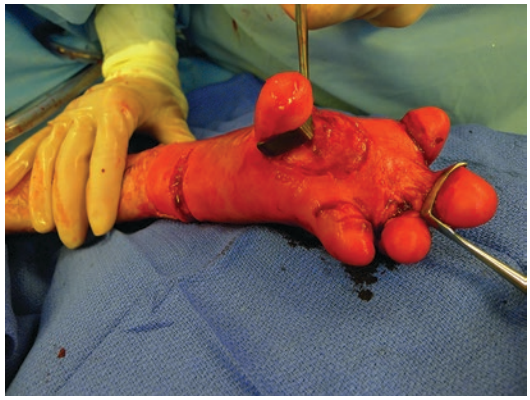

Fig. 26.17 Intraoperative image of patient in Fig. 26.16 after contracture release of the wrist, thumb, and fingers

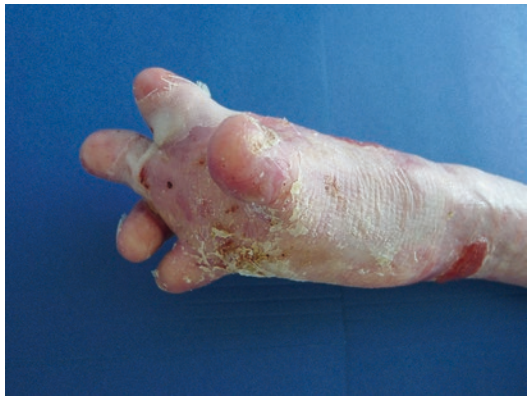

Fig. 26.18 Four-month postoperative image of patient in Fig. 26.16 following contracture releases

ning at age 4. At age 25, he presented to our clinic complaining of difficulty grasping objects and elected to undergo surgical treatment in an attempt to improve hand function. He underwent finger and thumb syndactyly and contracture releases in addition to release of his wrist contracture (Fig. 26.17). At his 4-month postoperative visit (Fig. 26.18), he was able to grasp an ace bandage and a pen (Fig. 26.19a, b). He is currently in college and is able to type by performing single key stokes with his thumb. He is scheduled to undergo a similar procedure of his left hand.

Conclusion

EB is a rare inherited disorder characterized by blister formation in the skin following minimal mechanical trauma. The severity of the disease will vary based on EB type. Hand deformities most commonly occur in patients with the RDEB subtype and can be a cause of significant disability in a child. The goal of surgical treatment is to improve hand function by restoring independent finger mobility, pinch, and grasp function. Patients and family members should be informed that recurrence is common and repeat surgery may be necessary to improve hand function.

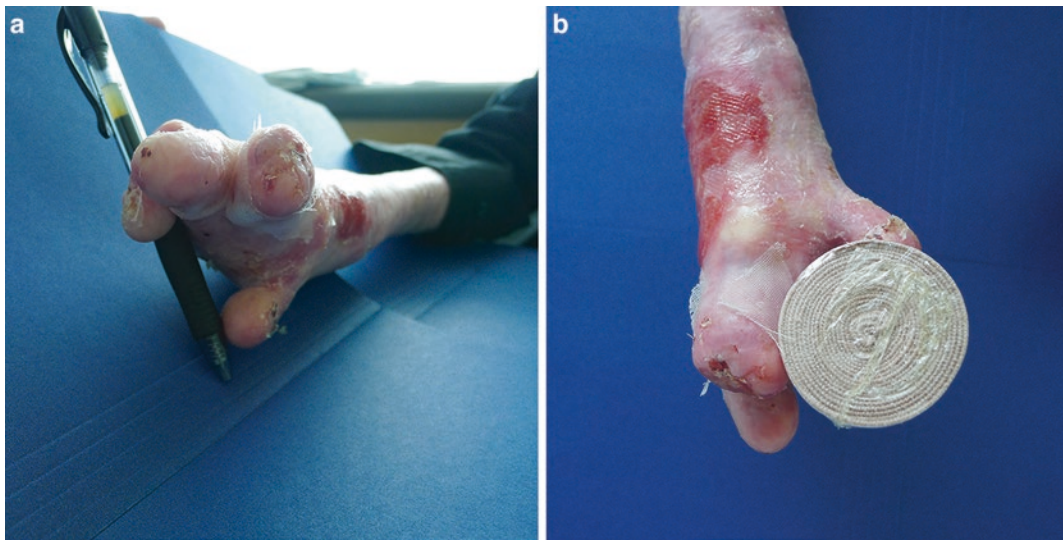

Fig. 26.19 (**a**, **b**) Four-month follow-up of patient in Fig. 26.17 demonstrating ability to grasp objects

References

1. Fine JD. Inherited epidermolysis bullosa. Orphanet J Rare Dis. 2010;5:12.
2. Gonzalez ME. Evaluation and treatment of the newborn with epidermolysis bullosa. Semin Perinatol. 2013;37(1):32–9.
3. Le Touze A, Viau D, Martin L, Depont R, Robert M. Recessive dystrophic epidermolysis bullosa: management of hand deformities. Eur J Pediatr Surg. 1993;3:352–5.
4. Fine JD, Bruckner-Tuderman L, Eady RA, Bauer EA, Bauer JW, Has C, et al. Inherited epidermolysis bullosa: updated recommendations on diagnosis and classification. J Am Acad Dermatol. 2014;70:1103–26.
5. Von Hebra F. Pemphigus: Arzlicher Bericht des K.K. Allgemeinen Krankenhauses zu Wein vom Jahre 1870. Vienna; 1870. p. 362–4.
6. Fox T. Notes on unusual or rare forms of skin disease. IV. Congenital ulceration of the skin (two cases) with pemphigus eruption and arrest of development generally. Lancet. 1879;I:766.
7. Cooper TW, Bauer EA. Epidermolysis bullosa: a review. Pediatr Dermatol. 1984;1:181–8.
8. Nischler E, Lausegger A, Huttner C, et al. Diagnostic pitfalls in newborns and babies with blisters and erosions. Dermatol Res Pract. 2009;2009:320–403.
9. Fine J, Johnson L, Weiner M, Stein A, Cash S. Pseudosyndactyly and musculoskeletal contractures in inherited epidermolysis bullosa: experience of the national epidermolysis bullosa registry, 1986–2002. J Hand Surg Br. 2005;30(1):14–22.
10. Mullett F, Atherton D. Physiotherapy for epidermolysis bullosa. Physiotherapy. 1990;76:660–2.
11. Chan J, Weisman A, King A, Maksomski S, Shotwell C, Baille C, et al. Occupational therapy for epidermolysis bullosa: clinical practice guidelines. Orphanet J Rare Dis. 2019;14:129.
12. Greider JL, Flatt AE. Surgical restoration of the hand in epidermolysis bullosa. Arch Dermatol. 1988;124:765–7.
13. Mullett F. A review of the management of the hand in dystrophic epidermolysis bullosa. J Hand Ther. 1998;11:261–5.
14. Cohn H, Teng J. Advancement in the management of epidermolysis bullosa. Curr Opin Pediatr. 2016;28:507–16.
15. Greider J, Flatt AE. Care of the hand in recessive epidermolysis bullosa. Plast Reconstr Surg. 1983;72(2):222–8.
16. Terrill PJ, Mayou BJ, Pemberton J. Experience in the surgical management of the hand in dystrophic epidermolysis bullosa. Br J Plast Surg. 1992;45:435–42.
17. Zarem HA, Pearson RW, Leaf N. Surgical management of hand deformities in recessive dystrophic epidermolysis bullosa. Br J Plast Surg. 1974;27:176–81.
18. Ladd AL, Kibele A, Gibbons S. Surgical treatment and postoperative splinting of recessive dystrophic epidermolysis bullosa. J Hand Surg Am. 1996;2lA:888–97.
19. Horner RL, Wiedel JD, Bralliar F. Involvement of the hand in epidermolysis bullosa. J Bone Joint Surg. 1971;53A:1347–56.
20. Cuono C, Finseth F. Epidermolysis bullosa: current concepts and management of the advanced hand deformity. Plast Reconstr Surg. 1978;62:280–5.
21. Goldschneider K, Lucky A, Mellerio J, Palisson F, Carmen Vinuela M, Azizkhan RG. Perioperative care of patients with epidermolysis bullosa: proceedings of the 5th international symposium on epidermolysis bullosa, Santiago, Chile, December 4–6, 2008. Paediatr Anaesth. 2010;20:797–804.

General Skeletal Disorders

27

Jennifer W. Lisle, Peter K. Twining, and Ryan A. Caldwell

Osteogenesis Imperfecta

Background

Descriptions of osteogenesis imperfecta (OI) date back to Egypt from 1000 BC, when a mummy was characterized as having a wormian skull bone, amber-colored teeth, and bowed legs [1]. Olaus Jacob Ekman provided the first scientific description of OI in 1788; however, the first use of the phrase "osteogenesis imperfecta" to describe the condition was by Willem Vrolik in 1849 [1, 2]. Since then, numerous other names have been used to describe OI: mollities ossium, fragilitas ossium, osteopsathyrosis idiopathica, osteoporosis fetalis, osteomalacia congenital, Lobstein's disease, Vrolik's disease, Eddome syndrome, and van der Hoeve syndrome [1, 3].

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Genetics

OI is characterized as a heterogeneous group of inherited disorders caused by mutations in genes that code for type I procollagen (COL1A1 and COL1A2) [1]. These genes are found on chromosomes 7 and 17, respectively [4], and 286 mutations of type I collagen have already been described [3]. The mutations of type I procollagen account for approximately 90% of all cases of OI [2] with the majority of these cases inherited in an autosomal dominant fashion or caused by a sporadic mutation [4]. Since 2006, 11 new genes have been identified that are associated with a portion of the remaining 10% of OI cases. These are autosomal recessive in inheritance and code for proteins involved in the post-translational modification of collagen, such as hydroxylation, folding, chaperoning, or cross-linking [5, 66].

Classification/Characterization

Multiple classification systems have been devised to characterize the varying phenotypic manifestations of OI. Initially categorized by Looser in 1906 as whether fractures were present at birth (congenital) or after birth (tarda), Seedorff expanded on this in 1949 to include fractures within the first year of life (tarda gravis) or after the first year of life (tarda levis) [3]. In 1985, Frederic Shapiro further divided the congenital

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and tarda into type A and B depending on the timing of initial fracture and the radiographic appearance of the bones at initial fracture. Congenita A is classified as in utero/at birth with crumpled femurs and ribs, and congenita B has normal bone contour. Tarda A is classified as fractures before walking age, and tarda B is fractures after walking age [3].

The classification system of Sillence, from 1979, is still the most widely used system and was initially broken up into four types. Type I is the mildest form, is autosomal dominant, and is broken up into type A (without dentinogenesis imperfecta) and type B (with dentinogenesis imperfecta). Patients will have blue sclera and a normal life expectancy. Type II is inherited in an autosomal recessive pattern and is lethal (primarily from respiratory failure, intracranial hemorrhage, or brainstem compression). Type III is a severe, autosomal dominant or recessive inheritance and typically presents with normal sclera and fractures around birth that can result in progressive deformity. Type IV is of intermediate severity, has an autosomal dominant inheritance, and has significant phenotypic variation [1, 3].

In 2004, the Sillence classification system was expanded to include types V–VII, which (like the original classification) were defined by phenotype [6]. Type V is autosomal dominant, has hypertrophic callus development after fracture, and can have calcification of the interosseous membranes that can limit pronation and supination and lead to radial head dislocation. Type VI is autosomal recessive, has moderate to severe skeletal deformity and fractures, and does not respond as well to bisphosphonate therapy. Type VII has moderate to severe skeletal deformity that includes coxa vara and rhizomelic limb shortening [3, 7].

As new causative mutations were identified, various authors added more types to the Sillence classification, and the number of types has increased as high as 14 [8]. This is confusing, considering the original types were defined by phenotype and therefore sometimes overlapped with the new categories, defined by genotype. In 2010, the International Nomenclature Group for Constitutional Disorders ICHG of the Skeleton (INCDS) reclassified osteogenesis imperfecta into five types, preserving the original four Sillence groups and adding a fifth. Each group is defined by its phenotype and identified with an Arabic numeral instead of a Roman numeral [9]. Despite this, many authors continue to use the expanded Sillence classification system [10].

Management

Operative and medical management of OI includes a multidisciplinary team effort to improve function, minimize disability, and maximize mobility status and quality of life [1]. Various systemic medical therapy strategies have been attempted and include calcitonin, sodium fluoride, calcium anabolic steroids, growth hormone, magnesium oxide, vitamin C, and vitamin D, all of which have had mixed results [1]. Bisphosphonates have consistently been shown to have a beneficial effect and are now considered the standard of care [4, 7]. The nitrogen-containing bisphosphonates inhibits protein prenylation and guanosine triphosphatase formation, which results in osteoclast apoptosis [3], and this ultimately results in increased cortical thickness and bone mineral density [4]. In addition to this, decreased chronic bone pain, improved ambulation scores, decreased fracture rates, increased vertebral height, and improved grip strength (with pamidronate therapy) have also been seen in the initial 6 weeks after bisphosphonate therapy [3, 4]. Cyclical intravenous pamidronate and zoledronic acid are the bisphosphonates most frequently used in patients with OI and is limited to a few years due to the unknown long-term effects of bisphosphonates [3, 4, 7]. Atypical femur fractures are a known complication of bisphosphonate therapy and have been reported to occur in patients with OI [11, 12]. Osteonecrosis of the jaw is associated with bisphosphonate therapy; however, there are no reports of this occurring in OI patients, and the risk of this is currently unknown [3, 13].

Other medical therapeutic options include teriparatide and denosumab. Teriparatide is a synthetic PTH analogue, most commonly used as an anabolic agent in patients with osteoporosis. In a double-blind randomized controlled trial, it was shown to increase bone mineral density (BMD) in the lumbar spine and proximal femur, although no difference in the rate of fractures was observed [14]. Denosumab is a monoclonal antibody that blocks the RANK receptor, preventing RANK ligand from activating osteoclasts. It has been shown to increase BMD and decrease fracture rates in children with type IV OI, which is known to respond poorly to traditional bisphosphonate therapy [15].

Bone marrow transplantation, gene therapy, and stem cell therapy are other areas of research that could be beneficial for OI patients but have yet been thoroughly investigated [3, 7].

Surgical principles and goals are designed to restore the normal bone axis by correcting deformity, minimize the incidence of fracture, avoid bone bowing, and use gentle technique to preserve muscle and minimize soft tissue injury [1, 3, 4]. Plates and screws are rarely indicated for fractures in OI patients, and the standard is use of an intramedullary device. Osteotomies are also used in conjunction with internal fixation to correct significant deformity. Multiple different rod systems have been proposed for use including double Rush rods, Bailey–Dubow and Sheffield rods, and Fassier–Duval telescoping nail with the overlying theme of selecting the largest diameter rod that will pass through the medullary canal at its narrowest point [3, 4]. The Fassier–Duval nail allows a minimally invasive technique to be used, can be used on multiple long bones during the same surgical setting, and thus far has had a lower revision rate [4].

Humeral intramedullary rods with either Rush rods or Fassier–Duval nails require the device to not impinge in the shoulder and the patient to have full range of motion at the end of the procedure. Forearm deformity can be corrected with ulnar intramedullary wires and radial osteotomy and intramedullary fixation with the latter being much more technically challenging [4].

Marfan Syndrome

Background

Antoine Marfan, a French pediatrician, first described the skeletal characteristics of Marfan syndrome in 1896 in a 5-year-old girl who presented a tall stature and slender digits; however, this was more likely a presentation of congenital contractural arachnodactyly [16]. Marfan further characterized features of Marfan syndrome including ectopia lentis and mitral valve disease. Ultimately, it was Victor McKusick who stated that Marfan syndrome was a connective tissue disorder that encompassed abnormalities of the cardiovascular (including aortic dissections and aortic valve pathology), ocular, and skeletal systems [16].

Genetics

Harry Dietz discovered the genetic cause of Marfan syndrome in 1991 when he reported that a mutation in genes that code for fibrillin-1, an extracellular matrix protein, leads to classic Marfan syndrome, which is characterized as a clinically and phenotypically variable inherited disorder [16, 17]. Approximately 25% of cases are thought to be from de novo mutations, primarily in genes for fibrillin-1, and the remaining cases are inherited in an autosomal dominant fashion [16]. FBN-1 gene, found on chromosome 15q21.1, is the only gene known to cause classic Marfan syndrome when mutated and is present in over 90% of Marfan syndrome patients [16, 17]. As of 2016, around 1850 different FBN-1 mutations have been identified, including nonsense, missense, splice site, frameshift, and whole gene deletions. The relationship between phenotype and genotype in affected individuals has not been fully elucidated; some individuals with identical mutations can have varying disease severity, age of onset, and specific organ involvement [18].

Fibrillin-1 also interacts with transforming growth factor (TGF)-β, a cytokine that influences cell proliferation, differentiation, extracellular

matrix formation, cell-cycle arrest, and apoptosis. Mutations in fibrillin-1 can lead to increased TGF-β activity and abnormal signaling pathways via this interaction. Mutations in TGFβR1, on chromosome 9, and TGFβR2, on chromosome 3, also alter the TGF-β signaling pathway. Mutations in TGFβR2 have been identified in patients diagnosed with Marfan syndrome (termed Marfan syndrome type II), yet these patients did not have characteristic findings of Marfan syndrome. Loeys–Dietz syndrome, which has many features similar to and unique from Marfan syndrome, is characterized by mutations in either TGFβR1 or TGFβR2 [16, 17]. Dietz states that patients with mutations in TGFβR1 and TGFβR2 tend to have a more aggressive vascular disease and risk of vessel rupture than patients with classic Marfan syndrome. These patients should be recognized and appropriately diagnosed with Loeys–Dietz syndrome, rather than Marfan syndrome type II, in order to further individualize care, counseling, and management [17].

Multiple related disorders are also caused by mutations in the FBN-1 gene and TGF-β signaling pathway including mitral valve prolapse syndrome, MASS phenotype (mitral valve prolapse, aortic enlargement, skin, and skeletal features), familial ectopia lentis, Shprintzen–Goldberg syndrome, Weill–Marchesani syndrome, Stiff skin syndrome (TB4 of FBN-1), geleophysic dysplasia (ADAMTSL2), acromicric dysplasia (TB5 of FBN-1), Loeys–Dietz syndrome (TGFβR1 and 2), Loeys–Dietz like syndrome (SMAD3), Myhre syndrome (SMAD4), and isolated skeletal or cardiovascular features of Marfan syndrome [16, 17, 19].

Classification/Diagnosis

The typical patient with Marfan syndrome is thin and tall and has long slender limbs (dolichostenomelia), arachnodactyly (long, thin, hyperextensible fingers), a pectus deformity, and scoliosis [16, 20]. The cardinal features are disproportionate long bone overgrowth, ectopia lentis, and aortic root aneurysm [21]. Common manifestations in the upper extremity include reduced elbow extension and contracture of the fingers (camptodactyly), especially in children with rapidly progressive disease [22]. The Ghent nosology, which was revised in 2009 and originally adapted from the Berlin criteria, is a set of diagnostic criteria including family history, personal medical history, physical exam, slit lamp evaluation, and echocardiography, used to assist in the diagnosis and treatment of Marfan syndrome [16, 17, 19, 21]. The nosology assesses aortic root dilation (two standard deviations above the mean is considered positive), ectopia lentis, FBN1 mutations, as well as systemic symptoms of six systems (skeletal, ocular, dura, skin and integument, cardiovascular, and pulmonary). The systemic symptoms are scored on a scale of 0 to 20 points, with ≥7 indicating systemic involvement. Skeletal symptoms include wrist and thumb sign, hindfoot deformity, pectus carinatum, protrusio acetabuli, reduced upper body-to-lower body ratio and increased arm length, scoliosis or kyphosis, reduced elbow extension, and certain craniofacial features. The nosology establishes the diagnosis of Marfan syndrome in a patient with no family history in one of four scenarios: (1) the presence of aortic dilation and ectopia lentis, (2) aortic dilation with FBN1 mutation, (3) aortic dilation and systemic involvement (≥7 points), or (4) ectopia lentis and FBN1 mutation associated with aortic disease. If a positive family history is present, the diagnosis is established if either aortic dilation, ectopia lentis, or systemic involvement is present [21].

The wrist and thumb signs are used to evaluate arachnodactyly. The wrist sign/test (aka Walker–Murdoch) is positive when the patient wraps their fingers around their contralateral wrist and their thumb overlaps the distal phalanx of their small finger. The thumb sign/test is positive when the patient grips their thumb in their palm and the entire nail of the thumb projects beyond the ulnar border of the hand [16, 17, 19, 20].

Management

Treatment options for patients with Marfan syndrome require a multidisciplinary team effort including geneticist, cardiologist and cardiothoracic surgeons, ophthalmologist, and an orthopedist [17]. The upper extremity manifestations usually require no treatment unless contractures become symptomatic, in which case

conservative management may be initiated [23]. This includes physical therapy and bracing for elbow and finger contractures. The hyperlaxity seen in Marfan patients typically requires no treatment; however, it may predispose them to easier dislocation. In certain circumstances, capsular reconstruction has been required to reduce pain and restore function [24]. It should be noted that the risk of postoperative complications is higher in patients with Marfan syndrome and cardiovascular abnormalities and other comorbidities are often present [25]. Ultimately, it is the responsibility of all providers to ensure that appropriate referrals have been made to the aforementioned specialists if there is any clinical suspicion for Marfan syndrome.

Pharmaceutical management is targeted at reducing aortic dilation, which is the leading cause of death in patients Marfan syndrome. β-blockers have been shown to be beneficial in reducing progression of aortic dilation, and angiotensin receptor antagonists are also being investigated due to their ability to modulate TGF-β signaling. A recent double-blind randomized controlled trial showed no significant difference in progression of aortic aneurysm in patients treated with losartan versus atenolol [26].

While it has been shown that patients with Marfan syndrome have a decreased bone mineral density, there is no difference in their risk for fracture [16]. However, participation in athletic activities that involve impact or increases in blood pressure should be avoided due to risk of lens dislocation or aortic damage, respectively [25].

Achondroplasia

Background

Disproportionate short stature, macrocephaly, depressed nasal bridge, foramen magnum stenosis, thoracolumbar kyphosis, spinal stenosis, prominent buttocks, protuberant abdomen, genu varum, possible radial head dislocation, and trident hands characterize achondroplasia. Jules Parrot first used the term achondroplasia, which means "without cartilage formation," in 1878 to help distinguish patients with achondroplasia (disproportionate short stature) from patients with rickets (proportionate short stature), although it was the art from Egypt, Greece, and Rome that first depicted examples of achondroplastic patients [27–29].

Genetics

Achondroplasia is inherited in an autosomal dominant fashion and is part of a spectrum of disorders caused by different mutations in the genes encoding fibroblast growth factor receptor 3 (FGFR3). This gene is found on chromosome 4p16.3, and this receptor is expressed in articular chondrocytes [30]. Achondroplasia is caused by an activating, rather than inactivating, mutation in FGFR3, almost always a G380R substitution. This increased activity of FGFR3 results in a constitutively active inhibitory signal on chondrocytes in the growth plate of cartilaginous bones [31]. Other disorders caused by FGFR3 mutations include hypochondroplasia, severe achondroplasia with developmental delay and acanthosis nigricans, and two types of thanatophoric dysplasia [28]. Approximately 80% of cases are due to sporadic mutations, and increased paternal age has been associated with an increased risk of new mutation [29, 30].

Classification/Characterization

Most features of achondroplasia can be traced back to the effect of increased FGFR3 signaling on endochondral bone growth [28]. These features are quite distinct, can present at different stages of life, and are typically recognized clinically or radiographically rather than via DNA analysis; however, approximately 20% of patients go unrecognized at birth [27–29]. Third trimester prenatal ultrasound can identify short limbs in the 3rd percentile or less, head circumference greater than the 95th percentile, and a low nasal bridge [27, 29, 30]. At birth, short stature, rhizomelic limb shortening, and characteristic facial features (frontal bossing, midface hypoplasia) are evident. In addition, certain joints may be hypermobile, primarily the knees and hands, yet contractures of the elbows and hips can also be

present [27–30]. In infancy, patients have normal mental development, although motor development is typically delayed secondary to muscular hypotonia, which, in combination with joint hypermobility, creates a "floppy" appearance [31]. Apnea symptoms from foramen magnum stenosis and thoracolumbar kyphosis can manifest as the individual grows [27, 29, 30].

In the upper extremity, the rhizomelic shortening is the result of short humeri with the fingertips only able to reach the top of the greater trochanters when resting at their side. Consequently, individuals may be unable to reach the top of their head [29, 30]. A flexion deformity of the distal humerus may give the appearance of an elbow contracture. Elbow deformities may also include radial head subluxation or dislocation [29]. The hands have equal length metacarpals and digits and have extra space between the third and fourth rays. This creates three groups of digits (thumb, index and long, and ring and small) and gives the hand a trident appearance [29, 30].

Management

A multidisciplinary team should be involved in the care of any patient with achondroplasia to improve function and positively affect their quality of life and should include but not be limited to pediatricians, pediatric and adult orthopedic surgeons (including spine surgeons), otolaryngologists, endocrinologists, and dentists. Operative and non-operative/medical management of achondroplasia is used primarily for symptomatic or cosmetic reasons. Human growth hormone has been trialed for achondroplastic children. While there is some improvement in growth rate and height, long-term follow-up results show no real benefit, and it is not currently recommended worldwide for treatment of achondroplasia [27–30]. Other medical therapies that are being investigated include the use of parathyroid hormone and C-type natriuretic peptide. These could activate signaling pathways that could counteract the excessive FGFR3 signals in physes [28–30]. Clinical trials of vosoritide, a C-type natriuretic peptide analog, are underway, and the drug has been shown to increase growth velocity in children with achondroplasia [32]. Drugs that act as FGFR3 decoy receptors, which bind FGF, have also entered early clinical trials [31]. Physical therapy has also been suggested to assist with flexion contractures, but in general, elbow contractures and radial head subluxation/dislocations do not require any intervention since there is no functional loss [27–29].

Elective surgical limb lengthening has been used to address the short status of achondroplasia patients who average between 112 and 145 cm in height, which corresponds to 6–7 standard deviations below the average of an unaffected adult [27–30]. This process is extremely time-consuming and is still controversial. While it may have significant social and emotional effects, there is little evidence to support any functional benefit. Most of the discussion surrounding surgical limb lengthening is in reference to lower extremity lengthening. This is partially due to the fact that upper extremity length discrepancies are less common and better tolerated than lower extremity discrepancies [33]. On the other hand, there have been reports of functional limitations from upper extremity length discrepancies and treated with humeral lengthening. Functional goals of humeral lengthening include independent perennial hygiene, improved reach, and restoration of normal proportions [34]. Humeral lengthening by distraction osteogenesis with a monolateral frame has shown improved functional results when compared to circular frames [33]. Still, complications with prolonged external fixation are common, including pin tract infections, postoperative fractures, radial nerve palsy, non-union, and device failure [35, 36]. However, recent use of intramedullary motorized nails has mitigated some of the complications associated with external fixators, such as pin site infections, as well as increasing patient satisfaction [37]. While robust data is lacking due to the rarity of the disease, humeral lengthening appears to relatively safe and effective in patients with achondroplasia, with a lower complication rate than lower extremity lengthening [38, 39].

Table 27.1 provides a brief description, the genetics, natural history, and treatment possibilities of these various conditions.

Table 27.1 Dysplasias, syndromes, and certain genetic conditions and their associated upper extremity skeletal anomalies

	Achondroplasia	*Hypochondroplasia*	*Pseudoachondroplasia*
Description	Rhizomelic shortening secondary to short humeri, flexion contractures from flexion deformities of distal humerus, elbow abnormalities, and trident appearance of hand [extra space between third and fourth rays]. Short stature noticeable at birth, foramen magnum stenosis, thoracolumbar kyphosis, spinal stenosis, and genu varum [29, 40]	Defective conversion of cartilage to bone. Less severe form of achondroplasia—body changes milder and often overlooked. Normal trunk length, disproportionately short arms and legs, hands and feet are broad and short. Differentiated from achondroplasia by lack of facial dysmorphism, less severe short stature, less obvious skeletal disproportion, and milder radiologic findings [40, 41]	Moderate to severe disproportionate short stature, ligamentous laxity, and progressive degenerative joint disease. Short-limb dwarfism with epiphyseal and metaphyseal involvement. Moderate brachydactyly, joint hyperextensibility in hands, restricted extension at elbows, and overall joint pain. Osteoarthritis in early adulthood [42–44]
	Radiographic findings: Rhizomelia, mesomelia, acromelia of extremities; brachydactyly, metacarpal metaphyseal cupping, phalangeal metaphyseal widening in hands; prominent deltoid insertion area in arms; third metacarpal shortening [45, 46]	Radiographic findings: same as achondroplasia, but milder [45]	Radiographic findings: brachydactyly proximally rounded and shortened metacarpals with small or cone-shaped epiphyses in hands, short phalanges, irregular metaphyses, and irregular carpals. Elbows may appear enlarged [42, 45]. Epimetaphyseal dysplasia of elbows, shoulders, and proximal humerus. Radial and humeral head subluxation. Hatchet-shaped humeral head [47]
Genetics	Autosomal dominant, fully penetrant, but 80% of cases are sporadic Locus—4p16.3; gene—FGFR3; protein—FGFR3 [9, 29]	Autosomal dominant; locus—4p16.3; gene—FGFR3; protein—FGFR3 [9]	Autosomal dominant; locus—19p12–13.1; gene—COMP; protein—cartilage oligomeric matrix protein (COMP) [9]
Natural history	Short stature is present at birth. Motor development may be delayed. Average height for adult male—131 cm (52 in.). Average height for adult female—124 cm (49 in.) [29, 48]	Same as achondroplasia, but milder [40, 41]	Normal length and facies at birth. Often presents at the onset of walking with a waddling gait. By 2 years of age, growth rate below the standard growth curve, which leads to disproportionate short-limb short stature. Average adult heights: 116 cm for females and 120 cm for males [42]
Treatment	Lower extremity limb lengthening is controversial. Upper extremity limb lengthening has been documented with an average arm length gain of 10.2 ± 1.25 cm. Surgical realignment may be performed as well [29, 48]	Growth hormone therapy and limb lengthening if necessary [49]	Evaluate for skeletal manifestations. Anterior/posterior radiographs of hands Assess ligamentous laxity. Analgesics for joint pain [42]
	Thanatophoric dwarfism/dysplasia type 1	*Thanatophoric dwarfism/dysplasia type 2*	*Marfan syndrome*

(continued)

Table 27.1 (continued)

	Achondroplasia	*Hypochondroplasia*	*Pseudoachondroplasia*
Description	Underdevelopment of the entire skeleton, short-curve long bones, metaphyseal flaring, underdeveloped pelvic bones, flat acetabular roof, flat and underdeveloped vertebral bodies, cloverleaf skull may or may not be present [50, 51]	In TD2, long bones not as short as in TD1, nor are they bent and/or bowed Metaphyses are flared and cupped. Flat vertebral bodies—but not as flat as TD1, almost all fetuses have cloverleaf skull. Overall, less severe bone involvement than TDI [50, 51]	Characterized by tall stature, thin habitus, long and slender digits, ligamentous laxity, arachnodactyly, and camptodactyly. Reduced upper-to-lower segment ratio Bones are typically osteopenic but have no increased risk of fracture [16, 46]
	Radiographic findings: Generalized micromelia, flat vertebral bodies, long bones of extremities are short and have telephone receiver-like appearance; skeletal maturation and ossification centers are not altered on radiograph [31, 45, 51]	Radiographic findings: generalized micromelia, long bones of extremities are short and have telephone receiver-like appearance; skeletal maturation and ossification centers are not altered on radiograph [45, 51]. Distinguished from TD1 with frequent observation of straight femurs and cloverleaf skull [52]	
Genetics	Autosomal dominant; locus—4p16.3; gene—FGFR3; protein—FGFR3 [9]		Autosomal dominant; locus—15q21.1; gene—FBN1; protein—fibrillin-1 [48]
Natural history	Most common type of lethal neonatal skeletal dysplasia; overall association with rhizomelic limb shortening, macrocephaly, and cloverleaf skull. Difficult to differentiate from other forms of short-limb dwarfism—most important difference is that TD has severe rib shortening, restricted lung volume, and respiratory distress leading to death within a few hours of birth. Without respiratory support, most infants do not survive past a few hours or days due to respiratory insufficiency [50, 51, 53]. Reports of long-term survival with adequate respiratory support exist [54]		Children taller than average for age. By adulthood, may reach 7 ft. tall [46]
Treatment	At birth, infant may require suboccipital decompression to alleviate craniocervical junction constriction. Joint contractures or joint hypermobility should be evaluated and followed [53]		Therapy with nighttime splinting in extension is often successful for treatment of camptodactyly. More severe cases may require tendon transfer, release of volar structures, and PIPJ. Surgery outcomes are unpredictable [55]

Table 27.1 (continued)

	Achondroplasia	*Hypochondroplasia*	*Pseudoachondroplasia*
	Osteogenesis imperfecta	*Nail–Patella syndrome*	*Diastrophic dysplasia*
Description	Characterized by fragile bones, low bone mass, blue sclerae, dentinogenesis imperfecta, hearing loss, and scoliosis. Frequent fractures produce limb deformities. Bowing may occur without prior fracture. Non-accidental injury must be considered in differential diagnosis [3, 7, 56]	Abnormal development of tissue derived from mesenchyme. Nail dysplasia or absence and radial head dislocation may be seen in the upper extremity Decreased muscle mass in proximal upper extremity [46, 57]	Endochondral ossification affected causing short stature from shortened limbs, progressive spinal deformities, foot deformities, frequent joint subluxation and dislocation, large joint contractures, ear pinnae deformities, and/or cleft palate. Hitchhiker thumb, shortened fingers, synostosis of the proximal interphalangeal joints, and ulnar deviation of fingers. Radial dislocation may also be seen clinically [58–60]
	Radiographic findings: Osteopenia, bone fractures, and bone deformities [56]	Radiographic findings: radial head and capitellum hypoplasia, elbow dislocation [45] Hypoplasia of the lateral epicondyle and prominence of the medial epicondyle [61]	Radiographic findings: micromelia; short, thick tubular bones; epiphyseal dysplasia; metaphyseal flaring of long bones; bifid or V-shaped distal humerus may also be pointed and hypoplastic; radial bowing; proximal radial dislocation at birth; brachydactyly and short ovoid first metacarpal; irregular carpal bones; joint dislocations [45, 58]
Genetics	*OI Types I–IV*: Autosomal dominant; gene—COL1A1 or COL1A2; protein—type 1 collagen *OI Type V*: Autosomal dominant; gene—IFITM5; protein—BRIL *OI Type VI*: Autosomal recessive; gene—SERPINF1; protein—PEDF *OI Type VII*: Autosomal recessive; gene—CRTAP; protein— CRTAP [66]	Autosomal dominant; locus—9q34.1; gene—LMX1B; protein—LIM homeobox transcription factor 1 [48]	Autosomal recessive; locus—5q32–33; gene—DTDST; protein—SLC26A2 sulfate transporter [9]
Natural history	More severe forms of OI may experience bone fragility and fracture in utero and/or at birth Milder forms may remain nearly absent in adulthood. Overall, fracture incidence decreases after puberty and increases after menopause and males in their 60s [1]	Non-progressive nail dystrophy and elbow deformities. Patellae may be absent or hypoplastic [46, 57]	Neonatal respiratory insufficiency requiring mechanical ventilation [58]. Diagnosis can be made through ultrasound and molecular genetic testing prenatally or clinically at birth. Normal mental status. Growth and motor capabilities greatly affected by deformities. Disproportionate dwarfism with a mean height of 130–140 cm can be seen in affected adults [62]

(continued)

Table 27.1 (continued)

	Achondroplasia	*Hypochondroplasia*	*Pseudoachondroplasia*
Treatment	Bisphosphonates may be used to decrease fracture frequency, improve vertebral bone density, and strengthen grip. Teriparatide and denosumab have a role in some cases. Surgical goal is to minimize fracture frequency, restore bone axis, and avoid bowing. Long bone internal fixation in children is common via multilevel osteotomies and telescopic intramedullary nail fixation. Long-term rod revision surgery may be required [3, 4]	Patient may be followed and regularly assessed. Surgery is sometimes necessary [46, 57]	Focus on improving mobility through casting to maintain joint positioning, physiotherapy, and other forms of therapy. Cervical spinal surgery only indicated with clinical or neurophysiological evidence of spinal cord impingement—otherwise, cervical kyphosis typically spontaneously corrects. In cases of premature degenerative arthrosis, arthroplasty is indicated. Early physical therapy may prevent joint contractures [58, 60]
	Kniest dysplasia	*Cleidocranial dysostosis/dysplasia*	*Niemann-Pick disease*
Description	Damage to articular and epiphyseal cartilage leading to disproportionate dwarfism Children present with enlarged elbow and wrist joints with restricted movement, abnormal hands with long, knobby fingers. Round faces and barrel-shaped kyphotic trunk [46, 63]	Abnormal development of membranous bones such as the clavicle Characterized by drooping shoulders, elongated neck, and shoulder adduction anteriorly. Central clavicle may be absent and a small piece of bone articulating with the acromion [49, 64]	Lipid storage disease. Previously not known to have skeletal involvement. Joint and/or limb pain has been reported as well as decreased bone mineral density [BMD] in both affected pediatric and adult patients [65]
	Radiographic findings: Generalized ossification delay; epiphyses becoming hypoplastic/dysplastic; cloudy effect in physeal plate in late childhood; metaphyseal flare and epiphyseal fragmentation; reduced joint space in small joints of hand [45, 60]. Bilateral radial head dislocations have also been reported [66]	Radiographic findings: multiple pseudoepiphyses of metacarpals and tapered distal phalanges in hands [45]	
Genetics	Autosomal dominant; locus—12q13.1; gene—COL2A1; protein—type 2 collagen [9]	Autosomal dominant; locus—6p21; gene—RUNX2; protein—runt-related transcription factor 2 [48]	Autosomal recessive; gene—SMPD1; locus—p11; protein—acid sphingomyelinase [9, 49]
Natural history	Bone formation in fetus and infant most affected. Slow growth. Normal milestones and intelligence [46,64]m cervical instability due to hypoplastic dens. High prevalence of ophthalmic disorders [67]	Mean adult height for males is 162 cm [49]	Patients with neurological involvement do not survive beyond 3 years. Patients without neurodegeneration usually survive into late childhood or adulthood [65] Children typically have delayed bone age as well as bone and joint pain [68]

Table 27.1 (continued)

	Achondroplasia	*Hypochondroplasia*	*Pseudoachondroplasia*
Treatment	UE management not well documented	Orthopedic intervention may be necessary if severe impairment or disability occurs [64]	No definitive treatment. Early intervention for low BMD such as load-bearing activities and muscle strengthening exercises. Frequent pulmonary disease and chronic fatigue must be considered [65]
	Mucopolysaccharidoses		
Description	Defective endochondral and membranous growth. Presents with dysostosis multiplex—short stature, platyspondyly with anterior beaking, "bullet-shaped" phalanges. Joint contractures and carpal tunnel syndrome are common. Osteopenia may occur in association with pathologic fractures		
	MPS I H—Hurler syndrome: carpal tunnel syndrome, joint contractures, and dysostosis multiplex		
	MPS I S—Scheie syndrome: carpal tunnel syndrome, joint contractures, and dysostosis multiplex		
	MPS II—Hunter syndrome: only X-linked MPS disorder, carpal tunnel syndrome, joint contractures, and dysostosis multiplex		
	MPS IIIA-B—Sanfilippo types A–B: less severe than I, II, VI, and VII		
	MPS IVA—Morquio type A: severe skeletal dysplasia, joint hypermobility, and dysplastic odontoid process		
	MPS IVB—Morquio type B: severe skeletal dysplasia, joint hypermobility, and dysplastic odontoid process		
	MPS VI—Maroteaux–Lamy syndrome: carpal tunnel syndrome, joint contractures, and dysostosis multiplex		
	MPS VII—Sly syndrome: joint contractures and dysostosis multiplex MPS IX – Natowicz syndrome: periarticular soft tissue masses, short stature [69–72]		
	Radiographic findings: Coarsened long bones, shortened ulna, Madelung deformity of distal radius, shortened metacarpals with proximal tapering, and broad clavicles [72]		
Genetics	Autosomal recessive; gene—varies by type of MPS [72]		
Natural history	Affected infants may appear healthy at birth. MPS presents later—timeline varies by form Often children have short stature and some have progressive mental deterioration [46, 72]		
Treatment	Carpal tunnel release and deformity correction. Splinting or surgery may be indicated for trigger finger [69] Bisphosphonates may be used to help increase bone density. Palliative and supportive care such as physical and occupational therapy when indicated [70–72]. Hematopoietic stem cell transplantation and enzyme replacement therapy are also available and can reduce pathological effects in bone [73]		
	Hereditary multiple exostoses/multiple osteocartilaginous exostoses/diaphyseal aclasis	*Fibrodysplasia ossificans progressiva*	*Chondroectodermal dysplasia/Ellis–van Creveld syndrome*
Description	Multiple cartilage-capped boney protuberances, or osteochondromas, at metaphyses of long bones Mild short stature and disproportionate short-limbs. Rarely, an enchondroma may undergo a malignant transformation into secondary chondrosarcoma. UE most commonly presents with length discrepancy between the radius and ulna—radial bowing, radial tilting, and radial head dislocation may occur [74]	Fibrous tissues, muscles, and periosteal regions undergo progressive ossification. Shortened and deformed thumbs [46]	Short stature, irregular bone growth and structure. Polydactyly also occurs [46]

(continued)

Table 27.1 (continued)

	Achondroplasia	*Hypochondroplasia*	*Pseudoachondroplasia*
Genetics	*HME-1*: Autosomal dominant, locus—8q23–24.1; gene—EXT1; protein—exostosin-1 *HME-2*: Autosomal dominant, locus—11p12–11; gene—EXT2; protein—exostosin-2 *HME-3*: Autosomal dominant, locus—19p [9]	Autosomal dominant; locus—4q27–31; gene—ACVR1/ALK2; protein— ALK2 [75]	Autosomal recessive; locus—4p16; gene— EVC1/EVC2 [76]
Natural history	Numerous osteochondromas develop near growth plates. During childhood and adolescence, osteochondromas create a pseudo-growth plate and cause deformity with growth [77]. Most commonly affects the knees, shoulders, elbows, and wrists [78]. In the hands, the ulnar side and bones surrounding the MCP joints are most affected, especially in childhood and adolescence [79]	At age 5, patient starts developing large ectopic osseous collections in muscular regions. These osseous collections cause severe disability and limits joint movement [46]. Characteristic great toe deformities can be identified at birth, with ossification following distinct pattern. Average survival around 40 years [80]	
Treatment	Growth deformity correction and removal of symptomatic osteochondromas. To manage impending or complete radial head dislocation: ulnar collateral carpal ligament release at the wrist and radial head resection at skeletal maturity. Ulnar wrist deviations are usually asymptomatic. If not, acute and guided-growth interventions may be successful. Malignant transformation into chondrosarcoma must be resected. Typically low grade [74]. In preliminary studies, hemiepiphyseal stapling has been shown to correct angular deformities of the distal radius [81]	No known effective treatment. Surgery, corticosteroids, and radiotherapy have been used. Bisphosphonates have been used to decrease ectopic osseous masses, but clinical benefits are not well established [83]. Glucocorticoids can be used to reduce severity of flare ups. Palovarotene, a retinoic acid receptor agonist, REGN2477, an anti-activin antibody, and rapamycin, an mTOR inhibitor, are all promising drugs undergoing clinical trials [83]	Surgical excision of polydactyly [55]
	Ehlers–Danlos syndrome (EDS)	*Spondyloepiphyseal dysplasia*	*Multiple epiphyseal dysplasia*
Description	Connective tissue disorder characterized by congenital joint hypermobility, skin hyperextensibility, and tissue fragility. Joint dislocations due to little to no trauma are common as is chronic limb pain Severity varies with type of EDS [84, 85]	Short stature due to growth disorder of spine and epiphyses. Short trunk [86], barrel chest, arm length exceeds height, short neck, dorsal kyphosis and lumbar lordosis [87]	Abnormal endochondral epiphyseal ossification centers lead to short stature Early degenerative arthritis and chondral lesions may present. Progression of the disease may atrophy muscles causing muscle fatigue and pain [88–90] Radiographic findings: Small, irregular, flattened epiphyses; small, irregular carpals; proximal metacarpal rounding; brachydactyly [45, 91]

Table 27.1 (continued)

	Achondroplasia	*Hypochondroplasia*	*Pseudoachondroplasia*
Genetics	Autosomal recessive; locus—15q14; gene—CHST14; protein—carbohydrate sulfotransferase 14, dermatan 4-sulfotransferase [9]	Autosomal dominant; locus—12q13.1; gene—COL2A1; protein—type 2 collagen [9]	Autosomal dominant; mutations in five different genes have been identified: COMP, COL9A1, COL9A2, COL9A3, and MATN3. Autosomal recessive; SLC26A2 75% autosomal dominant, with 66% COMP mutation, 10–20% cannot be identified [88, 92]
Natural history	May present in the first few years of life. Joint hypermobility progression leads to increased wear on joints, causing pain [93, 94]	Typically normal in size and proportion at birth. Osteoarthritis with progressive joint and back pain. Normal motor and cognitive milestones [87]	Autosomal dominant form may present in early childhood with knee pain and delayed ossification of femoral epiphyses. Autosomal recessive form presents in late adolescence or early adulthood and has more involvement of hands and feet [88, 92]
Treatment	Orthopedic intervention may be necessary with painful symptomatic events but is often considered last resort [94]	Joint replacement and pain management [87]	Early childhood intervention to minimize and/or counteract joint deformity and preserve mobility [89]. Total joint arthroplasty may be indicated in adults [92, 95]
	Metaphyseal chondrodysplasia (metaphyseal dysplasia)	*Chondrodysplasia punctata*	*Enchondroma*
Description	Short stature; short limbs, metaphyseal irregularity, normal epiphyses, normal vertebrae, bowed legs, waddling gait [96, 97]	Neonatal epiphyseal stippling and decreased growth	Usually a solitary, benign lesion. Multiple enchondromas have increased rate of recurrence. Approximately 40% of enchondromas occur in the hand, most commonly the proximal phalanges. Primary enchondromas of the hand typically present as pathological fracture, deformity with or without pain, and swelling. Long bone enchondromas are usually asymptomatic [98, 99]
	Radiographic findings: irregularity of expanded metaphyses, wide separation of epiphyses from metaphyses Hands have shortening with metacarpal and phalangeal cupping and coning [45]	Radiographic findings: Skeletal calcifications of the epiphyses and carpals	Radiographic findings: stippled calcifications, endosteal scalloping, cortical thinning, and medullary expansion [100, 101]
Genetics	McKusick—autosomal recessive Schmid, Jansen, Kozlowski—autosomal dominant [49]. Schmid type is the most common [96]	Most common form—X-linked dominant. Type 1; gene—ARSL; type 2; gene—EBP [102, 103]	

(continued)

Table 27.1 (continued)

	Achondroplasia	*Hypochondroplasia*	*Pseudoachondroplasia*
Natural history	Defects may be absent or minimal at birth and develop within months or years [97]	Most affected patients die within the first year of life [49]	Malignant transformation to chondrosarcoma possible but rare—must be considered in the differential [98, 99]. Enchondromatosis and other benign lesions must also be ruled out [104]
Treatment	UE management not well documented	UE management not well-documented	In absence of progressive changes, annual clinical and radiographic examination. Overall goal of surgeon is to prevent pathological fracture and remove tumor. Treatment options include observation, curettage, and curettage with autogenous bone grafting or bone graft substitute. Curettage is the standard of care for symptomatic lesions; however, there is no consensus on the optimal management of the post-curettage void [104]. Various bone graft materials may be used to fill the bony defect post-curettage. Sassoon et al. recommend use of an allograft or no graft to avoid donor graft site morbidity. Internal fixation may be necessary for cortical thinning and/or fracture stabilization [99, 100, 105].
	Ollier's disease/enchondromatosis	*Fibrous dysplasia*	*Camurati–Engelmann disease (progressive diaphyseal dysplasia)*
Description	Development of multiple benign enchondromas (3 or more required for diagnosis) located in the epiphyses of bones. Commonly seen in the phalanges. Also skeletal deformities, limb length discrepancies, pain, and the potential risk for malignant changes [106–109]	Bone-forming tissue unable to produce mature lamellar bone resulting in benign fibro-osseous lesion or lesions. Pain, swelling, deformity, and/or pathological fractures are common clinical presentations [110–112]	Sclerosing bone dysplasia causing progressive thickening of the diaphyses, bone pain, muscle weakness, and atrophy, most apparent in proximal lower limbs. Wide-based gait is common. Marfanoid habitus is seen in some individuals [113]
	Radiographic findings: broadened metaphyses, long bone bowing	Radiographic findings: intramedullary lesion causing bone expansion limited by cortical rim. Cortical thinning without periosteal reaction [110, 111]	
Genetics	SP, PTHR1, and PTPN11 mutations found in a few cases only, role still unclear [9] IDH1(most common) and IDH2 found in many cases [106]	SP; locus—20q13; gene—GNAS1; protein—guanine nucleotide-binding protein, alpha-stimulating activity subunit 1 [9]	Autosomal dominant; locus—19q13; gene—*TGFB1*; protein—transforming growth factor-β1

Table 27.1 (continued)

	Achondroplasia	*Hypochondroplasia*	*Pseudoachondroplasia*
Natural history	As child grows, enchondroma increases in size. Enchondroma subject to pathological fracture. Bony masses cause angular deformities and asymmetrical growth [107] Large clinical variability in presentation with respect to number and size of lesions as well as age at onset. However, most commonly appears in first decade or early adolescence [106].	Usually presents in first three decades of life. First sign is café-au-lait macules, which present at or shortly after birth [114]. Child may present with pain, limp, and/or pathologic fracture. Though rare, lesion may transform into either a benign or malignant tumor [110]	Most cases present in the first decade of life. Progression is slow and unpredictable Normal life span. Radial head dislocation is less common orthopedic problem [115]. Fracture healing is delayed, but there is no increase in incidence. Significant endosteal involvement can narrow medullary canal leading to anemia [113]
Treatment	Limb lengthening and deformity correction often with Ilizarov fixation or motorized intramedullary nail. Observation for possible malignant transformation. Surgical excision if chondrosarcoma occurs [106–108]	In absence of symptoms, regular radiographs and observation are indicated until satisfied that lesion is inactive. A growing child without symptoms should be seen twice yearly for clinical evaluation of range of motion, angular deformity, and limb length discrepancy. If symptomatic lesion, "conventional surgical procedures" In cases of deformity or mechanical deficit, orthopedic intervention may be necessary to remove lesion and graft defect. Internal fixation with intramedullary rods may be used. Bisphosphonate and denosumab, an anti-RANKL antibody, use has been reported to have successful outcomes; however, further investigation is needed [82, 111, 112, 116] Bone grafting has been shown to have limited value [117]	NSAIDs or corticosteroids for bone pain and physical therapy. Losartan has been shown to be beneficial in some patients [115]. UE management not well documented [49]
	Osteopoikilosis	*Osteopathia striata*	*Melorheostosis*
Description	Sclerosing bone dysplasia, usually asymptomatic, but can cause soft tissue fibrosis and joint contractures	Sclerosing bone dysplasia with linear striations in bone seen on radiograph Typically asymptomatic	Sclerosing dysplasia with painless, soft-tissue contractures. Linear hyperostosis progresses slowly
	Radiographic findings: well-defined, bilateral osteosclerotic nodules located in metaphyses and epiphyses of long bones, carpus, and scapulae. Lesions can resemble osteoblastic metastasis [118]	Radiographic findings: dense linear striations seen in tubular and flat bones	Radiographic findings: asymmetrical bands of sclerosis, described as "molten wax flowing down the side of a candle." Location varies with age—endosteal in children, extracortical, subperiosteal in adults. Hyperostosis patches seen in carpals
Genetics	Autosomal dominant. Gene—LEMD3 [119]	Autosomal dominant. Associated with deletions at the WTX locus [119]	SP; gene— MAP2K1 [120]

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Table 27.1 (continued)

	Achondroplasia	*Hypochondroplasia*	*Pseudoachondroplasia*
Natural history	Presents during childhood. Children reach normal stature. Often asymptomatic, joint effusions and pain in 15–20% of patients [118]		Presents by age 6 with joint contractures
Treatment	UE management for joint contractures and fibrosis if necessary [49] NSAIDs or other analgesics for pain relief [118]	Treatment unnecessary [49]	NSAIDs for pain. Lengthening, realigning, and contracture correction have been carried out successfully with the Ilizarov technique but with frequent complications [49] Bisphosphonates have been successfully used for symptomatic improvement in some cases [121]
	Pyknodysostosis	*Gorham disease/idiopathic osteolysis/disappearing bone disease*	*Dyschondrosteosis (Leri–Weill syndrome)*
Description	Failure of bone resorption leads to mild short stature and numerous skeletal deformities including pectus excavatum	Massive osteolysis originating from one bone may progressively involve adjacent bones. Resorbed bone is replaced by fibrous tissue	Mild mesomelic short stature. Forearm deformities, notably in the distal radius, causing a Madelung deformity
		Radiographic findings: intramedullary and subcortical radiolucent foci Foci progressively merge	Radiographic findings: Madelung deformity, humeral head hypoplasia
Genetics	Autosomal recessive	Non-hereditary	Autosomal dominant; Gene—*SHOX*
Natural history		Often presents in second and third decades of life	Short stature, forearm and/or wrist deformity, pain typically develops by 8 years of age Adult heights range from 135 to 170 cm
Treatment	Growth hormone therapy to increase stature [49]	Surgery with or without radiation therapy has shown some success, but not consistently [49]. Radiotherapy in combination with bisphosphonates has been used successfully in at least one case [122]	Growth hormone has been successful in some. If wrist pain occurs, use splint and anti-inflammatories. If wrist continue to be symptomatic, reconstruction may be necessary via double osteotomy of the distal radius and ulnar recession [49]
	Larsen syndrome	*Gaucher's disease*	*Craniocarpotarsal dysplasia-Freeman-Sheldon/"whistling face" syndrome distal arthrogryposis Type II*

Table 27.1 (continued)

	Achondroplasia	*Hypochondroplasia*	*Pseudoachondroplasia*
Description	Hypertelorism, multiple joint dislocations, focal bone deformities. Wide distal phalanx of thumb, no distal tapering of fingers, and hypotonia may be seen Radiographic findings: accessory ossification centers in the carpals and shortened metacarpals	Lysosomal storage disorder that causes bone pain, osteomyelitis, osteopenia, pathologic fractures, and osteonecrosis. Bone crises are common	The hands have same deformity as distal arthrogryposis. Joint contractures, elbow flexion deformities, limited range of motion in shoulder
Genetics	Both an autosomal dominant form and an autosomal recessive form. Gene—FLNB; protein— filamin B [123]	Autosomal recessive; gene—GBA1; locus—p1; protein—glucocerebrosidase [124]	Typically sporadic. Some evidence of autosomal dominant and autosomal recessive inheritance patterns. May be associated with MYH3 gene [125]
Natural history		Age of presentation varies by type. Mean age at diagnosis—25 years	Presents in the first decade of life. Dysphagia and aspiration may cause death in the affected infant. Normal intelligence in most cases, one-third of patients have some intellectual disability [125]
Treatment	UE management not well documented [49]	Opioid analgesics for severe pain. Supportive treatment of bone crisis, bearing in mind increased bleeding risk and abnormal bone [49]. Surgery may be necessary for avascular necrosis and pathologic fractures [124]	Treat contractures similarly to distal arthrogryposis. Physical and occupational therapy for the hands [49]
	Cornelia de Lange's syndrome	*Klippel–Trenaunay syndrome*	
Description	Syndrome caused by a genetic mutation affecting central nervous system development. Upper extremity involvement consists of a small hand, clinodactyly of the fifth digit, proximally placed thumb, and limited range of motion in the elbow. Radial head dislocation is common. Rarely, ulnar absence and a monodigital hand may occur Abnormal fusion of the radius and ulna. Upper extremity abnormalities are more common in males and most often asymptomatic [126]. Characteristic facial features: corners of mouth are down-turned, synophrys, elongated philtrum, and long eyelashes	Three major features of this developmental disorder—varicose veins, cutaneous capillary-venous malformation, and soft tissue and bone hypertrophy in affected limbs, more commonly lower limbs. Overgrowth of bones in girth, length, and width in affected limb. Finger deformities and carpal tunnel syndrome have both been documented [127]	
Genetics	Gene—*N1PBL (70%)* is more associated with upper extremity malformations *SMC1A (5%)* [126]	Gene—PIK3CA [127]	

(continued)

Table 27.1 (continued)

	Achondroplasia	*Hypochondroplasia*	*Pseudoachondroplasia*
Natural history	Intrauterine growth impedance. Child remains small in size. Low rates of survival in the first year of life. Mental retardation with delayed millstones	Typically presents at birth or infancy	
Treatment	Most deformities are asymptomatic, limiting the utilization of surgical intervention [49]	Regular compression has shown good results in the hypertrophied limb. Surgery may be utilized only in cases of severe debilitating deformities [49]	

References

1. Kocher MS, Shapiro F. Osteogenesis imperfecta. J Am Acad Orthop Surg. 1998;6(4):225–36. PubMed PMID: 9682085.
2. Van Dijk FS, Cobben JM, Kariminejad A, Maugeri A, Nikkels PGJ, Van Rijn RR, et al. Osteogenesis imperfecta: a review with clinical examples. Mol Syndromol. 2011/10/12. 2011;2(1):1–20. PubMed PMID: 22570641.
3. Burnei G, Vlad C, Georgescu I, Gavriliu TS, Dan D. Osteogenesis imperfecta: diagnosis and treatment. J Am Acad Orthop Surg. 2008;16(6):356–66. PubMed PMID: 18524987.
4. Esposito P, Plotkin H. Surgical treatment of osteogenesis imperfecta: current concepts. Curr Opin Pediatr. 2008;20(1):52–7. PubMed PMID: 18197039.
5. Marini JC, Reich A, Smith SM. Osteogenesis imperfecta due to mutations in non-collagenous genes: lessons in the biology of bone formation. Curr Opin Pediatr. 2014;26(4):500–7. PubMed PMID: 25007323.
6. Rauch F, Glorieux FH. Osteogenesis imperfecta. Lancet. 2004;363(9418):1377–85. PubMed PMID: 15110498.
7. Cheung MS, Glorieux FH. Osteogenesis imperfecta: update on presentation and management. Rev Endocr Metab Disord. 2008;9(2):153–60. PubMed PMID: 18404382.
8. Forlino A, Cabral WA, Barnes AM, Marini JC. New perspectives on osteogenesis imperfecta. Nat Rev Endocrinol. 2011;7(9):540–57. PubMed PMID: 21670757.
9. Mortier GR, Cohn DH, Cormier-Daire V, Hall C, Krakow D, Mundlos S, et al. Nosology and classification of genetic skeletal disorders: 2019 revision. Am J Med Genet Part A. 2019;179(12):2393–419. PubMed PMID: 31633310.
10. Chen A, Fertala A, Abboud J, Wang M, Rivlin M, Beredjiklian PK. The molecular basis of genetic collagen disorders and its clinical relevance. J Bone Joint Surg Am. 2018;100(11):976–86. PubMed PMID: 29870450.
11. Roberts TT, Cepela DJ, Uhl RL, Lozman J. Orthopaedic considerations for the adult with osteogenesis imperfecta. J Am Acad Orthop Surg. 2016;24(5):298–308. PubMed PMID: 27100300.
12. Meier RPH, Ing Lorenzini K, Uebelhart B, Stern R, Peter RE, Rizzoli R. Atypical femoral fracture following bisphosphonate treatment in a woman with osteogenesis imperfecta – a case report. Acta Orthop. 2012/09/24. 2012;83(5):548–50. PubMed PMID: 22998530.
13. Hennedige AA, Jayasinghe J, Khajeh J, Macfarlane TV. Systematic review on the incidence of bisphosphonate related osteonecrosis of the jaw in children diagnosed with osteogenesis imperfecta. J oral Maxillofac Res. 2013;4(4):e1. PubMed PMID: 24478911.
14. Orwoll ES, Shapiro J, Veith S, Wang Y, Lapidus J, Vanek C, et al. Evaluation of teriparatide treatment in adults with osteogenesis imperfecta. J Clin Invest. 2014/01/27. 2014;124(2):491–8. PubMed PMID: 24463451.
15. Orwoll ES, Shapiro J, Veith S, Wang Y, Lapidus J, Vanek C, et al. Evaluation of teriparatide treatment in adults with osteogenesis imperfecta. J Clin Invest. 2014;124(2):491–8. PubMed PMID: 24463451.
16. Shirley ED, Sponseller PD. Marfan syndrome. J Am Acad Orthop Surg. 2009;17(9):572–81. PubMed PMID: 19726741.
17. Dietz H. Marfan syndrome [Internet]. GeneReviews®. 1993.
18. Verstraeten A, Alaerts M, Van Laer L, Loeys B. Marfan syndrome and related disorders: 25 years of gene discovery. Hum Mutat. 2016;37(6):524–31. PubMed PMID: 26919284.
19. Bolar N, Van Laer L, Loeys BL. Marfan syndrome: from gene to therapy. Curr Opin Pediatr. 2012;24(4):498–504. PubMed PMID: 22705998.
20. Watt AJ, Chung KC. Generalized skeletal abnormalities. Hand Clin. 2009;25(2):265–76. PubMed PMID: 19380065.
21. Loeys BL, Dietz HC, Braverman AC, Callewaert BL, De Backer J, Devereux RB, et al. The revised Ghent nosology for the Marfan syndrome. J Med Genet. 2010;47(7):476–85. PubMed PMID: 20591885.

22. Judge DP, Dietz HC. Marfan's syndrome. Lancet (London, England). 2005;366(9501):1965–76. PubMed PMID: 16325700.
23. Marie-Josee Paris P, Marie Jose Benjamin O, Gayle Lang O RWP. Standard of care: Marfan syndrome. 2009.
24. Gomes N, Hardy P, Bauer T. Arthroscopic treatment of chronic anterior instability of the shoulder in Marfan's syndrome. Arthroscopy. 2007;23(1):110. e1–5. PubMed PMID: 17210441.
25. Bitterman AD, Sponseller PD. Marfan syndrome: a clinical update. J Am Acad Orthop Surg. 2017;25(9):603–9. PubMed PMID: 28837453.
26. Forteza A, Evangelista A, Sánchez V, et al. Efficacy of losartan vs. atenolol for the prevention of aortic dilation in Marfan syndrome: a randomized clinical trial. Eur Heart J. 2016;37(12):978–85.
27. Baujat G, Legeai-Mallet L, Finidori G, Cormier-Daire V, Le Merrer M. Achondroplasia. Best Pract Res Clin Rheumatol. 2008;22(1):3–18. PubMed PMID: 18328977.
28. Horton WA, Hall JG, Hecht JT. Achondroplasia. Lancet. 2007;370(9582):162–72. PubMed PMID: 17630040.
29. Shirley ED, Ain MC. Achondroplasia: manifestations and treatment. J Am Acad Orthop Surg. 2009;17(4):231–41. PubMed PMID: 19307672.
30. Amirfeyz R, Gargan M. Achondroplasia [Internet]. Curr Orthop. 2005:467–70.
31. Pauli RM. Achondroplasia: a comprehensive clinical review. PubMed PMID.
32. Savarirayan R, Irving M, Bacino CA, Bostwick B, Charrow J, Cormier-Daire V, et al. C-type natriuretic peptide analogue therapy in children with achondroplasia. N Engl J Med. 2019;381(1):25–35. PubMed PMID: 31269546.
33. Pawar AY, McCoy TH, Fragomen AT, Rozbruch SR. Does humeral lengthening with a monolateral frame improve function? Clin Orthop Relat Res. 2012/08/28. 2013;471(1):277–83. PubMed PMID: 22926491.
34. Balci HI, Kocaoglu M, Sen C, Eralp L, Batibay SG, Bilsel K. Bilateral humeral lengthening in achondroplasia with unilateral external fixators: is it safe and does it improve daily life? Bone Joint J. 2015;97-B(11):1577–81. PubMed PMID: 26530664.
35. Farr S, Mindler G, Ganger R, Girsch W. Bone lengthening in the pediatric upper extremity. J Bone Joint Surg Am. 2016;98(17):1490–503. PubMed PMID: 27605694.
36. Nakano-Matsuoka N, Fukiage K, Harada Y, Kashiwagi N, Futami T. The prevalence of the complications and their associated factors in humeral lengthening for achondroplasia: retrospective study of 54 cases. J Pediatr Orthop B. 2017;26(6):519–25. PubMed PMID: 28107267.
37. Morrison SG, Georgiadis AG, Dahl MT. Lengthening of the Humerus using a motorized lengthening nail: a retrospective comparative series. J Pediatr Orthop. 2019;1. PubMed PMID: 31567762.
38. Ko KR, Shim JS, Chung CH, Kim JH. Surgical results of limb lengthening at the femur, tibia, and Humerus in patients with achondroplasia. Clin Orthop Surg. 2019;11(2):226–32. PubMed PMID: 31156776.
39. Kim S-J, Agashe MV, Song S-H, Choi H-J, Lee H, Song H-R. Comparison between upper and lower limb lengthening in patients with achondroplasia: a retrospective study. J Bone Joint Surg Br. 2012;94(1):128–33. PubMed PMID: 22219260.
40. Hanson AA. Improving mobility in a client with hypochondroplasia (dwarfism): a case report. J Bodyw Mov Ther. 2010;14(2):172–8. PubMed PMID: 20226364.
41. Song S-H, Balce GCE, Agashe MV, Lee H, Hong S-J, Park Y-E, et al. New proposed clinico-radiologic and molecular criteria in hypochondroplasia: FGFR 3 gene mutations are not the only cause of hypochondroplasia. Am J Med Genet A. 2012;158A(10):2456–62. PubMed PMID: 22903874.
42. Briggs MD, Wright MJ. Pseudoachondroplasia. GeneReviews; 2004.
43. Jackson GC, Mittaz-Crettol L, Taylor JA, Mortier GR, Spranger J, Zabel B, et al. Pseudoachondroplasia and multiple epiphyseal dysplasia: a 7-year comprehensive analysis of the known disease genes identify novel and recurrent mutations and provides an accurate assessment of their relative contribution. Hum Mutat. 2011/10/31. 2012;33(1):144–57. PubMed PMID: 21922596.
44. Li Q-W, Song H-R, Mahajan RH, Suh S-W, Lee S-H. Deformity correction with external fixator in pseudoachondroplasia. Clin Orthop Relat Res. 2007;454(454):174–9. PubMed PMID: 16957646.
45. Alanay Y, Lachman RS. A review of the principles of radiological assessment of skeletal dysplasias. J Clin Res Pediatr Endocrinol. 2011;3(4):163–78. PubMed PMID: 22155458.
46. Mankin HJ, Jupiter J, Trahan CA. Hand and foot abnormalities associated with genetic diseases. Hand (N Y). 2010/10/26. 2011;6(1):18–26. PubMed PMID: 22379434.
47. Weiner DS, Guirguis J, Makowski M, Testa S, Shauver L, Morgan D. Orthopaedic manifestations of pseudoachondroplasia. J Child Orthop. 2019;13(4):409–16. PubMed PMID: 31489048.
48. Carter EM, Davis JG, Raggio CL. Advances in understanding etiology of achondroplasia and review of management. Curr Opin Pediatr. 2007;19(1):32–7. PubMed PMID: 17224659.
49. Lovell WW, Winter RB, Morrissy RTWS. Lovell and Winter's pediatric orthopaedics. 4th ed. Philadelphia: Lippincott-Raven; 1996.
50. Martínez-Frías ML, Egüés X, Puras A, Hualde J, de Frutos CA, Bermejo E, et al. Thanatophoric dysplasia type II with encephalocele and semilobar holoprosencephaly: insights into its pathogenesis. Am J Med Genet A. 2011;155A(1):197–202. PubMed PMID: 21204232.

51. Miller E, Blaser S, Shannon P, Widjaja E. Brain and bone abnormalities of thanatophoric dwarfism. AJR Am J Roentgenol. 2009;192(1):48–51. PubMed PMID: 19098178.
52. Ornitz DM, Legeai-Mallet L. Achondroplasia: development, pathogenesis, and therapy. Dev Dyn. 2017;246(4):291–309. PubMed PMID: 27987249.
53. Karczeski B, Cutting GR. Thanatophoric dysplasia. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews. 2013.
54. Baker KM, Olson DS, Harding CO, Pauli RM. Long-term survival in typical thanatophoric dysplasia type 1. Am J Med Genet. 1997;70(4):427–36. PubMed PMID: 9182787.
55. Watson S. The principles of management of congenital anomalies of the upper limb. Arch Dis Child. 2000;83(1):10–7. PubMed PMID: 10868991.
56. Renaud A, Aucourt J, Weill J, Bigot J, Dieux A, Devisme L, et al. Radiographic features of osteogenesis imperfecta. Insights Imaging. 2013/05/19. 2013;4(4):417–29. PubMed PMID: 23686748.
57. Heckman DS, McCoy AJ, Spritzer CE, Garrett WE. Intercondylar synovial septum in two patients with nail-patella syndrome. J Knee Surg. 2013;26 Suppl 1(S 01):S107–11. PubMed PMID: 23288746.
58. Bonafé L, Mittaz-Crettol L, Ballhausen D. Diastrophic Dysplasia Synonym: Diastrophic Dwarfism. In: Adam MP, Ardinger HH, Pagon RA, et al., editor. GeneReviews®. 2004.
59. Crockett MM, Carten MF, Hurko O, Sponseller PD. Motor milestones in children with diastrophic dysplasia. J Pediatr Orthop. 2000;20(4):437–41. PubMed PMID: 10912597.
60. Honório JC, Bruns RF, Gründtner LF, Raskin S, Ferrari LP, Araujo Júnior E, et al. Diastrophic dysplasia: prenatal diagnosis and review of the literature. Sao Paulo Med J. 2013;131(2):127–32. PubMed PMID: 23657516.
61. Reditary, Sweeney E, Hoover-fong JE, Mcintosh I. Nail-Patella Syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al., editor. 2014. p. 1–15.
62. Krüger L, Pohjolainen T, Kaitila I, Kautiainen H, Arkela-Kautiainen M, Hurri H. Health-related quality of life and socioeconomic situation among diastrophic dysplasia patients in Finland. J Rehabil Med. 2013;45(3):308–13. PubMed PMID: 23389768.
63. Subramanian S, Gamanagatti S, Sinha A, Sampangi R. Kniest syndrome. Indian Pediatr. 2007;44(12):931–3. PubMed PMID: 18175850.
64. Campos Júnior W, Cardoso RM, Fidelis R, da Silva ES, Ramos R. A familial case of cleidocranial dysostosis presenting upper limb ischemia. Sao Paulo Med J. 2005;123(6):292–4. PubMed PMID: 16444391.
65. Wasserstein M, Godbold J, McGovern MM. Skeletal manifestations in pediatric and adult patients with Niemann pick disease type B. J Inherit Metab Dis. 2013;36(1):123–7. PubMed PMID: 22718274.
66. Maldjian C, Chew FS, Klein R, Bonakdarpour A, McCarthy J, Kelly J. Kniest dysplasia: new radiographic features in the skeleton. Radiol case reports. 2007;2(2):72–7. PubMed PMID: 27303468.
67. Gregersen PA, Savarirayan R. Type II collagen disorders overview. In: Adam MP, Ardinger HH, Pagon RA, et al., editor. 1993.
68. Schuchman EH, Wasserstein MP. Types A and B Niemann-Pick disease. 2014. PubMed PMID.
69. Williams N, Challoumas D, Ketteridge D, Cundy PJ, Eastwood DM. The mucopolysaccharidoses: advances in medical care lead to challenges in orthopaedic surgical care. Bone Joint J. 2017;99-B(9):1132–9. PubMed PMID: 28860391.
70. Pastores GM. Musculoskeletal complications encountered in the lysosomal storage disorders. Best Pract Res Clin Rheumatol. 2008;22(5):937–47. PubMed PMID: 19028373.
71. White KK. Orthopaedic aspects of mucopolysaccharidoses. Rheumatology (Oxford). 2011;50 Suppl 5(Suppl. 5):v26–33. PubMed PMID: 22210667.
72. White KK, Sousa T. Mucopolysaccharide disorders in orthopaedic surgery. J Am Acad Orthop Surg. 2013;21(1):12–22. PubMed PMID: 23281467.
73. Tomatsu S, Alméciga-Díaz CJ, Montaño AM, Yabe H, Tanaka A, Dung VC, et al. Therapies for the bone in mucopolysaccharidoses. Mol Genet Metab. 2015;114(2):94–109. PubMed PMID: 25537451.
74. Jones KB. Glycobiology and the growth plate: current concepts in multiple hereditary exostoses. J Pediatr Orthop. 2011;31(5):577–86. PubMed PMID: 21654469.
75. Shore EM, Xu M, Feldman GJ, Fenstermacher DA, Cho T-J, Choi IH, et al. A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressiva. Nat Genet. 2006;38(5):525–7. PubMed PMID: 16642017.
76. Baujat G, Le Merrer M. Ellis-van Creveld syndrome. Orphanet J Rare Dis. 2007;2(1):27. PubMed PMID: 17547743.
77. Jäger M, Westhoff B, Portier S, Leube B, Hardt K, Royer-Pokora B, et al. Clinical outcome and genotype in patients with hereditary multiple exostoses. J Orthop Res. 2007;25(12):1541–51. PubMed PMID: 17676624.
78. D'Arienzo A, Andreani L, Sacchetti F, Colangeli S, Capanna R. Hereditary multiple exostoses: current insights. Orthop Res Rev. 2019;11:199–211. PubMed PMID: 31853203.
79. Woodside JC, Ganey T, Gaston RG. Multiple osteochondroma of the hand: initial and long-term follow-up study. Hand (N Y). 2015;10(4):616–20. PubMed PMID: 26568714.
80. Bauer AH, Bonham J, Gutierrez L, Hsiao EC, Motamedi D. Fibrodysplasia ossificans progressiva: a current review of imaging findings. Skelet Radiol. 2018;47(8):1043–50. PubMed PMID: 29445932.
81. Kelly JP, James MA. Radiographic outcomes of Hemiepiphyseal stapling for distal radius deformity due to multiple hereditary exostoses. J

Pediatr Orthop. 2016;36(1):42–7. PubMed PMID: 25633611.
82. Hickey J, Lemons D, Waber P, Seikaly MG. Bisphosphonate use in children with bone disease. J Am Acad Orthop Surg. 2006;14(12):638–44. PubMed PMID: 17077335.
83. Wentworth KL, Masharani U, Hsiao EC. Therapeutic advances for blocking heterotopic ossification in fibrodysplasia ossificans progressiva. Br J Clin Pharmacol. 2019;85(6):1180–7. PubMed PMID: 30501012.
84. Celletti C, Castori M, La Torre G, Camerota F. Evaluation of kinesiophobia and its correlations with pain and fatigue in joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type. Biomed Res Int. 2013/07/14. 2013;2013:580460. PubMed PMID: 23936820.
85. Karaa A, Stoler JM. Ehlers Danlos syndrome: an unusual presentation you need to know about. Case Rep Pediatr. 2013/05/16. 2013;2013:764659. PubMed PMID: 23762718.
86. Miyoshi K, Nakamura K, Haga N, Mikami Y. Surgical treatment for atlantoaxial subluxation with myelopathy in spondyloepiphyseal dysplasia congenita. Spine (Phila Pa 1976). 2004;29(21):E488–91. PubMed PMID: 15507788.
87. George E T, Vickie L H. Spondyloepiphyseal dysplasia tarda. In: Adam MP, Ardinger HH, Pagon RA, al., editors. GeneReviews®. 2001.
88. Dahlqvist J, Orlén H, Matsson H, Dahl N, Lönnerholm T, Gustavson K-H. Multiple epiphyseal dysplasia. Acta Orthop. 2009;80(6):711–5. PubMed PMID: 19995321.
89. Bajuifer S, Letts M. Multiple epiphyseal dysplasia in children: beware of overtreatment! Can J Surg. 2005;48(2):106–9. PubMed PMID: 15887789.
90. Taketomi S, Hiraoka H, Nakagawa T, Miyamoto Y, Kuribayashi S, Fukuda A, et al. Osteochondral autograft for medial femoral condyle chondral lesions in a patient with multiple epiphyseal dysplasia: long-term result. J Orthop Sci. 2012;17(4):507–11. PubMed PMID: 21559955.
91. Lachman RS, Krakow D, Cohn DH, Rimoin DL. MED, COMP, multilayered and NEIN: an overview of multiple epiphyseal dysplasia. Pediatr Radiol. 2005;35(2):116–23. PubMed PMID: 15503005.
92. Anthony S, Munk R, Skakun W, Masini M. Multiple epiphyseal dysplasia. J Am Acad Orthop Surg. 2015;23(3):164–72. PubMed PMID: 25667404.
93. Malfait F, De Coster P, Hausser I, van Essen AJ, Franck P, Colige A, et al. The natural history, including orofacial features of three patients with Ehlers-Danlos syndrome, dermatosparaxis type (EDS type VIIC). Am J Med Genet A. 2004;131(1):18–28. PubMed PMID: 15389701.
94. Ericson WB, Wolman R. Orthopaedic management of the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet. 2017;175(1):188–94. PubMed PMID: 28192621.
95. Briggs MD, Wright MJ, Mortier GR. Multiple epiphyseal dysplasia, autosomal dominant. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews®. 1993.
96. Al Kaissi A, Ghachem MB, Nabil NM, Kenis V, Melchenko E, Morenko E, et al. Schmid's type of metaphyseal chondrodysplasia: diagnosis and management. Orthop Surg. 2018;10(3):241–6. PubMed PMID: 30027601.
97. Camera A, Camera G. Distinctive metaphyseal chondrodysplasia with severe distal radius and ulna involvement (upper extremity mesomelia) and normal height. Am J Med Genet A. 2003;122A(2):159–63. PubMed PMID: 12955769.
98. Bickels J, Wittig JC, Kollender Y, Kellar-Graney K, Mansour KL, Meller I, et al. Enchondromas of the hand: treatment with curettage and cemented internal fixation. J Hand Surg Am. 2002;27(5):870–5. PubMed PMID: 12239678.
99. Sassoon AA, Fitz-Gibbon PD, Harmsen WS, Moran SL. Enchondromas of the hand: factors affecting recurrence, healing, motion, and malignant transformation. J Hand Surg Am. 2012;37(6):1229–34. PubMed PMID: 22542061.
100. Marco RA, Gitelis S, Brebach GT, Healey JH. Cartilage tumors: evaluation and treatment. J Am Acad Orthop Surg. 2000;8(5):292–304. PubMed PMID: 11029557.
101. Plate A-M, Lee SJ, Steiner G, Posner MA. Tumorlike lesions and benign tumors of the hand and wrist. J Am Acad Orthop Surg. 2003;11(2):129–41. PubMed PMID: 12670139.
102. Dempsey MA, Tan C, Herman GE. Chondrodysplasia Punctata 2, X-Linked. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews®. 1993.
103. Braverman NE, Bober M, Brunetti-Pierri N, Oswald GL. Chondrodysplasia Punctata 1, X-Linked. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews®. 1993.
104. Lubahn JD, Bachoura A. Enchondroma of the hand: evaluation and management. J Am Acad Orthop Surg. 2016;24(9):625–33. PubMed PMID: 27454024.
105. Yasuda M, Masada K, Takeuchi E. Treatment of enchondroma of the hand with injectable calcium phosphate bone cement. J Hand Surg Am. 2006;31(1):98–102. PubMed PMID: 16443112.
106. Kumar A, Jain VK, Bharadwaj M, Arya RK. Ollier disease: pathogenesis, diagnosis, and management. 2015;38(6). PubMed PMID: 26091223.
107. Pannier S, Legeai-Mallet L. Hereditary multiple exostoses and enchondromatosis. Best Pract Res Clin Rheumatol. 2008;22(1):45–54. PubMed PMID: 18328980.
108. Popkov D, Journeau P, Popkov A, Haumont T, Lascombes P. Ollier's disease limb lengthening: should intramedullary nailing be combined with circular external fixation? Orthop Traumatol Surg Res. 2010;96(4):348–53. PubMed PMID: 20472523.

109. Tomlinson PJ, Turner J, Monsell FP. The distribution of enchondromata in the hands of patients with Ollier's disease. J Hand Surg Eur Vol. 2010;35(2):154–5. PubMed PMID: 20118132.
110. Kashima TG, Gamage NM, Ye H, Amary MF, Flanagan AM, Ostlere SJ, et al. Locally aggressive fibrous dysplasia. Virchows Arch. 2013;463(1):79–84. PubMed PMID: 23760783.
111. Parekh SG, Donthineni-Rao R, Ricchetti E, Lackman RD. Fibrous dysplasia. J Am Acad Orthop Surg. 2004;12(5):305–13. PubMed PMID: 15469225.
112. Stanton RP, Ippolito E, Springfield D, Lindaman L, Wientroub S, Leet A. The surgical management of fibrous dysplasia of bone. Orphanet J Rare Dis. 2012/05/24. 2012;7 Suppl 1(Suppl. 1):S1. PubMed PMID: 22640754.
113. Wallace SE WW. Camurati-Engelmann disease. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews®.
114. Robinson C, Collins MT, Boyce AM. Fibrous dysplasia/McCune-Albright syndrome: clinical and translational perspectives. Curr Osteoporos Rep. 2016;14(5):178–86. PubMed PMID: 27492469.
115. Van Hul W, Boudin E, Vanhoenacker FM, Mortier G. Camurati-Engelmann disease. Calcif Tissue Int. 2019;104(5):554–60. PubMed PMID: 30721323.
116. Rotman M, Hamdy NAT, Appelman-Dijkstra NM. Clinical and translational pharmacological aspects of the management of fibrous dysplasia of bone. Br J Clin Pharmacol. 2019;85(6):1169–79. PubMed PMID: 30471134.
117. Leet AI, Boyce AM, Ibrahim KA, Wientroub S, Kushner H, Collins MT. Bone-grafting in Polyostotic fibrous dysplasia. J Bone Joint Surg Am. 2016;98(3):211–9. PubMed PMID: 26842411.
118. Korkmaz MF, Elli M, Özkan MB, Bilgici MC, Dağdemir A, Korkmaz M, et al. Osteopoikilosis: report of a familial case and review of the literature. Rheumatol Int. 2015;35(5):921–4. PubMed PMID: 25352085.
119. Boulet C, Madani H, Lenchik L, Vanhoenacker F, Amalnath DS, de Mey J, et al. Sclerosing bone dysplasias: genetic, clinical and radiology update of hereditary and non-hereditary disorders. Br J Radiol. 2016;89(1062):20150349. PubMed PMID: 26898950.
120. Wordsworth P, Chan M. Melorheostosis and Osteopoikilosis: a review of clinical features and pathogenesis. Calcif Tissue Int. 2019;104(5):530–43. PubMed PMID: 30989250.
121. Kotwal A, Clarke BL. Melorheostosis: a rare Sclerosing bone dysplasia. Curr Osteoporos Rep. 2017;15(4):335–42. PubMed PMID: 28676968.
122. Li M-H, Zhang H-Q, Lu Y-J, Gao P, Huang H, Hu Y-C, et al. Successful management of Gorham-Stout disease in scapula and ribs: a case report and literature review. Orthop Surg. 2018;10(3):276–80. PubMed PMID: 30101546.
123. Robertson S. FLNB-related disorders. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews®. 2008.
124. Stirnemann J, Belmatoug N, Camou F, Serratrice C, Froissart R, Caillaud C, et al. A review of Gaucher disease pathophysiology, clinical presentation and treatments. Int J Mol Sci. 2017;18(2). PubMed PMID: 28218669.
125. Gurjar V, Parushetti A, Gurjar M. Freeman-Sheldon syndrome presenting with microstomia: a case report and literature review. J Maxillofac Oral Surg. 2013;12(4):395–9. PubMed PMID: 24431877.
126. Kline AD, Moss JF, Selicorni A, Bisgaard A-M, Deardorff MA, Gillett PM, et al. Diagnosis and management of Cornelia de Lange syndrome: first international consensus statement. Nat Rev Genet. 2018;19(10):649–66. PubMed PMID: 29995837.
127. John PR. Klippel-Trenaunay Syndrome. Tech Vasc Interv Radiol. 2019;22(4):100634. PubMed PMID: 31864529.

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