Syndactyly: Apert Syndrome

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Brian C. Pridgen, Arhana Chattopadhyay, and James Chang

Introduction

History and Brief Description of Clinical Features

Apert syndrome is a rare congenital disorder characterized by premature 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]. Treating Apert patients requires a specialized team of clinicians who can provide close monitoring, carefully timed surgical interventions, and management of chronic symptoms.

In the late nineteenth century, there were a series of case reports, primarily in the French literature, describing 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]. Apert characterized acrocephalosyndactyly by both a tall skull that is flat in the back and sides but protruding abnormally in the front, resembling a French firefighter's helmet, and symmetrical syndactyly of the four limbs. 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 addition to characterizing the morphology of acrocephalosyndactyly anomalies, Apert also proposed potential etiologies. He theorized that a hereditary cause was unlikely because cases were isolated within families. One cause he proposed was polyhydramnios, which could cause amniotic compression of the fetus and, thus, deform the skull. He expressed skepticism, however, that this was the sole cause because amniotic compression generally caused both irregular deformities in the skull and congenital amputation of the digits accompanying the syndactyly, both of which were not consistent with his findings in acrocephalosyndactyly. He also admitted that his theory did not explain the highly uniform craniofacial features and symmetric syndactyly that were characteristic of the disease he observed [2].

Apert's critical look at his own theories paved the way for future researchers to search for the cause of acrocephalosyndactyly. A 1920 study by Park and Powers contested Apert's theory that acrocephalosyndactyly was a single disorder with a single etiology due to the great variability in its clinical presentation [4]. They cited the evidence that in several cases of acrocephalosyndactyly patients did not exhibit complete bilateral syndactyly. However, Blank resolved this discrepancy in 1959 with 54 case reviews, 34 of which he observed firsthand [5]. In this landmark study, 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 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. Blank referred to typical Type I acrocephalosyndactyly as "Apert syndrome," thereby coining the term.

Because genetic theory had been developed by 1959, Blank had an advantage over his predecessors in describing the cause of Apert syndrome. He suggested that sporadic instances of Apert, which constituted the majority of cases, resulted from mutations in parental germ cells and that there

B.C. Pridgen, M.D. • A. Chattopadhyay, B.A.
J. Chang, M.D. (✉)
Division of Plastic and Reconstructive Surgery, Stanford University Medical Center, 770 Welch Road, Suite 400, Palo Alto, CA 94304, USA
e-mail: jameschang@stanford.edu

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was a significant relationship between incidence of Apert syndrome and advanced paternal age [5]. 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*) [6]. Thereafter, studies using modern biochemical techniques continued to elucidate the molecular mechanisms underlying Apert syndrome, as will be discussed in the "Molecular etiology" section later in this chapter.

Prior to the discovery of the molecular basis of Apert syndrome, much of the work on the disease 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. Skull decompression and reconstruction techniques, including strip, linear, and circular craniectomies, were utilized until craniofacial skeletal advancement techniques were developed. Paul Tessier in particular considered Apert syndrome a prototype for other craniofacial deformities [7]. His methods for correcting 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 [8].

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 [9]. Ninety-eight percent of cases are due to two missense cytosine to guanine base substitutions in FGFR2: Pro253Arg and Ser252Trp [6]. *FGFR* is a member of the tyrosine kinase receptor family and is involved in normal limb bud patterning and connective tissue development during embryogenesis. Pro253Arg and Ser252Trp disrupt the linking region between the second and third immunoglobulin domains in FGFR2.

Of the 98 % of Apert cases caused by the two canonical FGFR2 mutations, the Pro253Arg mutation constitutes one-third of cases, and the Ser252Trp mutation constitutes two-thirds of cases [9]. 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 [10].

Biochemical and structural studies of mutant FGFR2 provide potential mechanisms linking genetic mutations and patient phenotype. During normal embryonic development, the FGFR2b isoform is expressed in epithelial tissue and is activated by mesenchymal FGF ligand. The FGFR2c isoform is expressed in mesenchymal tissue and is activated by epithelial FGF ligand [11]. In Apert syndrome, Ser252Trp and Pro253Arg mutations are thought to induce the FGFR2b and FGF2Rc isoforms to lose ligand specificity. Ser252Trp and Pro253Arg disrupt the linking region between the second and third immunoglobulin domains in FGFR2c so that mesenchymal FGF7 and FGF10 ligands become capable of activating mesenchymal FGFR2c. Thus, FGFR2c becomes abnormally susceptible to autocrine signaling, which is thought to result in Apert pathology.

Ibrahimi et al. theorize that clinical variability can arise from differential degrees of FGFR2 gain-of-function [12]. They suggest that more severe forms of syndactyly occur in Pro253Arg mutation patients through increased autocrine signaling. This is based on the prediction that mesenchymal Pro253Arg FGFR2c has a higher affinity for mesenchymal FGF7 and FGF10 than both wild type and Ser252Trp FGFR2c do. They further suggest that the increased incidence of cleft palate in Ser252Trp patients as compared to Pro252Arg patients occurs via enhanced activation of normal FGF signaling. This is based on the crystal structure prediction that mesenchymal Ser252Trp FGFR2c has a higher affinity for epithelial FGF2 than mesenchymal Pro253Arg FGFR2c does.

An alternate genetic mechanism for a minority of Apert patients is a de novo Alu element insertion either upstream or within exon C of FGFR2, which can cause ectopic expression of FGFR2b in the mesenchyme along with normal expression of FGFR2c [13].

Historically, the advanced age of fathers of Apert children has suggested that Apert syndrome, like achondroplasia, is influenced by the Paternal Age Effect (PAE) [5]. The PAE posits that the incidence of certain genetic disorders increases with increasing paternal age due to an increased number of accumulated germline mutations and an increased mutation rate in the sperm of older males [14]. However, the combined effect of the linear increase in cell divisions and the increased mutation rate was insufficient to explain the exponential increase in Apert birth incidence with increasing paternal age. Goriely et al. suggested that the Ser252Trp mutation may confer a selective advantage to sperm stem cells, leading to increased clonal expansion of mutant sperm [15]. 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 [16]. 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 [17]. Quintero-Rivera et al. point to fetal CNS abnormalities, such as agenesis of the corpus callosum (ACC) and ventriculomegaly, as early indicators of Apert syndrome that can be detected through MRI before pathognomonic morphologies can be discerned [16]. Thus, the algorithm for prenatal diagnosis is, after suspected Apert based upon detection of mild ventriculomegaly or ACC upon ultrasound, to follow up with an MRI and 3D ultrasound and confirmation using amniocentesis.

Epidemiology

Apert syndrome is a rare disorder that historically has been challenging to track, as most cases occur due to spontaneous mutations rather than due to familial inheritance; only 11 Apert patients have been documented to have had children [18]. It also has been difficult to distinguish Apert infants from patients with other craniosynostosis disorders or with multiple birth defects due to the great variability in clinical presentation [19]. Diagnosis and documentation of Apert syndrome has 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 hands and feet [19]. Based on data from seven sites, they calculated an Apert birth prevalence of 15.5 cases per million live births. They also 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 [18]. Prevalence was found to be highest among Asians and lowest among Hispanics with approximately equal numbers of affected males and females. In almost half of tracked cases, the age of the father was 35 or older, supporting the theory of the PAE and the association of Apert syndrome with mutations in paternal rather than maternal alleles.

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

The skulls of Apert syndrome patients are characterized by a large cranial volume, increased height, and decreased rostral-caudal head length [20]. Fearon and Podner categorize Apert skulls into type I skulls, which have a split metopic suture 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 [21]. In type I skulls, which are most common, the coronal suture is fused at birth, but other sutures and fontanels 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 fontanel. Bony islands form and coalesce to close the defect by age 2–4 [1]. This defect allows some early growth of the brain [21]. 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 [21]. 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 [22]. A cleft palate or bifid uvula may result in frequent otitis media. 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 [23].

CNS Abnormalities

Several CNS anomalies are associated with Apert syndrome. Most patients exhibit corpus callosum and limbic structure

malformation [24]. 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 the first surgical intervention on Intelligence Quotient (IQ) is contested. Renier et al. found that initial skull surgery before age 1 was the main factor that caused increased IQ, with some contribution from septum pellucidum morphology [25]. 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 [21]. 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 [26].

Visceral Anomalies

Apert patients can present with cardiac, genitourinary, and, less frequently, respiratory and gastrointestinal pathologies [27]. 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 dimples in the knuckles of Type I hands, increased sweat and sebaceous glands, oily skin, and acneiform lesions can be found in Apert patients [28]. 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, long, 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 [29]. Van Heest and Reckling proposed a classification system based on the radiographic appearance of hands in Apert syndrome patients [30]. However, the more widely used classification system was described by Upton and includes three types of hands [29]. Type I hands, or "spade" hands, are defined by a complex syndactyly between the index, long, 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 the ring and small fingers. Type III hands, or "rosebud" hands, are defined by a complex syndactyly between the thumb, index, long, 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 14.1 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

Table 14.1 Reported incidence of each of the Upton type hands in several groups' series

Reference	Number of patients	Type I	Type II	Type III
		Number (percent)	Number (percent)	Number (percent)
Upton [29]	68	28 (41 %)	24 (35 %)	16 (24 %)
Cohen and Kreiborg [31]	44	20 (45 %)	18 (39 %)	6 (16 %)
Holten et al. [32]	45	29 (64 %)	10 (22 %)	6 (13 %)
Chang et al. [33]	10	5 (50 %)	1 (10 %)	4 (40 %)
Fearon [34]	17	11 (65 %)	2 (12 %)	4 (24 %)
Guero [35]	52	11 (21 %)	19 (37 %)	22 (42 %)
Totals	236	104 (44 %)	74 (31 %)	58 (25 %)

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 20 years, adding to the prior body of literature, in which a variety of reconstructive plans have been outlined and modified. Although there are several common goals of each of these reconstructive plans, each author or group has their own preferences and biases. 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 feel and want to echo the sentiment of other authors [8, 35] 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, creating skin flaps and 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 on bilateral extremities simultaneously varies from 12 [33, 35, 36] to 18 [37] to 24 months [8] 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 [35] up to 3 [33] to 6 months [35, 36] to allow time for the contralateral hand to heal and become more functional.

Another consideration for timing, though mentioned in only one paper, was discussed by Hoover et al., who recommended waiting 6–9 months before operating on the same hand to allow time for adequate revascularization [8]. However, many authors do not wait this long and have not reported increased complications due to vascular compromise.

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 [8, 29, 38], while others state that in their experience this is not the case [34]. 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 [8]. Fearon, however, did not observe these problems in his patients that did not undergo early border digit release [34].

For those authors that 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-long and long-ring finger syndactylies. Releasing both of these syndactylies in the second and third web spaces requires operating on both sides of the long finger. Operating on both sides of the long finger during the same operation theoretically risks compromising the vascular supply to the long finger and having a shortage of flap skin [30, 34, 36]. To minimize this risk, the long 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, most surgeons release alternating web spaces, including releasing one side of the long finger syndactyly during the first operation while neglecting one of the two border digit syndactylies during the first operation [34].

As just mentioned, the concern for vascular compromise dictates operative staging and forces surgeons to choose either prioritizing border digit release or 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 [39]. 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 paying careful attention to the vascular anatomy based on the CT angiogram findings. 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, we feel that 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 leading to deviation of the finger or limitation of function. 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 [34]. 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 one piece of skin graft to each side of the finger (Fig. 14.1) Upton suggests the small finger should be treated with extra caution with regard to the use of straight-line incisions.

Because many syndactylized fingers in Apert syndrome are complex (involving bone at the tip), two specific operative maneuvers are critical. Zigzag fingertip flaps, attributed to Buck-Gramcko, are useful for recreating the nail folds [40] (Fig. 14.2). 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. 14.3).

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 [36]. Guero describes an omega-shaped dorsal flap [35]. Other authors perform a similar long dorsal flap for reconstruction of the web space. Fearon, however, uses equal length triangular dorsal and volar flaps [34]. This results in a length-to-width ratio that provides more favorable blood supply to the distal tip of the flap and better healing. 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 [34]. To accommodate for this, Upton recommends considering a wide rectangular flap being used initially, which can then more easily be advanced again if needed later in life. This is the flap design that we usually choose to use (Fig. 14.4).

For areas along the fingers that are not covered by the skin flaps raised during release of the syndactyly, full thickness

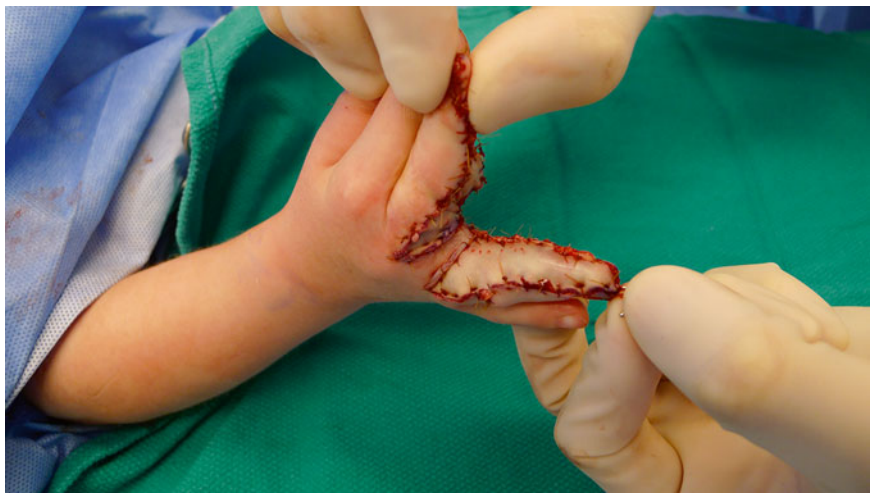

Fig. 14.1 Full thickness skin grafting after straight-line syndactyly release

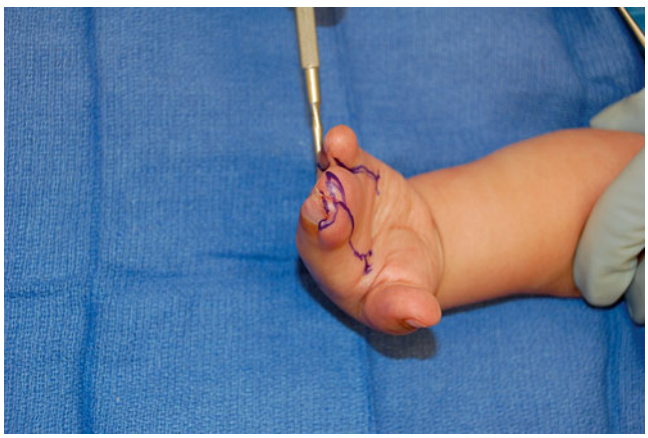

Fig. 14.2 Markings for zigzag fingertips for recreating the nail folds

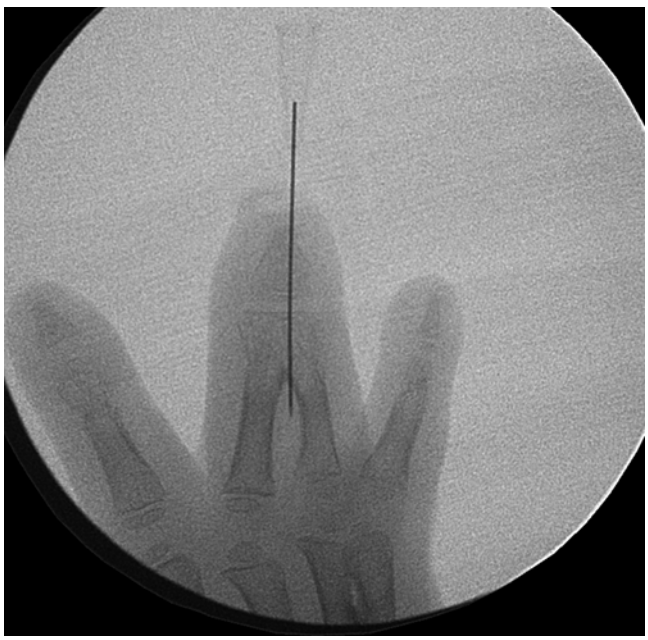

Fig. 14.3 Fluoroscopy image demonstrated needle positioning used to guide longitudinal osteotomy

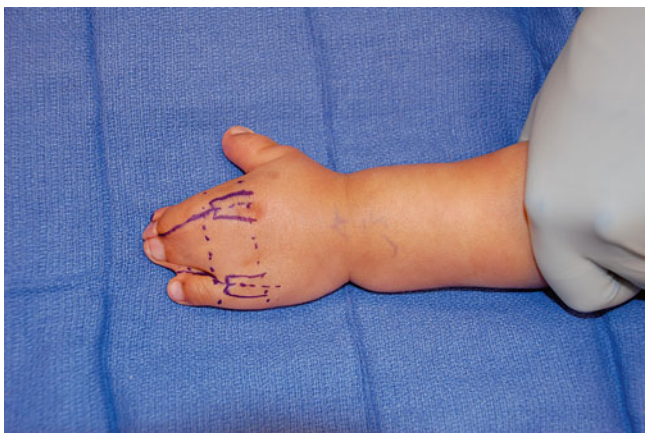

Fig. 14.4 Rectangular dorsal advancement flaps for web space reconstruction

skin grafts are typically applied. Split thickness skin grafts are rarely used due to graft contraction leading to decrease in size of the web space and due to the risk of recurrence of syndactyly. Full thickness skin grafts are typically harvested from the groin crease, avoiding the future hair-bearing skin, or occasionally from the antecubital crease. Skin harvested from circumcisions should never be used due to darkening of the harvesting 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 [34]. This reduced the need for full thickness skin graft tissue but without increasing wound healing complications. In addition to skin grafts, several other techniques of increasing complexity have been suggested for providing soft tissue coverage, including pedicle groin flaps [38], tissue expanders, and silastic sheets [41]. 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 techniques for the pedicle groin flap and tissue expansion are rather evident, but the use of silastic sheets warrants further discussion. This technique was described by Stefansson and Stilwell for use in cases in which extensive bone and soft tissue remains exposed after separation of complex syndactyly [41]. They developed this technique for cases in which they were concerned that the exposed bed of bone and cartilage would be poorly suited to a full thickness skin graft. After separating the digits, they interposed a 1-mm thick sheet of silastic along the exposed bone and cartilage and then closed the skin flaps in their original positions, leaving the silastic sheet in place. The silastic sheet was removed 1 month later, at which time they noticed a well-formed capsule covering the previously exposed bone. They then applied a full thickness skin graft from the groin, which survived. This is not usually necessary as small areas of exposed bone can be covered by skin grafts.

The role of digital amputation is a controversial topic with multiple practices described in the literature. Hoover recommended routine amputation of the long finger to provide additional soft tissue for coverage of the remaining index and ring fingers [8]. However, since Hoover's work in 1970, further discretion and nuance has 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 [35]. Chang et al., too, recommended routine amputation only in Upton Type III hands, and if one digit was markedly smaller than the others [33]. Van Heest et al. created a new classification system for hands in Apert syndrome based on the radiographic appearance of the hands [30]. 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, long, 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 III hands.

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 [34, 35]. Zucker 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 [38].

Upton, in his commentary on Fearon's article, describes his preferred method for facilitating thumb to small finger opposition [34]. 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 refusion 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 refusion. Guero prefers to interpose interosseous muscles [35]. 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 [33].

Fereshetian and Upton emphasized the importance of creating an adequate first web space during the first year of life to prevent delays in musculoskeletal and coordination development [37]. 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. [42]. The radial clinodactyly of the thumb had been attributed to a delta phalanx of the thumb [36] and a longitudinally bracketed diaphysis [29]. 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 [37] 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 [37]. 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 [42]. They had only two patients in their series, whom 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 [34].

Oishi and Ezaki expanded on Dao et al.'s work to describe additional techniques in the management of the Apert thumb [43]. 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 [34]. At the age 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 age 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 syndactyly, performing longitudinal ostectomy 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 [37]. The recommended duration for postoperative splinting ranges from 2 to 3 weeks [33, 34, 36]. 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 [44]. 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 [35, 37].

Secondary Syndactyly

"Web space creep" and recurrence of syndactyly is reported in most authors' series. This often requires revision at a later date ranging from 3 to 40 % in different authors' series [33, 34, 36]. 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 syndromes patients due to the ranging functional status of these patients, the young age at which they receive

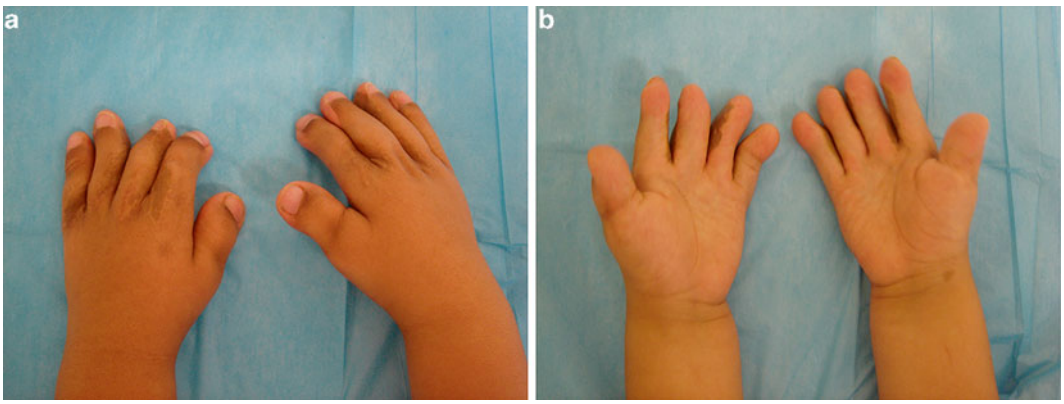

Fig. 14.5 Dorsal and volar views of a patient with a Type II Apert hand, 5 years after Apert syndactyly release and skin grafting

their reconstruction, and the unreliable follow-up that they receive. There are multiple anecdotal reports from authors describing variable functional improvements after reconstruction, although most patients do achieve opposition between the thumb and the most ulnar digit. 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. 14.5).

References

1. Cohen Jr MM, Kreiborg S. An updated pediatric perspective on the Apert syndrome. Am J Dis Child. 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. Park EA, Powers GF. Acrocephaly and scaphocephaly with symmetrically distributed malformations of the extremities: a study of the so-called "acrocephalosyndactylism". Am J Dis Child. 1920;20:235–315.
5. 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.
6. 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.
7. Lee DS, Chung KC. Eugène Apert and his contributions to plastic surgery. Ann Plast Surg. 2010;64:362–5.
8. Hoover GH, Flatt AE, Weiss MW. The hand and Apert's syndrome. J Bone Joint Surg Am. 1970;52:878–95.
9. 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.
10. 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.
11. Yu K, Herr AB, Waksman G, Ornitz DM. Loss of fibroblast growth factor receptor 2 ligand-binding specificity in Apert syndrome. Proc Natl Acad Sci U S A. 2000;97:14536–41.
12. Ibrahimi OA, Eliseenkova AV, Plotnikov AN, Yu K, Ornitz DM, Mohammadi M. Structural basis for fibroblast growth factor receptor 2 activation in Apert syndrome. Proc Natl Acad Sci U S A. 2001;98:7182–7.
13. Oldridge M, Zackai EH, McDonald-McGinn DM, Iseki S, Morriss-Kay GM, Twigg SR, et al. De novo alu-element insertions in FGFR2 identify a distinct pathological basis for Apert syndrome. Am J Hum Genet. 1999;64:446–61.
14. 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.
15. 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.
16. 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.
17. 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.
18. 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.
19. Cohen Jr MM, 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.
20. Rice DP. Clinical features of syndromic craniosynostosis. Front Oral Biol. 2008;12:91–106.
21. Fearon JA, Podner C. Apert syndrome: evaluation of a treatment algorithm. Plast Reconstr Surg. 2013;131:132–42.
22. Kreiborg S, Cohen Jr MM. Is craniofacial morphology in Apert and Crouzon syndromes the same? Acta Odontol Scand. 1998;56:339–41.
23. Oberoi S, Hoffman WY, Vargervik K. Craniofacial team management in Apert syndrome. Am J Orthod Dentofacial Orthop. 2012;141:S82–7.
24. Cohen Jr MM, Kreiborg S. The central nervous system in the Apert syndrome. Am J Med Genet. 1990;35:36–45.
25. 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.

26. 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.
27. Cohen Jr MM, Kreiborg S. Visceral anomalies in the Apert syndrome. Am J Med Genet. 1993;45:758–60.
28. Cohen Jr MM, Kreiborg S. Cutaneous manifestations of Apert syndrome. Am J Med Genet. 1995;58:94–6.
29. Upton J. Apert syndrome. Classification and pathologic anatomy of limb anomalies. Clin Plast Surg. 1991;18:321–55.
30. Van Heest AE, House JH, Reckling WC. Two-stage reconstruction of apert acrosyndactyly. J Hand Surg. 1997;22:315–22.
31. Cohen Jr MM, Kreiborg S. Hands and feet in the Apert syndrome. Am J Med Genet. 1995;57:82–96.
32. Holten IW, Smith AW, Bourne AJ, David DJ. The Apert syndrome hand: pathologic anatomy and clinical manifestations. Plast Reconstr Surg. 1997;99:1681–7.
33. 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.
34. 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.
35. Guero SJ. Algorithm for treatment of apert hand. Tech Hand Up Extrem Surg. 2005;9:126–33.
36. Barot LR, Caplan HS. Early surgical intervention in Apert's syndactyly. Plast Reconstr Surg. 1986;77:282–7.
37. Fereshetian S, Upton J. The anatomy and management of the thumb in Apert syndrome. Clin Plast Surg. 1991;18:365–80.
38. Zucker RM, Cleland HJ, Haswell T. Syndactyly correction of the hand in Apert syndrome. Clin Plast Surg. 1991;18:357–64.
39. 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.
40. Golash A, Watson JS. Nail fold creation in complete syndactyly using Buck-Gramcko pulp flaps. J Hand Surg Br. 2000;25:11–4.
41. Stefansson GM, Stilwell JH. Use of silastic sheet in Apert's syndactyly. J Hand Surg Br. 1994;19:248–9.
42. 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.
43. Oishi SN, Ezaki M. Reconstruction of the thumb in Apert syndrome. Tech Hand Up Extrem Surg. 2010;14:100–3.
44. Solomon LM, Fretzin D, Pruzansky S. Pilosebaceous abnormalities in Apert's syndrome. Arch Dermatol. 1970;102:381–5.