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Impact of genetics on the diagnosis and clinical management of syndromic craniosynostoses

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Abstract
Purpose More than 60 different mutations have been identified to be causal in syndromic forms of craniosynostosis. The majority of these mutations occur in the fibroblast growth factor receptor 2 gene (*FGFR2*). The clinical management of syndromic craniosynostosis varies based on the particular causal mutation. Additionally, the diagnosis of a patient with syndromic craniosynostosis is based on the clinical presentation, signs, and symptoms. The understanding of the hallmark features of particular syndromic forms of craniosynostosis leads to efficient diagnosis, management, and long-term prognosis of patients with syndromic craniosynostoses.
Methods A comprehensive literature review was done with respect to the major forms of syndromic craniosynostosis and additional less common FGFR-related forms of syndromic craniosynostosis. Additionally, information and data gathered from studies performed in our own investigative lab (lab of Dr. Muenke) were further analyzed and reviewed. A literature review was also performed with regard to the genetic workup and diagnosis of patients with craniosynostosis.
Results Patients with Apert syndrome (craniosynostosis syndrome due to mutations in *FGFR2*) are most severely affected in terms of intellectual disability, developmental delay, central nervous system anomalies, and limb anomalies. All patients with FGFR-related syndromic craniosynostosis have some degree of hearing loss that requires thorough initial evaluations and subsequent follow-up.
Conclusions Patients with syndromic craniosynostosis require management and treatment of issues involving multiple organ systems which span beyond craniosynostosis. Thus, effective care of these patients requires a multidisciplinary approach.

Keywords Syndromic craniosynostoses · Craniosynostosis syndromes · Management craniosynostosis · Craniosynostosis · Diagnosis craniosynostosis · FGFR craniosynostosis

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Introduction

In 1906, Eugene Apert, one of France's most eminent pediatricians, described a group of nine different individuals with common physical characteristics and clinical findings. These patients were suffering from acrocephaly ("acro" is Greek for "peak" and "cephalo," also from Greek, means "head"; together, they mean "peaked head") and symmetric syndactyly (a condition where the bone or skin between the toes and fingers fuses together) of the hands and feet to varying degrees. This condition was named acrocephalosyndactyly by Apert [10] (see Fig. 1 for an early drawing of a child with Apert syndrome). Soon thereafter, other physicians began describing clusters of patients with similar constellations of physical characteristics and clinical features. These included Louis Crouzon (1912, Crouzon syndrome),

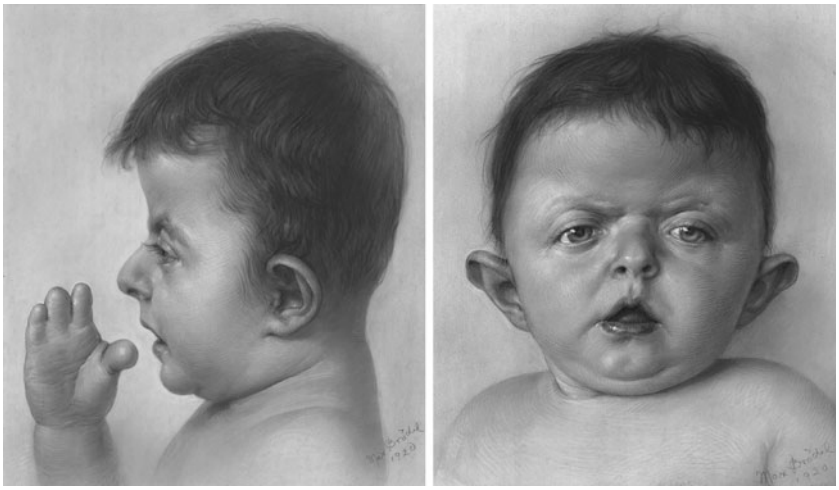

Fig. 1 Early drawing (1920) of a child with Apert syndrome. Original illustrations (nos. 506 and 507) are housed in the Walters Collection of the Max Brödel Archives in the Department of Art as Applied to Medicine, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

Haakon Saethre and Fritz Chotzen (1931–1932, Saethre–Chotzen syndrome), and Rudolf Pfeiffer (1964, Pfeiffer syndrome) [17, 31, 82, 93]. For most of the twentieth century, these syndromes were diagnosed, identified, and characterized by clinicians on a purely clinical basis. The late twentieth century was a period of advancement for the field of molecular genetics. Scientists had the ability to screen genomes, find plausible candidate genes, and sequence genes for mutations. This led to a surge of gene discovery and a paradigm shift in the way conditions such as those described above were diagnosed, defined, and clinically managed. In this period, the genetic bases of Apert, Saethre–Chotzen, Crouzon, and Pfeiffer syndromes were discovered [50, 54, 61, 73, 92, 96, 105].

It was during this time period that Muenke syndrome was first defined. The story of the discovery of Muenke syndrome demonstrates the paradigm shift that occurred during this time in the diagnosis of syndromic forms of craniosynostosis. Muenke syndrome was initially defined on a molecular genetic basis, not on a clinical basis like the earlier forms of syndromic craniosynostosis defined in the early 1900s. The Muenke lab performed linkage analysis, a statistical method that is used to link specific genetic markers with phenotypic traits using, in this case, numerous large kindreds who were initially diagnosed clinically as segregating Pfeiffer syndrome. The initial result of the genome-wide linkage analysis combining the data from all families did not result in the identification of a chromosomal location. Only after data were combined from families with linkage peaks over similar chromosomal regions were specific regions identified: 8p, 10q, and 4p, respectively. Pfeiffer syndrome was mapped to chromosomes 8p and 10q [96]. Candidate gene studies in families linked to chromosome 4p found that affected individuals had a common mutation in *FGFR3* [14, 74]. Dr. Victor McKusick named this syndrome Muenke syndrome.

Four genes have been identified that encode four fibroblast growth factor receptors (*FGFRs*). Mutations in three of these genes, namely, *FGFR1*, *FGFR2*, and *FGFR3*, have been implicated in the most common forms of syndromic craniosynostosis: Apert syndrome, Crouzon syndrome, Pfeiffer syndrome, and Muenke syndrome. Additionally, mutations in *TWIST*, an upstream modulator of the FGFRs, is implicated in Saethre–Chotzen syndrome. Mutations in *MSX2* (muscle segment homeobox 2) and *EFNB1* (ephrin B1) cause Boston-type craniosynostosis and craniofrontonasal syndrome, respectively [53, 101].

In aggregate, syndromic craniosynostoses are estimated to comprise 15 % of all craniosynostoses. There are over 180 craniosynostosis syndromes identified to date. Currently, more than 60 different mutations have been identified to be causal in syndromic craniosynostoses, the majority of which occur in *FGFR2* [37].

In this article, attention will be paid to syndromic craniosynostoses with regard to the diagnosis, genetic workup, and clinical management. Though most attention will be paid to the most common forms of syndromic craniosynostoses, it is important to keep in mind that there are numerous rare craniosynostosis syndromes that are less well characterized, both clinically and molecularly [84]. The clinical issues that occur in several of the uncommon craniosynostosis syndromes may be very different from the major syndromes. For example, severe mental impairment and perinatal death are more frequent in some of the uncommon syndromes, leading to a heavier focus on prenatal diagnosis, cognitive development, and genetic counseling [63].

Hallmark clinical features of major syndromic craniosynostoses

The major forms of syndromic craniosynostoses described in this article all have an autosomal dominant pattern of

inheritance, with the exception of craniofrontonasal syndrome (X-linked; see Table 1 for additional information on the following syndromes).

Apert syndrome

Apert syndrome is characterized by the triad of midface hypoplasia, craniosynostosis most commonly of the coronal suture, and symmetric syndactyly of the hands and feet [105] (Fig. 2). It occurs in 15–16 of every 1,000,000 births [19]. Apert syndrome is associated with two mutations in *FGFR2*: the p.P253R mutation accounts for 33 % of the cases of Apert syndrome and is associated with more severe syndactyly when compared to the other causative mutation of Apert syndrome, p.S252W, which accounts for 66 % of cases and is strongly associated with cleft palate [28, 59, 62, 103, 105].

Crouzon syndrome

Multiple different mutations in the *FGFR2* gene cause Crouzon syndrome, which is characterized clinically by craniosynostosis commonly involving the coronal suture, maxillary hypoplasia, shallow orbits, and prominent eyes (proptosis), secondary to early coalition of the skull sutures [54, 86].

Pfeiffer syndrome

Pfeiffer syndrome is associated with mutations in *FGFR1* or *FGFR2* [73, 92, 96]. In addition to craniosynostosis of the coronal suture, patients with Pfeiffer syndrome characteristically have midface hypoplasia; broad, medially deviated halluces; and variable soft tissue syndactyly (Fig. 3) [91]. Limb anomalies in Pfeiffer syndrome are independent of whether the mutation causing Pfeiffer syndrome occurs in *FGFR1* or *FGFR2* [90]. Additionally, mutations in *FGFR2* are associated with more severe forms of Pfeiffer syndrome. Historically, three clinical subtypes of Pfeiffer syndrome have been described. Type 1 consists of the above description of Pfeiffer syndrome. Type 2 is characterized by, in addition to the above, cloverleaf skull (panysynostosis, where all calvarial sutures prematurely fuse), frequent elbow ankylosis/synostosis, and additional unusual anomalies. Type 3 is characterized by a very short anterior cranial base, ocular proptosis, elbow ankylosis/synostosis, and additional unusual anomalies. Some clinical overlap occurs between these subtypes [21, 26].

Muenke syndrome

Muenke syndrome is characterized by craniosynostosis, most commonly of the coronal suture, carpal, and/or tarsal bone fusion, and hearing loss (Fig. 4). Muenke syndrome is the most common form of syndromic craniosynostosis, with an incidence of 1 in 30,000 births. Unlike the syndromic craniosynostoses described here, a single defining point mutation is responsible for all cases of Muenke syndrome: c.749C>G, in the *FGFR3* gene, resulting in p.Pro250Arg. Of note is that the homologous mutation in *FGFR1* is responsible for the milder type of Pfeiffer syndrome, while the homologous mutation in *FGFR2* is responsible for 33 % of cases of Apert syndrome.

Saethre–Chotzen syndrome

Coronal suture craniosynostosis, broad or bifid great toes, ptosis, characteristic appearance of the ear (small pinna with a prominent crus), and soft tissue syndactyly characterize Saethre–Chotzen syndrome, which is caused by mutations in the *TWIST* gene [50]. There is some phenotypic overlap of this syndrome with Muenke syndrome [60]. However, detailed clinical examination can differentiate the two syndromes from one another. For example, anomalies of the external ear are characteristic of Saethre–Chotzen syndrome, while extremely rare in Muenke syndrome (Fig. 5).

Craniofrontonasal syndrome

Caused by mutations in the *EFNB1* (*Ephrin B1*) gene, which encodes one of eight known ephrin ligands, craniofrontonasal syndrome is characterized by marked hypertelorism, coronal suture synostosis, and a broad or bifid nasal tip [104]. It is an X-linked developmental malformation syndrome with an unusual inheritance pattern as females are more severely affected than males, the latter of which often only display hypertelorism and occasionally cleft lip and/or palate [89].

Molecular genetics in the testing and diagnosis of patients with craniosynostosis

Genetic testing is an essential part of the diagnostic workup of patients with suspected genetic conditions. Craniosynostosis is an etiologically heterogeneous disorder that may result from environmental as well as genetic factors. With the genetic testing available today, a genetic cause can be identified for 45 % of patients with craniosynostosis [56, 72, 106].

There are many advantages to identifying the genetic cause. These include the ability thereafter to more precisely predict the expected clinical course, determine the optimal care (for example, when deciding the timing of corrective surgery), and an improvement in genetic counseling ability, including as relates to reproductive decisions.

The stages of diagnostic workup in patients with craniosynostosis can be divided into three parts [46]: (1) clinical

Table 1 Overview of major forms of syndromic craniosynososes, genetic causes, and clinical findings

	Apert syndrome	Crouzon syndrome	Pfeiffer syndrome	Muenke syndrome	Saethre–Chotzen syndrome	Craniofrontonasal syndrome
Genetic cause	*FGFR2*: Ser252Trp, Pro253Arg	*FGFR2*: multiple mutations	*FGFR1*: Pro252Arg *FGFR2*: multiple mutations	*FGFR3*: Pro250Arg in all patients	*TWIST*: multiple mutations, rarely deletions	*EFNB1*: multiple mutations, rarely deletions; X-linked
Skull phenotype	Bilateral coronal synostosis	Bilateral coronal synostosis, pancranio-synostosis, cloverleaf skull	Bilateral coronal synostosis, cloverleaf skull in type 2 Pfeiffer	Unilateral or bilateral coronal synostosis, macrocephaly	Unilateral or bilateral coronal synostosis, metopic synostosis	Unilateral or bilateral coronal synostosis
Facial features	Hypertelorism, down-slanting palpebral fissures, cleft palate, high arched palate, midface hypoplasia	Hypertelorism, beaked nose, proptosis, rarely cleft palate, mandibular prognathism, midface hypoplasia	Hypertelorism, down-slanting palpebral fissures, proptosis, rarely cleft palate, midface hypoplasia	Hypertelorism, down-slanting palpebral fissures, high arched palate, mild midface hypoplasia	Ptosis, ear anomalies—small ears with prominent crus, low frontal hairline, rarely cleft palate, midface hypoplasia	Hypertelorism, broad nasal bridge, broad or bifid nasal tip; rarely cleft lip and/or palate (females more severely affected)
Limb anomalies	Complex bony and soft tissue syndactyly, elbow ankylosis/synostosis, progressive tarsal bone fusion	Tarsal bone fusion (calcaneocuboid), clinodactyly, symphalangism	Broad, medially deviated toes and thumbs, tarsal bone fusion, elbow ankylosis, elbow synostosis, cutaneous syndactyly	Carpal and/or tarsal bone fusion, broad toes and thumbs, symphalangism	Cutaneous syndactyly, hallux valgus, duplicated distal phalanx of the hallux	Asymmetric lower limb shortness, broad hallux, joint laxity, cutaneous syndactyly, grooved nails
Visceral organs	Cardiac and genitourinary anomalies	None	Cardiac and genitourinary anomalies occur in types 2 and 3 Pfeiffer syndrome	None	Congenital heart malformations	Rarely umbilical and diaphragmatic hernia, sacro-coccygeal teratoma
Neurocognitive	Severe intellectual disability and/or developmental delay, conductive hearing loss common	Intellect usually normal; conductive hearing loss common	Intellect normal in type 1 Pfeiffer. In types 2 and 3 Pfeiffer intellectual disability and developmental delay common, conductive hearing loss common	Intellectual disability and/or developmental delay common, low-frequency sensorineural hearing loss common	Intellect usually normal, developmental delays common in those w/gene deletions, conductive, mixed, and profound sensorineural hearing loss	Normal intellect in >50 %, 10–50 % with developmental delay, occasionally learning difficulties (mild), sensorineural hearing loss

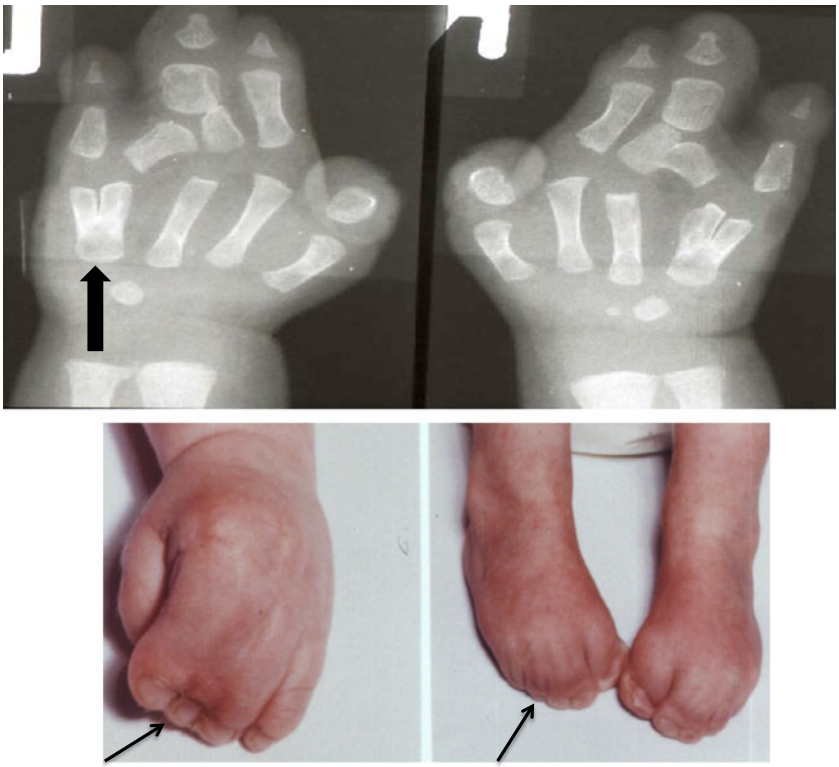

Fig. 2 Symmetric cutaneous and bony syndactyly in Apert syndrome

evaluation; (2) molecular genetic workup and testing; and (3) test result interpretation, genetic counseling, and management.

Part 1: Clinical evaluation

The first step should come prior to genetic testing. In this step, the clinician should complete a full history, including family history (with attention to craniosynostosis, abnormal head shape, cranial surgery, skeletal or seizure disorders, developmental delay, or other potential genetic conditions in the family); past medical history (including results of brain MRI if performed, maternal pregnancy history, and exposures); past surgical history; developmental history; and birth history. Additionally, in this step, patients should receive a full physical examination to assess for involved cranial sutures and head shape, craniofacial dysmorphisms, brain malformations, hearing, and limb anomalies [for example, clinicians should examine patient's fingers and toes for syndactyly, (Apert syndrome) medial deviation of toes or thumbs (Pfeiffer syndrome), and for other anomalies].

Part 2: Molecular genetic workup and testing

In part 2, the clinician takes the armamentarium of what was uncovered in the history and physical to execute the next step, which is genetic testing. Whether or not genetic testing is indicated and performed depends mainly on the specific suture involved and the presence of additional anomalies, as well as the desires of the patients and their families.

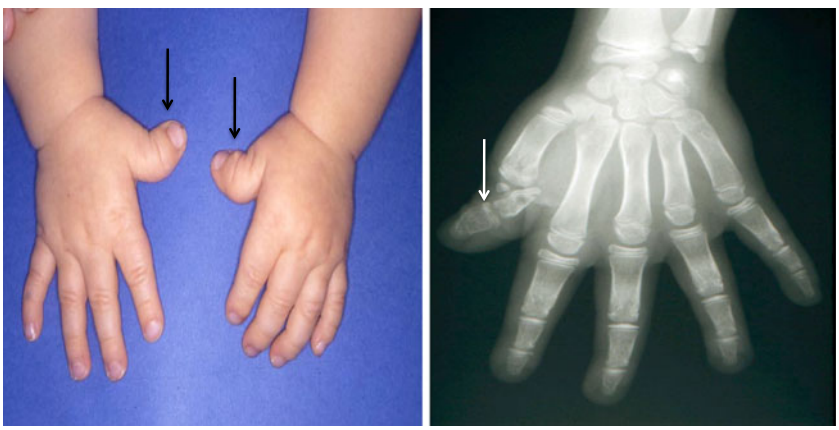

Fig. 3 Broad, medially deviated thumbs in a patient with Pfeiffer syndrome (*black* and *white arrows*). Photos courtesy of Prof. Dr. H Collmann

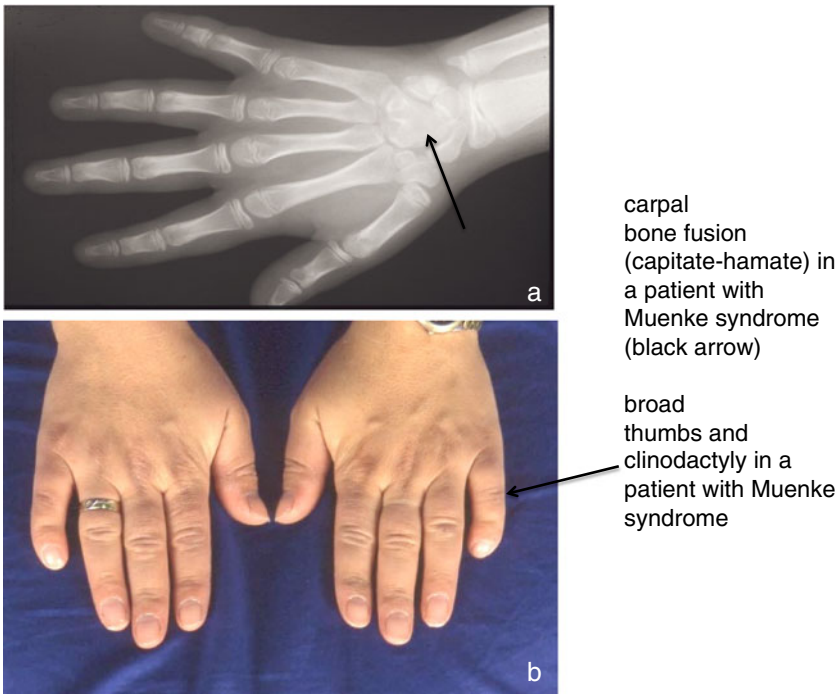

Fig. 4 **a** Carpal bone fusion (capitate–hamate) in a patient with Muenke syndrome (*black arrow*). **b** Broad thumbs and clinodactyly in a patient with Muenke syndrome. Photos courtesy of Prof. Dr. H Collmann

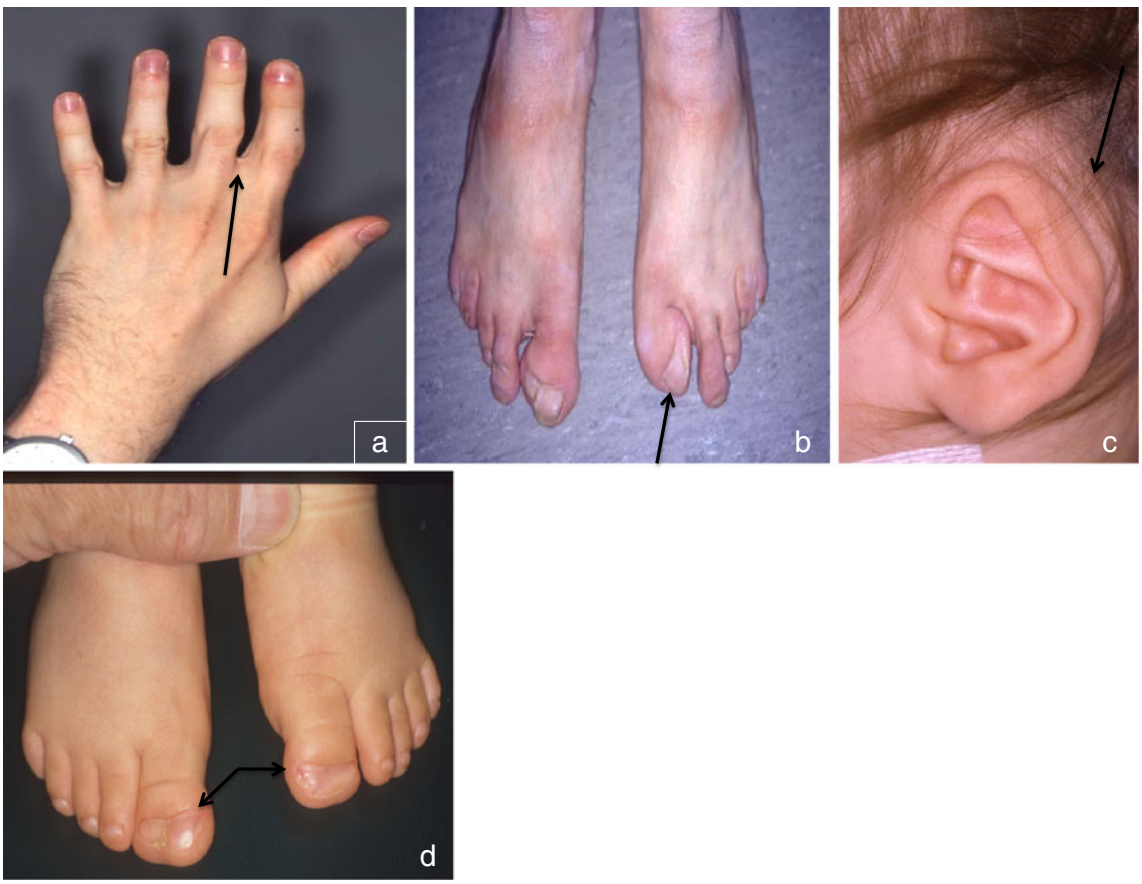

Fig. 5 **a** Cutaneous syndactyly in a patient with Saethre–Chotzen syndrome. **b** Lateral deviation of the large toes in a patient with Saethre–Chotzen syndrome. **c** Ear anomalies in a patient with Saethre–Chotzen syndrome. **d** Duplication of the distal phalanx of the hallux (large toe) in a patient with Saethre–Chotzen syndrome. Photos courtesy of Prof. Dr. H. Collmann

In situations where there are additional malformations beyond craniosynostosis and/or the presence of profound developmental delay, a trained dysmorphologist should be included to evaluate whether the craniosynostosis is occurring as part of a more complex chromosomal or monogenic disorder. For these patients, first-line testing is chromosomal microarray to look for genomic imbalances (chromosomal duplications or deletions) [71]. Due to issues related to test availability, routine karyotype may also be considered. When an obvious syndrome-specific appearance is present (for example, the severe syndactyly of Apert syndrome or the hypertelorism, bifid nose, and longitudinal ridging of the nails in a female with craniofrontonasal syndrome), diagnosis is more straightforward and can often be confirmed by syndrome-specific testing. In such cases, a clinical diagnosis is generally confirmed with the appropriate molecular gene studies. With new technologies dramatically changing the way in which gene sequencing is performed, it is likely that in the near future, the approach will involve simultaneously sequencing large numbers of craniosynostosis-related genes as part of the standard genetic workup in affected patients.

Figure 6 demonstrates a genetic approach to the genetic testing for patients with craniosynostosis that has been adopted by many centers [106]. This algorithm is based on the involved sutures, resulting craniofacial dysmorphisms, and additional malformations.

Although targeted genetic testing is appropriate for patients in whom a specific diagnosis is suspected, the general issue arises whether those with non-syndromic synostosis should be offered genetic testing. Non-syndromic does not imply that a condition is not genetic as it is a term simply used to describe the absence of additional, clinically apparent anomalies that typically co-occur in the context of a syndrome. In a 2010 retrospective genetic study of craniosynostosis, causative mutations were present in 11 % of multi-suture, 37.5 % of bilateral coronal, and 17.5 % of unilateral coronal synostosis, but were absent in all patients with non-syndromic sagittal, metopic, and lambdoid synostosis [107]. Although the numbers of patients studied in some groups were relatively small, the low success rate of molecular diagnosis in sagittal synostosis has been independently confirmed. The positive diagnostic yield from molecular genetic testing in patients with non-syndromic craniosynostosis was substantially higher among children with isolated fusion of the coronal sutures [107]. Thus, patients with isolated, non-syndromic coronal craniosynostosis warrant genetic testing (these patients represent the first column of Fig. 6), whereas genetic testing is generally not advised for patients with isolated, non-syndromic sagittal, lambdoidal, or metopic synostoses.

Genetic testing in patients with isolated coronal suture synostosis begins with *FGFR3* testing (Muenke syndrome). Testing then proceeds with testing of *FGFR2*, *FGFR1*, and *TWIST* (for Crouzon syndrome, Pfeiffer syndrome, Saethre–Chotzen syndrome, and Jackson–Weiss syndrome). The last step in the genetic testing of these patients, if a causative mutation has not been found, is the assessment of copy number variations (such as whole-gene deletions) of the aforementioned genes.

For patients with additional malformations and/or profound developmental delay, the specific testing varies based on the specific suture involved. Among these patients, metopic synostosis is unique. The first step for patients with metopic craniosynostosis in the presence of additional malformations/anomalies and/or profound developmental delay is a chromosomal array study, which is indicated in order to determine the presence of genetic copy number variations (deletions or duplications of involved genes) as patients with syndromic metopic synostosis may frequently have chromosomal imbalances [56]. Interpretation of array studies may require parental studies.

Genetic testing should be performed by certified genetic laboratories (i.e., CLIA-certified) with expertise in the testing and interpretation of genetic testing for patients with craniosynostosis. Databases such as http://www.ncbi.nlm.nih.gov/sites/GeneTests/lab?db=GeneTests contain updated lists of genetic laboratories that offer appropriate genetic testing. In this database, laboratories can be searched by gene name or suspected disease name.

Part 3: Test result interpretation, genetic counseling, and management

The results of genetic testing should be reported to families, keeping in mind that a negative result does not exclude other genetic causes that may not be covered by the analysis performed. For example, if one tests a patient with isolated coronal craniosynostosis for Muenke syndrome and the test is negative, the results should be reported as such, while being aware that this patient may have another genetic alteration that is not detected by the specific testing for Muenke syndrome. Thus, patients and families should be made aware that although one test is negative, it does not mean that the patient does not have a syndrome or that there is not a genetic etiology to the craniosynostosis.

Whenever possible, the results should be reported to families with a genetic counselor through a genetic counseling session. Genetic counseling before any genetic testing may be extremely beneficial so that patients can be informed what tests are being done and why, and what a positive and negative result may mean. In the cases of the craniosynostosis syndromes described, often, entire families may be tested or suspected to be affected due to the autosomal dominant inheritance pattern, with variable expressivity, of most of these syndromes. Families should be made aware that the testing of a proband (the first individual with a condition who presents to medical attention) may indicate that a parent is possibly affected as well. Families of patients often assume that because they have no medical issues, or are apparently clinically unaffected, they are automatically

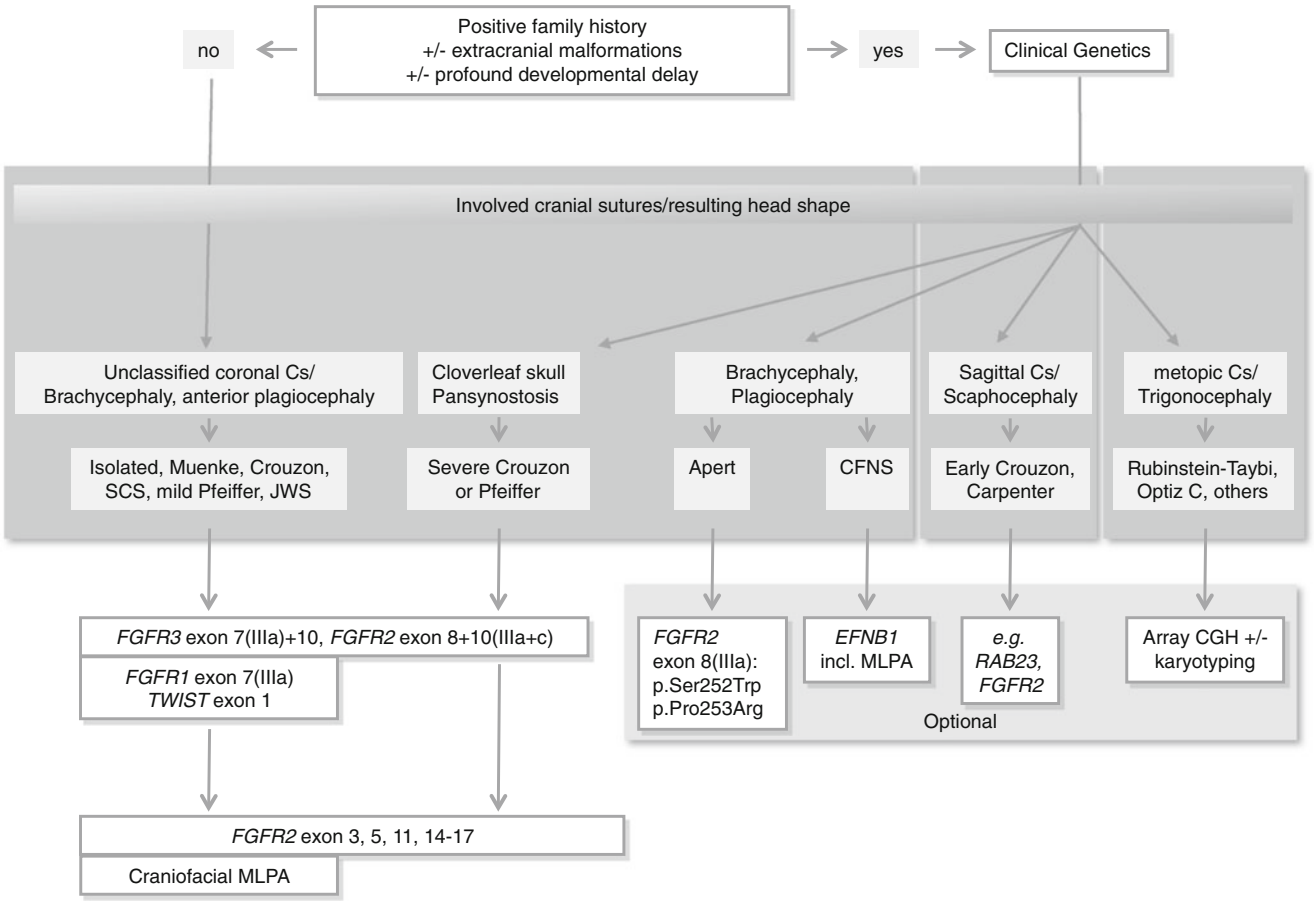

Fig. 6 Proposed genetic workup in a patient with craniosynostosis

unaffected. However, for example, in Muenke syndrome, it is often the case that a seemingly clinically normal parent may give birth to a more severely affected child.

Patients should also be made aware that the presence of a genetic condition or syndrome does not change who they are or how they define their family. Rather, it provides an explanation for what they are experiencing medically. Additionally, this explanation can help them in the future to prepare them for what to expect clinically. For example, a patient with Muenke syndrome should be screened for low-frequency sensorineural hearing loss and should have developmental evaluations. Early intervention, made possible by awareness of the genetic basis for a patient with craniosynostosis, can lead to the most optimal outcome.

Management

Central nervous system, neurodevelopment

Central nervous system anomalies are common in patients with Apert and Pfeiffer syndromes. The most common anomalies are agenesis of the corpus callosum and ventriculomegaly [18, 23, 27, 45]. Anomalies of the corpus callosum have also been reported in patients with Muenke syndrome [1, 36]. Epilepsy has been reported in patients with Muenke syndrome, Saethre–Chotzen syndrome, and Apert syndrome [32, 35, 87, 88]. Patients with Apert syndrome, Pfeiffer syndrome types 2 and 3, or who have neurologic abnormalities, developmental abnormalities, and/or epilepsy should receive a brain imaging study to identify structural anomalies.

Individuals with Apert syndrome, Pfeiffer syndromes types 2 and 3, and some individuals with Muenke syndrome commonly have some degree of neurocognitive impairment, whereas individuals with Crouzon syndrome, Pfeiffer syndrome type 1, and Saethre–Chotzen syndrome tend to have normal cognitive function [26, 27, 108]. An exception in Saethre–Chotzen syndrome is those individuals with a microdeletion encompassing the *TWIST* gene [41, 58]; these individuals with Saethre–Chotzen often have profound developmental delay and/or intellectual disability. All patients with newly diagnosed craniosynostosis should receive developmental and cognitive screening evaluation, with appropriate therapies provided as needed. In children with

developmental delay, particularly speech delay, a hearing evaluation may identify a potential contributing factor [42].

Intracranial hypertension is an important consideration in patients with craniosynostosis. Patients with multi-suture involvement and patients with *FGFR2* mutations have the highest risk of increased intracranial pressure [39]. Fundoscopic exam should routinely be performed in these patients to evaluate for papilledema. The finding of papilledema warrants urgent surgical attention. Additional indicators of intracranial hypertension include headache, vomiting, abrupt change in behavior, lethargy, and a "copper beaten skull appearance" on skull radiographs (Fig. 7).

Surgical intervention

In the absence of intracranial hypertension, surgical intervention—cranial vault reconstruction—is performed in the first 6–8 months of life, when the re-ossification potential is high [29]. Additionally, recently, endoscopic strip craniectomies have been performed, in which patients undergo the endoscopic suture release at a younger age (3 months), followed by postoperative helmet therapy [16, 57].

Preoperatively, attention should be paid to the growth and development of the midface, particularly in patients with syndromic craniosynostosis as patients with Pfeiffer, Crouzon, or Apert syndrome are more likely to have anesthetic complications compared to non-syndromic patients (e.g., difficult intubation due to midface hypoplasia) [13, 76]. The main surgical risks are intraoperative blood loss and re-bleeding. For many families, the major concern is the risk of brain injury or injury to the optic nerve. The risk of this is actually significantly low.

Even after surgical correction, various levels of recurrent deformity and/or elevated intracranial pressure may occur. These issues occur with a greater severity and higher frequency in patients with syndromic craniosynostosis [49, 99]. Thus, these patients should receive long-term postoperative surveillance until approximately 12 years of age, when brain bulk growth is complete. This surveillance program should include ophthalmoscopic exams at 3-month intervals in patients with multi-suture synostosis (including patients with Crouzon, Apert, Pfeiffer, Saethre–Chotzen, and Muenke syndromes) and at 6-month intervals in patients with sagittal suture synostosis and other single-suture synostoses [29]. Additionally, patients with central nervous system malformations including hydrocephalus and Chiari malformations should receive appropriate monitoring and treatment for these issues.

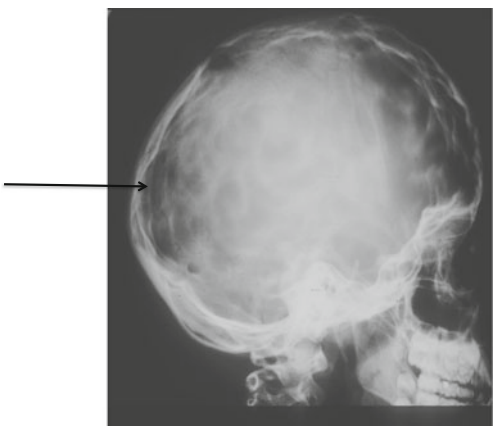

Fig. 7 Copper beaten skull in a patient with Saethre–Chotzen syndrome. Photo courtesy of Prof. Dr. H. Collmann

Ophthalmologic considerations

As described, in patients with syndromic craniosynostosis, fundoscopic exams are indicated both pre- and postoperatively and should be done repeatedly. The occurrence of papilledema, a marker of intracranial hypertension, is most common in patients with *FGFR2*-related craniosynostoses (Apert, Crouzon, and Pfeiffer syndromes). Papilledema may occur in patients without an identified genetic mutation, but is more common in patients with a known genetic mutation. The etiology of this phenomenon is unknown, though it is likely that the increased intracranial pressure observed in these former patients is an effect of the combination of differences in the formation and morphology of the skull, brain, dura, and cranial sutures that occurs due to the underlying genetic mutation.

In some cases, craniosynostosis leads to shallow orbits, which can cause proptosis, or forward displacement of the globe. In severe proptosis, a patient may be unable to close the eyelids, leading to exposure keratitis and corneal ulcers, resulting in visual impairment and scarring. To prevent this, lubricants should be used if the palpebral fissure remains open >2 mm during sleep [42]. In some severe cases, patients may require tarsorrhaphies (surgical procedure in which the eyelids are partially sewn together to narrow the opening) or urgent cranial vault reconstructive surgery to correct the deformity. Additional ophthalmologic issues that can occur include tear duct stenosis and ptosis (commonly in Saethre–Chotzen syndrome), hypertelorism, downslanting palpebral fissures, strabismus, and amblyopia. Cranial vault surgery can correct several of these issues, particularly strabismus and hypertelorism, and thus strabismus correction should be deferred until after the patient undergoes cranial vault reconstruction. Interestingly, an ophthalmologic outcomes study in 2009 demonstrated that children with unilateral coronal craniosynostosis who received endoscopic strip craniectomy had improved ophthalmologic outcomes (measured by strabismus severity) compared to those who received fronto-orbital advancement (cranial vault reconstruction) [68].

Respiratory considerations

Patients with syndromic craniosynostosis may have obstructive sleep apnea, feeding difficulties, failure to thrive, and cor pulmonale as a result of midfacial hypoplasia, choanal stenosis, and narrowing of the nasopharyngeal space [20]. Midface advancement may lead to respiratory improvements in these patients [78].

Special care should be taken in the planning process for anesthesia and intubation of these patients. Additionally, patients with Pfeiffer syndrome types 2 and 3 may have a tracheal cartilaginous sleeve, a condition where a continuous segment of cartilage extends from below the subglottis to the carina or mainstem bronchi, which can result in the need for a tracheostomy and indicate a relatively poor prognosis [48].

Oral considerations

Palatal anomalies, including cleft palate and high arched palate, have been reported in the most common craniosynostosis syndromes, including Pfeiffer syndrome (associated with mutations in *FGFR1* and *FGFR2*), Saethre–Chotzen syndrome (*TWIST)*, Apert syndrome (*FGFR2*), Muenke syndrome (*FGFR3*), and Crouzon syndrome (*FGFR2*) [3, 59, 81, 97, 98]. Thus, all patients with syndromic craniosynostosis should have a palatal exam. In patients with a high arched palate, a palatal expander may be considered as it has been shown to reduce the resultant effect of the high arched palate on dental crowding and malocclusion [3]. Due to a combinatory effect of growth failure of the skull base, high arched palate, and craniosynostosis, dental issues commonly encountered in this patient population include overbite, crossbite, and dental crowding.

Audiologic and otologic considerations

Chronic otitis media occurs with a high frequency in patients with syndromic craniosynostosis. There are many contributory factors, including the effect of the high arched palate on the function of the tensor veli palatini, a muscle that functions in the opening and closing of the Eustachian tube, as well as growth deficiency in the skull base. Additionally, in those patients with cleft palate, the aberrant attachment of the levator veli palatini leads to impaired ventilation of the middle ear, which can result in recurrent otitis media with effusion. Recurrent otitis media leads to conductive hearing loss, a type of hearing loss that is common in syndromic forms of craniosynostosis. Muenke syndrome is unique among the other *FGFR*-related craniosynostoses as it is the only craniosynostosis syndrome characterized by a low-frequency sensorineural hearing loss in almost all patients [33, 49].

A literature review of hearing loss in craniosynostosis syndromes revealed that hearing loss occurs as a component part of or has at least been reported in all of the FGFR-related craniosynostosis syndromes (Agochukwu 2012, Muenke lab, unpublished; see Table 2 for a summary of the audiologic and otologic manifestations of these syndromic craniosynostoses).

Once a patient has a confirmed diagnosis of a craniosynostosis syndrome, a comprehensive audiologic evaluation should follow. In Muenke syndrome, hearing testing should devote particular attention to low frequencies due to characteristic low- to mid-frequency hearing loss. This is of particular importance as newborn hearing screens and many school-based hearing screens tend to focus on the mid and high frequencies [33]. If hearing loss is confirmed, the next steps depend on whether it is a sensorineural, conductive, or a mixed hearing loss. Patients with confirmed hearing loss should have a comprehensive otologic and inner ear evaluation, including imaging, to thoroughly evaluate the otologic structures. Inner ear imaging studies in Apert syndrome, Pfeiffer syndrome, and Crouzon syndrome have demonstrated that patients have a high frequency of inner and middle ear anomalies including, but not limited to, malformations and/or hyoplasia of middle ear ossicles, dysmorphic semicircular canals, and atresia of the auditory canals [12, 15, 38, 51, 64, 67, 75, 85, 102, 109] (Table 2).

Patients with otitis media with effusion may benefit from tympanostomy tube insertion and antibiotic treatment as recurrent otitis media with effusion is a known cause of conductive hearing loss. There are many sequelae of recurrent otitis media that may lead to hearing loss in addition to other problems, including tympanic membrane perforation, tympanic membrane atelectasis, and cholesteatoma. Additionally, persistent conductive hearing loss in childhood has been associated with the development of sensorineural hearing loss later in life [79]. Amplification via hearing aids or cochlear implants should be recommended as indicated by the severity of the hearing loss. Regardless of the type and severity of hearing loss, these patients mandate close follow-up. Although hearing loss may remain stable, it can also progress, leading to the necessity of new interventions (e.g., cochlear implants or hearing aids). School-aged children with hearing loss greatly benefit from special accommodations such as sound field amplification and preferential seating, which has been shown to improve speech perception [65].

Visceral organs

Patients with Apert syndrome, Pfeiffer syndrome types 2 and 3, and patients with craniosynostosis due to chromosomal imbalances should receive an echocardiogram and ultrasound of the kidneys and urinary tract. These

Table 2 Otologic and auditory manifestations in FGFR craniosynostoses

Syndrome	Hearing loss		Otologic manifestations
	No. of patients/no. examined (%)	Type of hearing loss, *n* (%)	
Muenke syndrome	160/262 (61 %)	Sensorineural: 126 (79 %)	Low-set posteriorly rotated ears
		Conductive: 14 (9 %)	Standard variant venous dysplasia of left petrous bone
		Mixed: 8 (5 %)	Tinnitus
		Not specified: 12 (8 %)	Auricles low-set and posteriorly rotated
			Small accessory auricles
			Prominent crus helicis
			Hypoplastic right auricle, absent right external auditory meatus, bony atresia of right external auditory canal
			Low-set ears and apical cartilage deformity
Apert syndrome	100/125 (80 %)	Conductive: 93 (93 %)	Low-set ears
		Sensorineural: 2 (2 %)	Microtia
		Mixed: 5 (5 %)	Macrotia
			Abnormal surface configuration of pinna
			Posteriorly rotated external ears
			Eustachian tube dysfunction
			Constricted external canal
			Chronic middle ear effusion
			Recurrent otitis media
			Ossicular fixation (stapes footplate fixation)
			Wide cochlear aqueduct
			Dilatation/enlargement of vestibule
			Bulbous vestibule, fusion of bulbous vestibule and lateral semicircular canal
			Cochlear hypoplasia
			High riding jugular bulb
			Posterior semicircular canal dehiscence
			Malformed and/or fused ossicles
			Opacified mastoid air cells
Pfeiffer syndrome	35/38 (92 %)	Conductive[a]: 22 (81 %)	Fixed ossicular chain
		Sensorineural: 1 (4 %)	Ankylosis of stapes
		Mixed: 4 (15 %)	Bilateral dilatation of internal acoustic meatus
			Chronic, recurrent otitis media with or without effusion
			Atresia/Stenosis of external auditory canal
			Enlarged middle ear cavity
			Hypoplastic middle ear cavity
			Hypoplasia of middle ear ossicles
			Fusion/Fixation of middle ear ossicles to wall of tympanic membrane
			Separation of middle and apical coils of the cochlea
			Granulation tissue in the external auditory canal
			Bilateral ossicular malformation with fusion of ossicles to scutum
			Bilateral capacious cochlear aperture
			Bilateral vestibular enlargement and proximal limbs of semicircular canals
			Symmetrical dilatation of internal auditory canals
			Underpneumatization of mastoid bones
			Right encephalocele
			Ossicles abutting brain tissue

Table 2 (continued)

Syndrome	Hearing loss		Otologic manifestations
	No. of patients/no. examined (%)	Type of hearing loss, *n* (%)	
			Posterior semicircular canal dehiscence
			Bilateral fluid in semicircular canal, vestibules and cochleas
			Dysmorphic semicircular canal
			Bilateral short internal auditory canal
			Absence of left cochlear nerve
			Sclerosis of mastoid air cells
			Small and opacified middle ear cavities without bone destruction
			Slight angulation of ossicles
			Mild enlargement of confluence of semicircular canals
Crouzon syndrome	43/58 (74 %)	Conductive: 26 (60 %)	Microtia
		Sensorineural: 11 (26 %)	Low-set ears
		Mixed: 6 (14 %)	Posteriorly rotated ears
			Thickened tympanic membrane
			Retracted tympanic membrane
			Perforation of tympanic membrane
			Atrophic tympanic membrane
			Tympanosclerosis
			Otorrhea
			Otitis media with effusion
			Otosclerosis of stapes
			Malalignment of the pinna
			Atresia of external auditory canal
			Narrowed and tortuous ear canals
			Abnormal and fixed incus
			High riding jugular bulb
Jackson–Weiss syndrome	15/22 (68 %)	Conductive: 8 (53 %)	Otitis media with effusion not described
		Sensorineural: 4 (26 %)	Otologic findings not described in the literature
		Mixed: 3 (20 %)	
Beare–Stevenson syndrome	1/26 (4 %)	Conductive: 1 (100 %)	Skin pitting on ears
			Posteriorly angulated/rotated ears
			Pre-auricular creases/furrows
			Corrugated skin overlying the ears
			Low-set ears
			Stenosis of external auditory canals
			Absent ear lobule
			Prominent antitragus
			Macrotia
			Hypoplastic lobule
			Displaced ears
			Dysplastic ears
Crouzon syndrome with acanthosis nigricans	5/36 (14 %)	Conductive: 2 (40 %)	Recurrent otitis media
		Sensorineural: 1 (20 %)	
		Not Specified: 2 (40 %)	

[a] In Pfeiffer syndrome cases, type of hearing loss was documented in a total of 27 / 35 patients with reported hearing loss

Table 3 Tarsal coalition in FGFR-related craniosynostosis syndromes

Syndrome	% affected (no. of patients affected/no. examined)	Types of coalition reported	*p* value (incidence of tarsal coalition in syndrome vs. general population)	Additional Limb Anomalies Described	References
Apert syndrome (*FGFR2*)	91 % (91/100)	Progressive fusion of all tarsal bones, sparing talonavicular joint	<0.0001	Bony syndactyly, synonychia, short metatarsals, malformed metatarsals, metatarsal coalition, symphalangism, carpal bone coalition, clinodactyly, postaxial polydactyly, abnormal bone configuration, winging of scapula, short humeri, glenoid dysplasia, genua valga, elbow ankylosis/synostosis, hypoplastic changes of: scapula, humerus, radius, ulna, pelvis, and femur	[5]; [23, 25]; [95]; [69]
Crouzon syndrome (*FGFR2*)	13 % (3/24)	Calcaneocuboid	0.5078	Clinodactyly, carpal bone fusion, hypoplastic 4th metacarpal, short metacarpals, soft tissue syndactyly, brachydactyly, hypoplastic/absent phalanges, broad phalanges, pseudoepiphyses of 1st and 5th metacarpals, broad metatarsals, pseudoepiphysis of 1st and 5th metatarsals, dysplastic cuneiforms, symphalangism	[7, 8]; [30]; [83]
Jackson–Weiss syndrome (*FGR2*)	82 % (23/28)	Calcaneocuboid, calcaneonavicular, navicular-1st cuneiform, navicular–medial cuneiform	<0.0001	Brachydactyly, cone shaped epiphyses, hypoplastic phalanges, carpal bone malsegmentation, bipartite lunate, short and broad metatarsals, broad phlanages, hallux varus, metatarsus adductus, metatarsal coalition, symphalangism, cutaneous syndactyly, short and broad toes, cone shaped epiphyses, malformed metatarsals, malformed phalanges	[55]; [2]; [47]; [66]; [80]
Muenke syndrome (*FGFR3*)	25 % (27/109)	Calcaneocuboid, calcaneonavicular, cuboid–cuneiform, talocalcaneal	0.0006	Brachydactyly, clinodactyly, broad toes and thumbs, cone shaped epiphyses, thimble like phalanges, symphalangism, short, broad phalanges, hypoplastic/absent phalanges, partial syndactyly	This report; [74]; [100]
Pfeiffer syndrome (*FGFR1*, *FGFR2*)	50 % (20/40)	Medial cuneiform-navicular, calcaneocuboid, cuneiform–cuneiform	<0.0001	Broad halluces, hallux varus, soft tissue syndactyly, broad medially deviated thumbs, metatarsus adductus, malformed metatarsals, symphalangism, hypoplastic/absent phalanges, metatarsal thinning, coxa valgus, shallow acetabulae, elbow ankylosis, elbow synostosis, triangular phalanges, clinodactyly	[91]; [40]; [90]; [9, 6]; [94]; [11]; [77]; [43]

individuals often have structural abnormalities of these organs [21, 24, 34, 70]. In a study of Apert syndrome, it was found that cardiac anomalies and genitourinary anomalies were present in 10 and 9.6 % of patients, respectively [24].

Musculoskeletal considerations

Limb anomalies are common in Apert, Pfeiffer, Crouzon, Jackson–Weiss, Saethre–Chotzen, and Muenke syndromes (Table 3). Skeletal anomalies, including carpal and tarsal bone fusions and/or cervical spine abnormalities, are common in Apert, Pfeiffer, Crouzon, Jackson–Weiss, Saethre–Chotzen, and Muenke syndromes [4]. Additional anomalies of the limb include radiohumeral synostosis, short humeri, and elbow ankylosis/synostosis in Apert and Pfeiffer syndromes [7, 8, 22, 25] (Table 3). In patients with syndromic craniosynostosis and symptoms of extremity pain, limping, arthralgias, abnormal gait, and/or other similar symptoms, imaging should be considered due to the known associated limb anomalies.

Limb anomalies in Apert syndrome extend beyond tarsal coalition, are more severe in the upper limb, and are the most severe of all the craniosynostosis syndromes. Illegitimate autocrine activation of mutated mesenchymal FGFR2c p.P253 by the fibroblast growth factor 10 (FGF10) ligand is responsible for the syndactyly in Apert syndrome; the p.P253R mutation accounts for 33 % of cases of Apert syndrome and is associated with more severe syndactyly when compared to the other causative mutation of Apert syndrome, p.S252W, which accounts for 66 % of cases [28, 44, 52, 62, 103, 105]. This is confirmed by a mouse model of Apert syndrome in which Fgf10 knockdown rescues some of the skeletal anomalies [44].

Patients with Apert syndrome should be evaluated by an experienced hand surgeon within the first 6 months of life; syndactyly release is typically performed in stages.

Conclusions

Historically, the early care of infants and children with syndromic craniosynostosis has focused purely on the surgical correction of the synostotic suture. However, clinical studies and research have shown that these individuals have a number of other medical issues. Though not always as obvious as the craniosynostosis, recognition and management of these other issues can be beneficial in terms of both short- and long-term outcomes and can help both the proband as well as other family members who may be ultimately found to be affected. These issues affect multiple systems and warrant considerations that frequently require a multidisciplinary approach. The care of these patients has evolved to include a diverse team of specialists including plastic surgeons, neurosurgeons, geneticists, dentists, neurologists, speech pathologists, audiologists, otolaryngologists, orthopedists, and social workers, among others.

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