Review Article

A narrative review of craniofacial deformities

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Background and Objective: A lot has been learned on the different craniofacial deformities over the past half-decade. The objective of this review was to discuss our current understanding and the latest findings on craniofacial deformities and their diagnosis, prevention, treatment, and management.

Methods: This narrative review was completed by reviewing the literature, namely the databases PubMed and Google Scholar, to identify all relevant studies in English regardless of the study design or date of publication to allow for a comprehensive review.

Key Content and Findings: There are several craniofacial deformities, each of which is characterized by its own distinct set of features. Orofacial clefts are the layperson's notion of craniofacial deformities being the most common type of craniofacial deformity. Orofacial clefts can clinically present as an isolated cleft lip (CL), isolated cleft palate (CP), or cleft lip with cleft palate (CL/P). The second most common craniofacial deformity is hemifacial microsomia (HFM). Because the first and second pharyngeal arches are affected, the afflicted anatomical structures include the jaws, ears, facial soft tissue, orbits, and facial nerve function. Two craniofacial deformities often confused for one another due to their clinical similarities, namely the prominent hypoplastic mandible, are mandibulofacial dysostosis (MD) and robin sequence (RS). In MD, each anomaly, namely the hypoplastic mandible, the ophthalmic abnormalities, and the conductive hearing loss, has its unique pathogenesis. In RS, the different anomalies that clinically present are all caused by a single mastermind anomaly: the hypoplastic mandible. Finally, craniosynostosis is defined as the premature fusion of cranial sutures. This congenital deformity can be either syndromic or non-syndromic. Syndromic craniosynostoses often involve multiple sutures and are accompanied by various symptoms depending on the syndrome at hand. Non-syndromic craniosynostoses only affect a single suture and are more benign.

Conclusions: Our understanding of craniofacial deformities has dramatically evolved with time as it relates to their etiology, diagnoses, treatment, and management. Craniofacial research is in a constant state of flux as we continue to disentangle the following craniofacial deformities on our way to the future.

Keywords: Orofacial clefts; craniosynostosis; mandibulofacial dysostosis (MD); robin sequence (RS); hemifacial microsomia (HFM)

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Orofacial clefts

Isolated cleft palate (CP), as well as cleft lip with or without cleft palate (CL/P) is the most common congenital orofacial malformation in the United States, with an estimated prevalence of 16.86 cases for every 10,000 live births (1). Individuals with operated orofacial clefts have irregular faces, distinct from that of unaffected individuals. These deviations stem from variations intrinsically associated with the cleft anomaly itself, functional adaptations to the anomaly, or iatrogenic consequences of the surgical procedures performed to correct the anomaly (2). Twin studies have illustrated a 40–60% concordance rate among monozygotic twins, implying a substantial genetic component within the etiology of CL/P (3). CL/P exhibits polygenic inheritance since many different genes have been articulated CL/P through linkage and association studies, such as IRF6, ABCA4, and MAF (4). Environmental risk factors for CL/P maternal alcohol & cigarette use, herbicides (i.e., dioxin) exposure, and vitamin deficiencies during the periconception period. Such environmental risk factors have been shown to interact with certain genes within the pathogenesis of CL/P. Examples of gene-environment interactions include TGFB3/Smoking and MSX1/Smoking (3).

Combined clefts of the lip and palate involve structures of the embryonic primary palate and secondary palate. Clefts of the primary palate range in their dimensions; they can merely affect the maxillary arch, resulting in an alveolar cleft, or extend through both the hard and soft palates. Similarly, clefts of the secondary palate can only affect the uvula or the entire structure, extending up until the incisive foramen (5). The incidence of CL/P varies according to race and ethnicity, with Native Americans illustrating the highest reported prevalence at birth. Socioeconomic factors also influence the incidence of CL/P. Individuals born in more rural, lower socioeconomic status conditions, with all other things being equal, have a higher risk of CL/P than individuals from a higher socioeconomic background. CL/P comes in two forms: syndromic and non-syndromic. The distinction between the two forms has important implications on establishing the appropriate treatment plan and the recurrence risks for patients and their families. There are no clear-cut definitions that separate syndromic CL/P from the non-syndromic form; it varies across institutions (2). One study, for instance, drew the line between syndromic and non-syndromic as follows: if any additional major anomaly or three or more minor anomalies were present, then the case was a syndromic CL/P. Major anomalies were defined as those that entailed functional or cosmetic significance requiring medical intervention, while minor anomalies were defined as those lacking functional or cosmetic relevance (6).

Amongst all cases of CL/P, the non-syndromic (70–80%) form comprises the majority. The cleft in non-syndromic CL/P exhibits laterality, while that of syndromic CL/P is situated in the midline. Amongst non-syndromic CL, unilateral involvement is more common than bilateral involvement. Further, left-sided clefting is more common than right-sided clefting. The cleft itself varies in its extent. Complete clefts involve the entire upper lip, extending into the naris. On the other hand, incomplete clefts contain a variable amount of tissue that joins the upper lip. This amount could be a simple, narrow band referred to as the Simonart band. Most cases of CL/P involve both the primary palate and secondary palate (2).

Isolated CP only involves structures of the embryonic secondary palate. Unlike CL/P, CP illustrates no predispositions with regards to race or ethnicity. The prevalence of CP is equal in all populations. It is also important to mention that CP is genetically distinct from CL/P, reflected by different inheritance patterns. In contrast to CL/P, most CP cases are syndromic, with Stickler's syndrome being the most common. Further, the abnormal craniofacial morphogenesis in patients with isolated CP renders its association with additional malformations, such as bimaxillary retrognathia, reduced length and posterior height of maxilla, reduced length of the mandible, and retrognathia. Further, due to the retrognathia, the upper airway dimensions are volumetrically reduced in CP patients. Isolated cleft lip (CL) only involves structures of the embryonic primary palate. In contrast to CP, the craniofacial morphology in CL is more or less ordinary, apart from the slight protrusion of the premaxilla. This protrusion increases with the extent of the cleft, with bilateral complete CLs exhibiting the greatest degree of protrusion (2).

CL/P can be diagnosed during the prenatal stage using ultrasonography. Recent three-dimensional (3-D) approaches enable clinicians to accurately assess the hard and soft palates of the mouth and distinguish them from normal anatomy (7,8). Molecular diagnosis of the established culprit genes in the future may enable families to anticipate the risk for CL/P in advance of the prenatal stage (3).

CP can be surgically treated via one-stage or two-stage palatoplasty to divide the oral and nasal cavities and restore the competency of the velopharyngeal sphincter (9,10).

Nevertheless, patients can develop an oronasal fistula post-operatively due to inadequate healing or breakdown of the primary repair, prompting the need for revisional surgeries (11). Revisional surgery is also performed for cases where primary palatoplasty failed to achieve normal velopharyngeal function (12). In a retrospective review of patients who underwent the Furlow palatoplasty, Basta *et al.* determined that speech outcomes were similar between syndromic and nonsyndromic CP patients. Nevertheless, CP patients with the 22q11.2 deletion syndrome were more likely to have borderline-incompetent speech and require revisional surgery to correct velopharyngeal insufficiency (12). Unfortunately, revisional surgery is at risk for wound dehiscence, which could indicate the importance of optimizing the primary palatoplasty (9).

CL can be surgically addressed by layered closure of the skin, muscle, and oral mucosa without causing tension. The goal of CL repair is to establish adequate orofacial function and facial aesthetics (13,14). CL can be repaired through various skin closure techniques using either resorbable sutures, non-resorbable sutures, or adhesives (15). The most common complication post-surgery is skin dehiscence, which was prevalent among bilateral CL patients (16).

Prevention of CL/P can rule out the need for complex surgery and the potential complications that follow. Adequate levels of vitamins during the periconceptional period can is one means for preventing the occurrence of CL/P. Loffredo *et al.* determined that mothers who gave birth to CL/P children were less likely to have supplemented with dietary and supplemental vitamins relative to mothers who gave birth to normal children. The authors concluded that vitamin supplementation, particularly within the first four months of pregnancy, has a protective effect against both CP and CL/P (17). We present this article in accordance with the Narrative Review reporting checklist (available at https://fomm.amegroups.com/article/view/10.21037/fomm-21-85/rc).

Craniosynostosis

Craniosynostosis is a congenital disorder characterized by the premature fusion of one or more cranial sutures (18). When skull sutures fuse prematurely as an isolated event, the resulting craniosynostosis is deemed non-syndromic. On the other hand, when skull sutures fuse in conjunction with other anomalies in a clinically recognizable pattern, the resulting craniosynostosis is considered syndromic (18). Non-syndromic craniosynostosis (typically single-sutured) is more common than syndromic craniosynostosis (frequently multi-sutured). While it affects roughly 1 in 2,000 live births, syndromic craniosynostosis affects 1 in 30,000 to 100,000 live births (19).

The etiology of craniosynostosis is multifactorial. Genetic mutations in the genes of the transcription-derived growth factors, FGFR1, FGFR2, FGFR3, and TGF-β, are common, especially in syndromic craniosynostosis (19,20). Environmental etiologies that have been reported include paternal occupations such as agriculture, maternal age, exposure to tobacco smoke, and medication use during pregnancy (i.e., warfarin) (19).

The sequelae from craniosynostosis all stem from the limited volume of the associated cavities (i.e., cranial vault). The brain illustrates rapid growth during the first few years of life, more than tripling in size by the age of two years old (19). Thus, craniosynostosis that manifests during this phase of rapid growth could impede the normal growth of the brain and result in several functional problems. The primary concern is raised intracranial pressure (ICP), which is defined as >15 mmHg, symptomatically stamped by headaches, irritability, and difficulty sleeping. The greater the number of sutures involved in the craniosynostosis, the smaller the associated cavities, the greater the chance of developing increased ICP. Renier *et al.* reported elevated ICP in 14% of patients with single suture craniosynostosis and 47% of patients with multiple suture craniosynostosis (21).

Raised ICP is considered the primary indication for intervention in craniosynostosis to prevent the sequela of neuropsychiatric disturbances that can follow, such as behavioral problems or mental retardation. As early as 1840, Bir *et al.* reported some mental retardation secondary to the microcephaly of craniosynostosis. Further, Bir *et al.* determined that excision of the fused sutures could prevent later intellectual impairment (22). Single suture craniosynostosis suffices for the development of raised ICP; neurodevelopmental delay in single suture craniosynostosis patients can be as high as 37%. Nevertheless, it is unclear whether raised ICP can fully explain neuropsychiatric disturbances in craniosynostotic patients. There are arguments that defective development of the brain independent of the limited cranial vault accounts for the observed neuropsychiatric disturbances. The impaired venous outflow from the sagittal sinus can also lead to either form of hydrocephalus. Finally, the globe is also affected due to underdeveloped or misshapen orbits and is consequently displaced from its normal position (i.e., exorbitism) (18).

Isolated (non-syndromic) craniosynostosis

Non-syndromic craniosynostosis usually involves only one of the following sutures listed in decreasing order of frequency: sagittal, coronal, metopic, and lambdoid (23). While most non-syndromic craniosynostosis involves a single suture only, they can also simultaneously involve multiple sutures.

Sagittal craniosynostosis

Sagittal craniosynostosis is the most common form of craniosynostosis overall. It is also the most common non-syndromic craniosynostosis, comprising about 50–60% of reported isolated cases (24-26). Sagittal synostosis results in a boat-shaped deformity (i.e., scaphocephaly) due to growth restriction in the width and excessive compensatory growth in the anterior to posterior direction. Frontal bossing and occipital cupping are standard features of sagittal synostosis.

Coronal craniosynostosis

Coronal craniosynostosis is the second most common form of non-syndromic craniosynostosis, composing 40% of all non-syndromic synostosis. This form of craniosynostosis results in anterior plagiocephaly. This aberrant skull shape develops from compensatory growth at the contralateral patent suture induced by the fused ipsilateral suture. The restricted coronal suture impairs the ventral expansion of the anterior cranial fossa, and the middle cranial fossa bows ventrally and does not descend. This altered cranial base influences the developing shape of both the mandible and the midface. Due to the restricted ventral growth mentioned earlier, the forehead of the affected side appears flattened. Further, the brow and orbit demonstrate superior and posterior displacement with the characteristic "Harlequin Eye" deformity and globe proptosis. It is worth mentioning that clinical reports of uncorrected unilateral coronal synostosis exhibited progressive cranial and mandibular asymmetry (27).

Metopic craniosynostosis

In a tie with coronal craniosynostosis, metopic craniosynostosis is the second most common form of non-syndromic craniosynostosis (40% of all non-syndromic synostosis). The combination of a midline forehead ridge at the site of the fused suture and laterally restricted frontal bone growth and compensatory growth of the remaining skull gives rise to the characteristic trigonocephaly: this is characterized by a triangular-shaped forehead with associated bitemporal narrowing and orbital hypotelorism (28-30).

Unlike the other craniosynostosis, the incidence of metopic craniosynostosis has been rising over recent decades. Supraorbital retrusion is graded as mild, moderate, or severe depending upon the size of the frontal angle (31). The frontal angle is formed by the line through Pterion (bilaterally) and the line through the Nasion. According to this formula, trigonocephaly is deemed severe when the frontal angle is less than 89°, moderate when between 90° and 95°, mild when between 96° and 103°, and normal when measuring 104° or more (31). It is crucial to mention that an overriding suture can create metopic ridging after normal fusion several months after birth. Further, metopic ridging has even been described in the presence of an open suture. Because of these findings, a metopic ridge should not be considered definitive proof of metopic craniosynostosis (32).

Diagnosis and treatment of non-syndromic craniosynostosis

Plain radiography is often utilized as an initial diagnostic tool for patients with potential non-syndromic craniosynostosis. Nevertheless, CT scan is the most sensitive and specific method. In addition to providing three-dimensional views of the cranial bone, CT scan also outlines the current state of the brain. In response to concerns on the levels of ionizing radiation that accompanies CT scans, alternative diagnostic methods for craniosynostosis have been explored. One such method is ultrasonography, which exhibits imaging capabilities equal to that of CT imaging (33).

Patients with non-syndromic craniosynostosis are primarily operated on at an early age, between the ages of six and nine months (33). The decision to surgically normalize skull shape depends not only on aesthetic considerations but also functional impairments, namely raised ICP, and intra-operative blood loss (33,34). For sagittal synostosis, open vault remodeling has been traditionally executed, particularly for infants with severe synostoses and high cephalic indices (35). This can be performed in a single operation or be staged according to region, remodeling the anterior vault and subsequently the posterior vault or vice versa (36). A less invasive alternative is the strip craniectomy (i.e., suturectomy) within which the sagittal suture is excised endoscopically (37). Anterior

cranial vault expansion is indicated for metopic and coronal synostoses. The fronto-orbital advancement can achieve this goal, recontouring the forehead and advancing the supraorbits (34). The supraorbital bar can be sectioned and amplified with bone grafts to increase bitemporal and interorbital distance (38).

Post-operatively, children are monitored to ensure adequate neurological development. Secondary procedures may be necessary to correct any residual defects. For instance, hypertelorism can subsist among patients with metopic synostosis post-operatively. Patients who received open vault remodeling may require secondary procedures for hardware removal and recontouring. A small share of patients who underwent initial suturectomy may require total or subtotal cranial vault remodeling (34).

Syndromic craniosynostosis

While there are around 100 syndromic craniosynostoses, the most common ones, constituting at least 90% of syndromic craniosynostosis, are Apert, Crouzon, Pfeiffer, Saethre-Chotzen, and Muenke syndromes (39). Unlike non-syndromic craniosynostosis, the syndromic subtype typically affects multiple sutures, with the coronal suture being the most commonly affected one (40). Almost all these syndromic craniosynostosis, except for Saethre-Chotzen syndrome, genetically exhibit incomplete penetrance and variable expressivity. As a result, such syndromes entail a broad spectrum of clinical presentations, ranging broadly in terms of severity. Further, syndromic craniosynostoses follow an autosomal dominant inheritance pattern with a high rate of *de novo* mutations, most commonly with a paternal origin of mutation associated with increased age (40).

Apert's syndrome

Bicoronal craniosynostosis, severe midfacial hypoplasia, shallow orbits with mild hypertelorism, and complex symmetric syndactyly of the hands and feet are mainly pathognomonic for Apert's syndrome. The premature fusion of both coronal sutures results in turribrachycephaly: a skull that is elongated transversely and foreshortened anterior-posteriorly (18). The severe midfacial hypoplasia in tandem with a regularly developing mandible result in class III malocclusion and, more critically, airway compromise to an extent that warrants a tracheostomy. The hand syndactyly often involves fusion of the second, third, and fourth fingers, resulting in mid digital hand mass. A similar fusion pattern is also seen in the toes bilaterally. The shallowness of the orbits results in ocular proptosis (i.e., exorbitism) (41). Mental retardation is common in Apert's syndrome, though the degree of cognitive impairment is variable, with many patients capable of developing average intelligence (18).

Seven different gain-of-function mutations in the *FGFR2* gene on chromosome 10q have been identified in Apert's syndrome, which result in enhanced osteoblast differentiation. Specifically, the two missense mutations Ser252Trp and Pro253Arg, are responsible for approximately 98% of cases of Apert's syndrome (42,43).

Crouzon's syndrome

Crouzon syndrome is characterized by Bicoronal synostosis, shallow orbits with subsequent ocular proptosis, midfacial hypoplasia, and an anterior open bite. As a consequence of the premature fusion of sutures, a brachycephalic head shape results, although scaphocephaly, trigonocephaly, and a cloverleaf skull have all been reported with Crouzon's syndrome. Crouzon's syndrome is phenotypically similar to Apert syndrome, except it lacks limb anomalies (i.e., syndactyl).

Crouzon's syndrome is observed in one in every 25,000 live births, rendering it the most common form of syndromic craniosynostosis. Similar to Apert's syndrome, Crouzon's syndrome is caused by mutations in the FGFR2 gene (41). However, the missense mutation Ala391Glu in the FGFR3 gene has been explicitly reported in the subtype of Crouzon's syndrome with acanthosis nigricans (18).

It is essential to mention that earlier closure of sagittal and lambdoid sutures, in addition to bicoronal craniosynostosis, have also been reported in Crouzon's syndrome. This premature incident leads to higher rates of intracranial hypertension and, over time, progressive hydrocephalus and tonsillar herniation. It has been documented that the incidence of elevated ICP in a population of patients with Crouzon's syndrome is around 65%, with the remainder having borderline elevated ICP (41). Further, the incidence of hydrocephalus reported in this patient population ranges from 9% to 26%, which can present as headaches, nausea and vomiting, mental status changes, and seizures (44). Patients typically have average intelligence (18).

Pfeiffer's syndrome

Consistent with Apert and Crouzon, the majority of cases of Pfeiffer syndrome entail a mutation in FGFR-2.

However, roughly 5% of patients express an FGFR-1 mutation associated with a less severe phenotype. Cohen Jr. proposed a classification system that clusters Pfeiffer's syndrome into three subtypes based upon their clinical features and degree of severity. Type I represents the classic Pfeiffer syndrome characterized by a turribrachycephalic head shape due to bicoronal craniosynostosis, midface hypoplasia, relative mandibular prognathism, exorbitism, broadly deviated thumbs, and partial soft tissue syndactyly of hands and feet. Although type I is often associated with average intelligence, some patients are mentally disabled. Type II is more severe and is associated with a cloverleaf skull (i.e., Kleeblattschädel) due to involvement of the coronal, lambdoid and sagittal sutures, extreme proptosis often with inability to close the eyelids, broad and medially deviated thumbs and halluces, elbow ankylosis or synostosis, developmental delay and neurological complications. Type III Pfeiffer syndrome is similar to Type II but without a cloverleaf skull; it is believed to be the most severely affected subtype. Both types II and III confer poor prognosis with an increased risk of early death due to neurological or respiratory compromise (45). A review of 28 patients treated at a single institution reported that the distribution of the aforementioned subtypes of Pfeiffer syndrome was as follows: 61% of patients were type I, 25% of patients were type II, and 14% of patients were type III (46).

Saethre-Chotzen syndrome

Unlike the previous syndromic craniosynostosis, Saethre-Chotzen syndrome does not stem from a mutation of the FGFR protein. Instead, it involves the TWIST1 gene, a basic helix-loop-helix transcription factor that lies on chromosome 7p21. However, TWIST is an upstream negative regulator of some FGFRs, such that mutations in TWIST1 lead to premature termination of the protein and increased activity of FGFRs (47,48).

It is characterized by unilateral coronal (18–27%), bilateral coronal (45–76%), or multi-suture (6–18%) craniosynostosis, facial asymmetry, low frontal hairline, eyelid ptosis, and characteristic ear deformities with a small pinna and prominent crus extending through the conchal bowl. Limb abnormalities are rare and are usually minor, not causing severe impairment. They can include syndactyly of the second and third digits on the hand, brachydactyly, clinodactyly, or a broad hallux. Intelligence is often average, except in individuals with large gene deletions who often exhibit some degree of developmental delay (18,49,50).

Because the midface is often of normal morphology in Saethre-Chotzen, this syndrome was referred to by Tessier as "upper Apert." At the same time, the cranial vault is turribrachycephalic, and the supraorbital rim is recessed from the coronal craniosynostosis (18,41).

Treatment of syndromic craniosynostosis

Unlike non-syndromic craniosynostosis, syndromic craniosynostosis is characterized by deformities and complications beyond the cranium per se. In addition to the intracranial hypertension and hydrocephalus, syndromic patients also present with proptosis, hearing loss, airway obstruction and malocclusion. As such, syndromic craniosynostosis are managed by a diverse multidisciplinary care team, including ophthalmologists, audiologists, and dentists (51).

Several surgical techniques are designed to correct the dysmorphology of patients with syndromic craniosynostosis. Fronto-orbital advancement with cranial vault remodeling normalizes the shape of the forehead, advances the orbital bar (protecting the globe), and increases intracranial volume (reducing the risk of intracranial hypertension). Posterior cranial vault distraction is also performed prophylactically at an early stage when intracranial hypertension is suspected. Endoscopic suturectomy with subsequent helmet orthotic therapy is a less invasive alternative to the forementioned techniques. The sub cranial Le Fort III osteotomy or monobloc advancement corrects the midfacial deficiency. Orthognathic surgery is performed to corrects any residual dentofacial defects (51,52).

Mandibulofacial dysostosis (MD)

MD, also known as Treacher Collins syndrome and Franceschetti-Zwahlen-Klein syndrome, is an autosomal dominant disorder of craniofacial morphogenesis. It is estimated to occur in one of every 50000 live births (53,54). Mutations in the *TCOF1* gene and, less commonly, in the *POLR1D* and *POLR1C* genes are responsible for the characteristic phenotype in patients with MD. It is essential to mention that no mutations within these three genes are detected in some patients with MD. Further, the subsequent craniofacial morphogenesis in MD has a wide range of interfamilial and intrafamilial phenotypic variability (55).

Hypoplasia of the facial bones, namely the mandible and zygomatic complex, is pathognomonic for MD. The mandible in MD is retrognathic: the ramus is short, the

ramus body angle is more obtuse, the mandibular plane angle is larger than usual, and a deep antegonial notch is often present. In severe cases, the zygomatic arches may be not even have formed. As a consequence of the retrognathic, hypoplastic mandible, the airway is compromised, and obstructive sleep apnea commonly occurs. Obstructive sleep apnea in Treacher Collins syndrome occurs in both children and adults, and its prevalence and severity do not change with aging (55).

Ophthalmic abnormalities include the characteristic downward slanting of the palpebral fissures (89%) with notching of the lower eyelids (69%) and a scarcity of lid lashes medial to the defect (69%) (56). Although periorbital soft-tissue defects are well described in MD, the true ophthalmologic sequelae are seldom mentioned. These include vision loss (37%), amblyopia (33%), significant refractive errors (58%), anisometropia (17%), refractive errors (86%), and regular astigmatism (36%) in patients with MD (55).

Computed tomographic findings reveal complex auditory deformities in patients with MD. The external auditory canal is shown to be normal (0–15%), stenotic (28–31%), and atretic (54–72%). Middle ear cavity deformities are usually symmetric and consist of hypoplastic, ankylosed ossicles (33–82%) or missing ossicles (22–67%), particularly the malleus and incus. As a consequence of the following auditory malformations, unilateral or bilateral conductive hearing loss is a common functional defect in patients with MD. The inner ear is normally developed in most cases (78–100%). Hence, sensorineural hearing loss is rare in patients with MD (55).

Malocclusion is the most commonly reported dental abnormality in patients with MD; however, other dental abnormalities include widely spaced teeth, mispositioned teeth, or hypodontia (56).

Because MD is characterized by various deformities, multidisciplinary care is needed. To maintain a secure airway, a tracheostomy is placed in some patients. Other treatment options include oxygen supplementation, continuous positive airway pressure (CPAP), and bilevel positive airway pressure. A long-term solution to the airway obstruction and associated breathing abnormalities (i.e., OSA) is mandibular distraction osteogenesis. Alternatively, genioplasty distraction osteogenesis in tandem with hyoid advancement can alleviate the airway obstruction. Orthodontic therapy is needed to address the malocclusion and can be indicated alongside orthognathic surgery. To correct the hearing loss, bone anchored hearing aids can significantly enhance hearing and improve the quality of life for MD patients. In contrast, reconstructive surgery of the ear is ineffective, seldom correcting the associated hearing loss. Calvarial bone grafts are used to reconstruct the zygomatic hypoplasia (57).

Robin sequence (RS)

RS is characterized by a clinical trial of congenital micrognathia, glossoptosis, and airway obstruction. Sometimes, a U-shaped cleft of the soft palate and posterior hard palate is seen in RS patients. Around 85% of RS patients present with a concomitant cleft. RS is estimated to occur in every 8,500 to 20,000 live births (58,59).

It is important to emphasize that RS is not a syndrome but instead is a sequence. A patient with a syndrome is defined as having multiple anomalies, with each anomaly having its unique pathogenesis. On the other hand, a patient with a sequence also has numerous anomalies. Still, all or some of the anomalies are caused secondarily by one of the anomalies present in that person. The primary pathology in RS is the micrognathia, from which the sequelae of anomalies result. For instance, the micrognathia causes the tongue to remain high and retroposed, impinging against the nasopharynx. This impingement decreases the cross-sectional area of the oropharynx, limiting the flow rate of oxygen during respiration. Hence, breathing problems occur (59,60). The breathing problems in RS vary in severity. While some patients exhibit minimal respiratory symptoms at birth, others have significant airway obstruction that is potentially life-threatening, with stridor, retractions, and even cyanosis. This abnormal position of the tongue also physically prevents the appropriate elevation, medialization, and fusion of the two palatal shelves, usually between the 8th and 10th weeks of gestation. This very mechanical disruption of palatal closure, not any molecular or genetic factor, leads to the palatal cleft.

Approximately 26% to 83% of RS patients will ultimately have an associated syndrome. There are many different syndromes associated with RS, including Stickler, Velocardiofacial (22q11.2 DS), Nagar, and Fetal alcohol syndrome (61).

Respiratory distress is the main culprit to be treated among RS patients. A simple yet highly successful solution to the OSA among RS patients is prone positioning therapy. Among patients whose respiratory distress remains in spite of prone positioning, sleep studies are advised to diagnose OSA. Subsequent treatment options fall into the surgical

or non-surgical categories. Non-surgical options include nasopharyngeal airway, CPAP, and oxygen supplementation. Surgical options are deemed the last resort in the RS treatment algorithm and include tongue-lip adhesion, tracheostomy, mandibular traction, and mandibular distraction osteogenesis. Most children with RS outgrow their airway obstruction as the mandible develops with age, supporting the case against surgery. Feeding difficulty is another notable issue among RS patients and, if severe, can be addressed via a nasogastric feeding tube or a gastrostomy tube (62).

Hemifacial microsomia (HFM)

Gorlin and Pindborg first introduced the term HFM in 1964 (63). HFM is a congenital disorder caused by developmental disorders of the first and second pharyngeal arches that mainly affect the jaws, ears, facial soft tissue, orbits, and facial nerve function (64). HFM is the second most common congenital disorder of the face following CL and palate: the incidence is estimated to be in 1:3,000 to 1:5,000 live births.

Vascular pathogenesis likely underlies HMF. Poswillo suggested hematoma might be involved in the development of HFM in rodents and primates (65). He observed a hematoma at the site of the developing stapedial artery and mandibular hypoplasia among the offspring of CS1 mice treated with triazene during gestation. This vascular phenomenon is supported clinically in humans, as carotid flow was observed to be diminished on the affected side of HFM cases (66). External environmental factors, namely thalidomide, triazene, and retinoic acid, interplay with the proposed vascular pathogenesis and contribute to the development of HMF. While most cases of HFM are *de novo*, familial occurrence in 2–10% of patients suggests a degree of heritability with reported mutations in OTX2, PLCD3, and MYT1 (67).

The clinical hallmark of HMF is the vast phenotypic spectrum of the disorder. There is considerable variability in the extent and severity of the HFM phenotypes; patients diagnosed with HFM can be quite divergent. Although the prefix "Hemi" refers to the half of the face, up to 30% of patients are bilaterally affected, with one side being more deformed than the other (63,68,69).

While a consistent pattern of craniofacial regions is affected in HMF, each region often displays varying hypoplasia degrees, hence the phenotypic heterogeneity that typifies HMF. Over time, many classification systems have been proposed to summarize HMF into a clear and all-encompassing clinical picture that could serve as a useful diagnostic tool. In the 1960s, Pruzansky described a system that classifies patients into three grades according to the mandibular phenotype, precisely the degree of hypoplasia. While type I represents a morphologically normal mandible, particularly the ramus and condyle, it is diminished in size. On the other end of the spectrum, type III mandible represents pronounced distortion or complete agenesis of the ramus. Various clinicians subsequently put forth more comprehensive classification systems that focused on more than one feature of HMF. Nevertheless, they were nebulous and ineffective. The OMENS classification system, developed by Vento in 1991, defied the formidable variability of HMF and can accurately categorize the diverse features of HMF. The OMENS classification focuses on five core anatomical manifestations of HFM, each constituting one letter of the acronym: Orbital asymmetry, Mandibular hypoplasia, Ear deformity, Nerve dysfunction, and Soft-tissue deficiency. Each anatomical manifestation is sub-stratified on a scale from 0 to 3 according to the degree of dysmorphia, which is judged by conventional radiographs, physical examination, and photographs (70).

Mandibular hypoplasia occurs in 49% to 100% of HMF patients. It can manifest as simply inconsiderable flattening of the condylar process or complete absence of the whole condyle, ramus, as well as glenoid fossa. Such deformations of the mandible can impair adequate functioning of the temporomandibular joint (TMJ) (71). This deformation is further exacerbated by the potential loss of muscles of mastication (72). Unilateral hypoplasia of the TMJ in patients with HMF not only disturbs occlusion but also deviates the chin towards the deformation, repositioning the facial midline (72).

Auricular structural disturbances illustrate variability. Microtia (66–99%), defined as a deformed or reduced auricle, and anotia, defined as complete aplasia of the auricle, can both occur in HMF patients. Both disorders can lead to conductive hearing loss (73). Concerning the eye, disorders such as displacement of the orbit, narrowing of the palpebral fissure, colobomas of the upper eyelid or iris with eyelash deficits, unilateral microphthalmia, or even anophthalmia can be observed in HMF patients (74,75).

Similar to the different syndromic craniosynostoses and MD, HFM requires multidisciplinary care. The goals of treatment include achieving facial symmetry, lengthening the hypoplastic ramus, reconstructing the hypoplastic TMJ, and correcting the malocclusion. Ideal timing of surgery

is inconclusive. While early reconstruction in children can benefit their psychosocial development, delaying it until skeletal maturity can achieve better aesthetic results with lower complication rates owing to older patients obeying medical advice more strictly. The specific type of reconstruction is dictated by the severity of HFM. Costochondral cartilaginous rib grafts are harvested to correct the TMJ in Pruzansky type IIb and III patients. Distraction osteogenesis is indicated for the less severe forms (i.e., Pruzansky type I and IIa). Le Fort I osteotomy can be performed to achieve an adequate occlusion. It is also important to correct the ear deformities in HFM patients. Costochondral grafts can establish the cartilage framework and local flaps and can form the soft tissue coverage (76).

Conclusions

Our understanding of craniofacial deformities has dramatically evolved with time as it relates to their etiology, diagnoses, treatment, and management, which has greatly attenuated the burden on the afflicted patients especially as it relates to their quality of life. Nevertheless, craniofacial research is in a constant state of flux as we continue to disentangle the following craniofacial deformities. From identifying novel mutations to more effective treatment modalities, each step brings us closer to the future of the different craniofacial deformities.

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