100 Craniofacial Malformations

KELLY N. EVANS, ANNE V. HING, AND MICHAEL L. CUNNINGHAM

KEY POINTS

- Craniofacial malformations can impact swallowing, breathing, hearing, vision, speech, and development and for some neonates can result in life-threatening airway compromise.
- Early recognition and assessment of craniofacial conditions that include appropriate diagnostic studies, identification of associated health concerns, and family education can have a positive impact on the care of the newborn.
- Timely referral of the newborn with a craniofacial condition for multidisciplinary craniofacial team care is an important step in the provision of coordinated medical and surgical management.

The neonatologist is often the first point of contact for a child born with a craniofacial malformation. Abnormalities of the face and head can be distressing to a new parent, who is immediately wondering, "Is my child going to look, feel, and develop normally?" Having a basic understanding of the relationship between craniofacial abnormalities and feeding, breathing, hearing, vision, speech, and overall development will help the neonatologist begin to counsel a family. Airway compromise is well described in multiple craniofacial syndromes, and early identification can be lifesaving. Prompt recognition of a constellation of anomalies pointing toward a syndrome or diagnosis will result in better targeted evaluations and therapies for that patient. (Tables 100.1–100.2 contain a concise presentation of potential intensive care unit [ICU] issues that may be encountered with certain craniofacial malformations and syndromes.) This chapter highlights the most relevant craniofacial malformations that a neonatologist will encounter. We describe here the epidemiology, genetics, diagnosis, phenotype, and potential ICU issues as well as basic management recommendations to help guide the neonatologist in caring for an infant with craniofacial malformations.

Micrognathia/Robin Sequence

Epidemiology

The triad of micrognathia, glossoptosis, and airway obstruction, originally described in 1923 by Pierre Robin, is known as *Robin sequence* (RS) or *Pierre Robin sequence*. Whether cleft palate is an obligatory feature of RS is debatable. Approximately one-quarter of infants with cleft palate (CP) were found to have RS in a multisite, population-based, case–control study (Genisca et al., 2009). The tremendous heterogeneity and lack of uniformly accepted diagnostic criteria for, or definitions of, RS make it challenging to know the true prevalence. However, estimates of birth prevalence range from 1 in 8500 to 1 in 14,000 births (Bush and Williams, 1983; Printzlau and Andersen, 2004).

Phenotype

RS is an etiologically and phenotypically heterogeneous disorder. More than half of children with RS have an associated syndrome, with Stickler syndrome being the most common. While there is great variation in severity, RS is characterized by the following phenotypic features: micrognathia (small and symmetrically receded mandible), glossoptosis (tongue of variable size falls backward into the postpharyngeal space), and resultant upper airway obstruction, often with a cleft palate (Breugem et al., 2016; Fig. 100.1A–B). Caouette-Laberge et al. (1994) described CP (U-shaped CP more common than V-shaped CP) in 90% of 125 individuals with RS. Infants with RS often have airway obstruction, feeding difficulties, and challenges gaining weight, and they may have associated anomalies, including hypotonia and limb reduction defects. Congenital heart defects are present in up to 25% of babies with RS who die in early infancy (Hennekam et al., 2010a). It has been reported that a portion of individuals with RS experience developmental delay, cognitive impairment, and poorer school achievement; overall morbidity and mortality are higher in syndromic RS or RS with associated anomalies compared with isolated RS (Caouette-Laberge et al., 1994; Persson et al., 2013). Clinical judgment can be made about whether the patient represents "isolated RS," "RS plus," or a syndromic form of RS, and the diagnostic work-up should include investigation of the common associated anomalies and syndromes (Tan et al., 2013; Gomez-Ospina and Bernstein, 2016).

Intensive Care Unit Concerns

In infants with RS the tongue is displaced toward the posterior pharyngeal wall or up into the cleft, resulting in upper airway

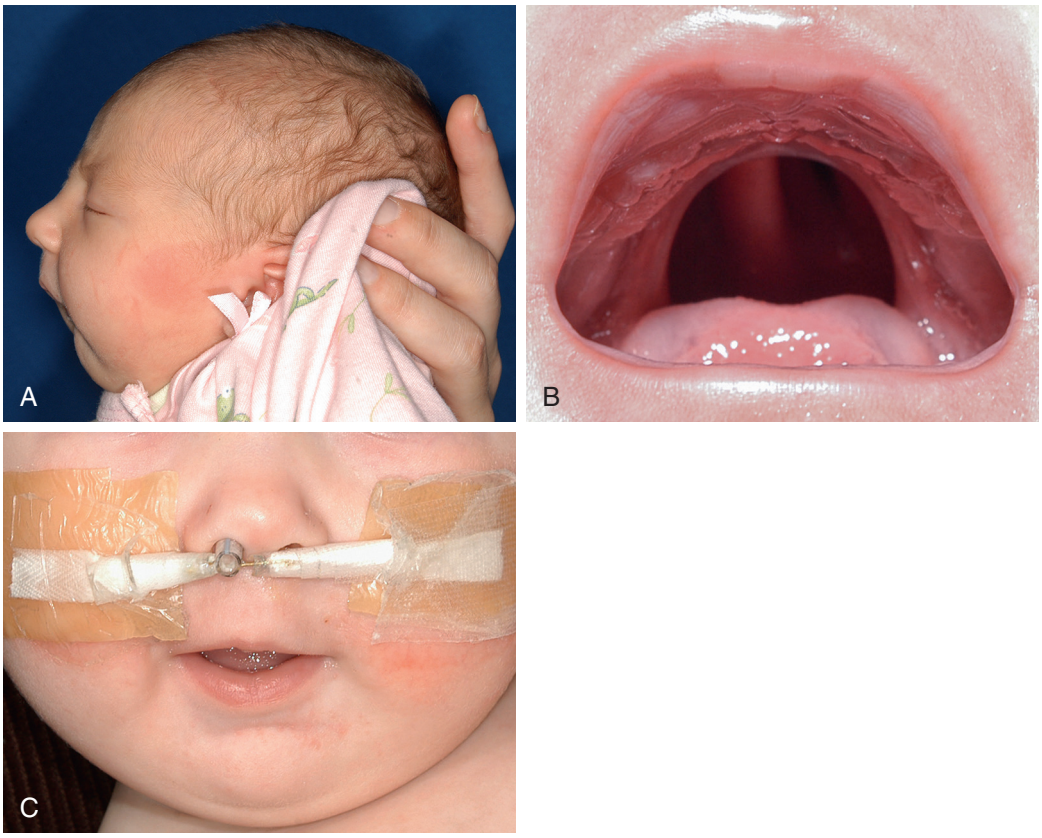
TABLE 100.1 Craniofacial Syndromes Commonly Associated With Cleft Lip and/or Cleft Palate

Syndrome	Phenotype	ICU Issues	OMIM
Robin sequence[a]	Micrognathia, glossoptosis with upper airway obstruction, cleft palate	Airway obstruction, feeding difficulties	na
Stickler syndrome[a]	Cleft palate, micrognathia, glossoptosis (Robin sequence), high myopia, risk of retinal detachment and blindness, midface hypoplasia, hearing impairment, arthropathy, pectus, short fourth and fifth metacarpals	Airway obstruction, feeding difficulties	180300, 604841, 184840, 614134, 614284
22q11.2 deletion syndrome (velocardiofacial syndrome, DiGeorge syndrome)[a]	Cleft palate and submucous cleft palate, small mouth, myopathic facies, retrognathia, prominent nose with squared-off nasal tip, hypoplastic nasal alae, short stature, slender tapering digits	Cardiac anomalies, airway obstruction, feeding difficulties, aspiration	192430, 188400, 611867
Opitz oculogenitolaryngeal syndrome (Opitz BBB/G syndrome)[a]	Hypertelorism, telecanthus, cleft lip and/or palate, dysphagia, esophageal dysmotility, laryngotracheoesophageal cleft (aspiration), hypospadias, bifid scrotum, cryptorchidism, agenesis of the corpus callosum, congenital heart disease, mental retardation	Laryngotracheoesophageal clefting (stridor, feeding difficulties, choking, aspiration)	145410, 300000
Pallister–Hall syndrome[a]	Cleft palate, flat nasal bridge, short nose, multiple buccal frenula, microglossia, micrognathia, malformed ears, hypothalamic hamartoblastoma, hypopituitarism, postaxial polydactyly with short arms, imperforate anus, genitourinary anomalies, intrauterine growth restriction	Laryngotracheoesophageal clefting (stridor, feeding difficulties, choking, aspiration), panhypopituitarism	146510
IRF6-related disorders (including Van der Woude and popliteal pterygium syndrome)	Cleft lip with or without cleft palate, cleft palate only, lower lip pits or cysts, ankyloglossia; popliteal pterygium syndrome will also have popliteal pterygia, bifid scrotum, cryptorchidism, finger and/or toe syndactyly, abnormalities of the skin around the nails, syngnathia and ankyloblepharon	Not anticipated	119300, 119500
CHARGE syndrome[a]	Coloboma of the eye, heart malformations, choanal atresia, growth retardation, genital anomalies, ear abnormalities and/or deafness, facial palsy, cleft palate, dysphagia	Airway obstruction in bilateral choanal atresia, cardiac anomalies, feeding difficulties, aspiration	214800
Smith–Lemli–Opitz syndrome[a]	Cleft palate, micrognathia, short nose, ptosis, high square forehead, microcephaly, hypospadias, cryptorchidism, ventricular septal defect, tetralogy of Fallot, hypotonia, mental retardation, postaxial polydactyly, 2–3 toe syndactyly, defect in cholesterol biosynthesis	Cardiac anomalies, airway hypotonia, and airway obstruction	270400
Ectrodactyly, ectodermal dysplasia, and clefting syndrome	Cleft lip and/or palate, split-hand/split-foot, ectodermal dysplasia (sparse hair, dysplastic nails, hypohidrosis, hypodontia), genitourinary anomalies	Not anticipated	129900, 604292, 129400
Ankyloblepharon, ectodermal dysplasia, and clefting syndrome	Cleft lip with or without cleft palate, cleft palate only, intraoral alveolar bands, maxillary hypoplasia, ankyloblepharon (eyelid fusion), ectodermal dysplasia (sparse hair, dysplastic nails, hypohidrosis, anodontia)	Not anticipated	106260
Orofaciodigital syndrome	Median cleft of upper lip, cleft palate, accessory oral frenula, lobulated tongue with hamartomas, broad nasal root, small nostrils, syndactyly, brachydactyly, postaxial polydactyly, polycystic renal disease, agenesis of the corpus callosum	Not anticipated	311200
Kabuki syndrome[a]	Cleft palate, arched eyebrow, long palpebral fissures, eversion of lateral third of lower eyelid, brachydactyly, short fifth metacarpal, cardiac anomalies, postnatal growth deficiency/dwarfism, mental retardation	Cardiac anomalies	147920, 300867
Fryns syndrome[a]	Cleft lip with or without cleft palate, micrognathia, coarse facies, diaphragmatic hernia, distal limb hypoplasia, malformations of the cardiovascular, gastrointestinal, genitourinary, and central nervous systems	Congenital diaphragmatic hernia, pulmonary hypoplasia; cardiac anomalies	229850

TABLE 100.1 Craniofacial Syndromes Commonly Associated With Cleft Lip and/or Cleft Palate—cont'd

Syndrome	Phenotype	ICU Issues	OMIM
Miller syndrome (postaxial acrofacial dysostosis)[a]	Cleft palate (more than cleft lip), malar and mandibular hypoplasia, downslanting palpebral fissures, lower eyelid coloboma, microtia/atresia, conductive hearing loss, postaxial limb deficiency, absent fifth digit	Airway obstruction	263750
Treacher Collins syndrome (mandibulofacial dysostosis)[a]	Cleft palate, malar and mandibular hypoplasia, downslanting palpebral fissures, lower eyelid coloboma (missing medial lower eyelid lashes), microtia/atresia, conductive hearing loss	Airway obstruction	154500, 613717, 248390
Aarskog syndrome (faciodigitogenital syndrome)	Hypertelorism, widow's peak, ptosis, downslanting palpebral fissures, strabismus, maxillary hypoplasia, broad nasal bridge with anteverted nostrils, occasional cleft lip and/or palate, floppy ears, brachydactyly, clinodactyly, joint laxity, shawl scrotum	Not anticipated	100050
Wolf–Hirschhorn syndrome (4p deletion syndrome)[a]	Cleft lip and palate, coloboma, hypertelorism, growth deficiency, microcephaly, mental retardation, cardiac septal defects	Congenital diaphragmatic hernia, cardiac anomalies, seizures, airway hypotonia/ obstruction	194190
Amnion rupture sequence[a]	Cleft lip and palate, oblique facial clefts, focal areas of scalp aplasia, constriction bands with terminal limb amputations and syndactylies, occasional anencephaly, encephalocele, and ectopia cordis	Encephalocele, oropharyngeal/airway deformation	217100

[a]Potential ICU issues.
ICU, Intensive care unit; *OMIM*, online mendelian inheritance in man.



• **Fig. 100.1** (A) Infant with Robin sequence and significant micrognathia. (B) U-shaped cleft palate. (C) Infant with Robin sequence and a nasopharyngeal tube in place.

obstruction. The tongue can act as a ball valve, leading to inspiratory obstruction. In addition to glossoptosis, other mechanisms may contribute to airway obstruction in individuals with RS, such as pharyngeal hypotonia and airway inflammation from associated gastroesophageal reflux. The principal physiologic sequelae of RS are the inability to effectively feed and breathe due to airway obstruction. In the immediate neonatal period, patients with RS may have increased inspiratory work of breathing, cyanosis, and apnea. Obstruction is more common in the supine position and can be exacerbated during feeding and in sleep or in any state where there is loss of pharyngeal tone. Chronic obstruction can lead to failure to thrive, carbon dioxide retention, pulmonary hypertension, and eventually right-sided heart failure (cor pulmonale).

Airway obstruction is the main cause of feeding and growth issues in infants with RS. Feeding problems can also be related to abnormal coordination, primary swallowing dysfunction, and pharyngeal hypotonia, and suction mechanics are complicated by the presence of a cleft palate. Increased energy expenditures because of the increased work of breathing may lead to failure to thrive if the infant is not receiving adequate caloric intake. Gastroesophageal reflux is common in infants with RS, as it is in other infants who have increased work of breathing.

Management

First and foremost, the airway must be addressed. Placement of a nasopharyngeal (NP) airway or endotracheal tube may be required in an emergency, and it is important to realize that severe, life-threatening airway obstruction can present in the delivery room. Although uncommon, a prenatal diagnosis of micrognathia allows the involvement of neonatologists and otolaryngologists in the delivery room (Costello et al., 2010).

A number of therapeutic maneuvers can be used to stabilize the upper airway in RS, ranging from positioning to surgery. Placing the baby in the prone or lateral decubitus position will often open up the airway and decrease the degree of obstruction. This may improve airway patency and air exchange, which decreases the work of breathing and may also improve tolerance of oral feeding. When prone positioning fails to stabilize the airway, alternative approaches include the use of an NP airway, noninvasive positive pressure, treatment with tongue–lip adhesion (TLA), and mandibular advancement through distraction osteogenesis. Children with isolated airway obstruction at the base of tongue without other medical comorbidities may be considered for mandibular distraction osteogenesis (MDO) (Paes et al., 2013). The surgery consists of surgical osteotomy and placement of distraction device that slowly increases mandibular length and ramus height and brings the base of the tongue forward, thereby increasing the airway space. This procedure will not achieve respiratory stabilization in patients with concomitant airway anomalies, lung disease, central apnea, or the need for positive pressure ventilation. Tracheotomy may be necessary to provide a safe and secure airway in some infants. Treatment protocols differ across institutions (Bookman et al., 2012), and an example of the initial evaluation and clinical team discussion for the neonate with tongue-based airway obstruction is provided in Box 100.1. While the threshold for intervention and the management options differ substantially, most providers agree that most neonates with RS can be treated nonsurgically.

An NP airway provides a temporary way to bypass the infant's airway obstruction (see Fig. 100.1C). An endotracheal tube can be modified so that it can be passed through the nares into the hypopharynx above the epiglottis, allowing oxygenation/ventilation by bypassing the obstruction at the base of the tongue (Parhizkar et al., 2011). The NP airway may prevent the need for more invasive procedures and allows the team to address oral skills and feeding (Wagener et al., 2003). In some institutions the infant is discharged home with an NP airway in place (Abel et al., 2012). Infants are monitored with oximetry, and parents are taught NP airway maintenance (suctioning) and replacement. The NP tube is typically in place for 3 to 6 months or less if symptoms resolve or other interventions become necessary. Airway compromise and stability are assessed by physical examination, CO_2 levels, oxygenation, overnight sleep studies, and growth, monitored over time (Evans et al., 2011).

When airway obstruction is localized to the tongue base and positioning has not improved breathing and feeding, a TLA may be a temporizing measure to minimize obstruction while allowing for mandibular growth (Schaefer and Gosain, 2003). In some institutions, TLA has been shown to have a high initial success rate for correction of airway obstruction in a neonate. However, long-term follow-up indicates that many infants require secondary interventions to manage their feeding and airway (Denny et al., 2004).

The infant's clinical status, perceived need for long-term respiratory support, and failure of less invasive interventions will

• BOX 100.1 Evaluation and Decision Making for Neonates With Tongue-Based Airway Obstruction

Initial Evaluation in the Neonatal ICU:

Physical examination (supine vs prone): attention to craniofacial features, respiratory status, cardiac and limb differences
Evaluation for presence of glossoptosis, stertor, obstructive apnea, and work of breathing
Capillary blood gas and total CO_2 level
Oxygen saturation monitoring
Growth parameters
Dysmorphology evaluation
Craniofacial and otolaryngology consultations
Consider genetics evaluation if there are multiple anomalies or a concerning family history (micrognathia, cleft palate, childhood hearing loss/myopia/joint problems)
Consider airway endoscopy (guided by airway severity and response to interventions)
Consider airway imaging (guided by airway severity and response to interventions)

Multidisciplinary Team Treatment Discussions May Address:

Does the patient need escalation in care to treat airway obstruction?
Have appropriate subspecialty consults and evaluations been obtained? (Varies by institution, but can include specialists with expertise in neonatal intensive care, craniofacial and pediatric care, airway evaluations, airway surgery, jaw surgery, parent/family support)
Should the patient undergo CT to assess the possibility of craniofacial skeleton and MDO (if so, when and how to proceed safely)
Has the distal part of the airway been evaluated to look for other levels of airway obstruction?
Does the patient need a tracheostomy tube, or is he/she a candidate for mandibular distraction?
What is the family and social context?
What will the disposition be once airway has been stabilized?

CT, *Computed tomography;* ICU, *intensive care unit;* MDO, *mandibular distraction osteogenesis.*

determine whether more invasive surgery is indicated (Evans et al., 2011; Cielo et al., 2016). For some neonates, mandibular distraction osteogenesis may be an alternative to tracheostomy. Airway endoscopy helps to delineate the level of obstruction, and computed tomography (CT) of the facial skeleton provides optimal understanding of jaw anatomy and tooth bud position before distraction. Recognition of other airway anomalies or issues, such as laryngotracheomalacia, subglottic stenosis, and poor secretion handling, will affect decision making regarding airway management. Children with RS associated with syndromes, skeletal dysplasia, or neurologic conditions may have more than one factor contributing to their airway obstruction such that a tracheostomy may be the best approach to alleviate respiratory compromise. Thus infants with RS who have airway obstruction unresponsive to positional techniques (side or prone) for whom surgical options are being considered (mandibular distraction versus tracheostomy) should have a comprehensive airway evaluation as well as a diagnostic evaluation for an underlying syndrome or associated malformations that might impact respiratory status and response to therapies.

Nutrition can be maintained with a hypercaloric formula and/or fortified breast milk given by side-lying feeding using a cleft feeder, via a nasogastric feeding tube, or via a gastrostomy tube. Oral feeding can and should be introduced when the airway is stable. Oral stimulation is important to prevent oral aversion. As tone improves, the child gains better control of the tongue, and growth ensues, feeding will become less of a problem. Close observation for symptoms of gastroesophageal reflux with proactive pharmacologic treatment can minimize airway inflammation.

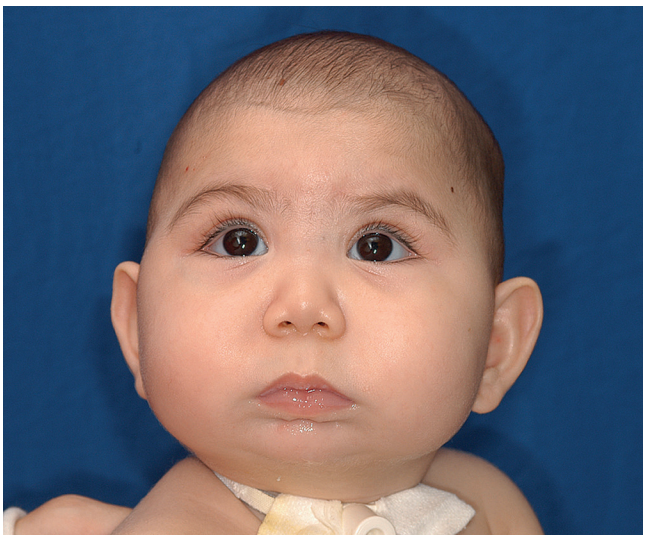
Given the association with cognitive and motor delay, close monitoring of development and referral to early intervention services, such as a Birth to Three program, are recommended.

Stickler Syndrome

The most common syndrome associated with RS is Stickler syndrome. Between 20% and 30% of individuals with RS will have Stickler syndrome (Izumi et al., 2012). Stickler syndrome is most commonly an autosomal dominant (with variable expressivity) connective tissue disorder with ophthalmic, orofacial, auditory, and articular manifestations and has been divided into six types (Stickler syndrome types I and II have ocular findings, type III is nonocular, and types IV to VI are recessive conditions) (Robin et al., 2017).

Stickler syndrome is characterized by cleft palate, hearing loss, arthropathy, joint hypermobility, reduced height, and eye abnormalities, including myopia, cataracts, glaucoma, and retinal detachment. The myopia of Stickler syndrome is usually congenital, nonprogressive, and of high degree. Facial features include flat midface with depressed nasal bridge, short nose, anteverted nares, and micrognathia, telecanthus, and epicanthal folds with a concave facial profile (Fig. 100.2). Sensorineural hearing loss is more common in type II Stickler syndrome.

The diagnosis of Stickler syndrome should be considered in any neonate with RS or a cleft palate, especially when associated with myopia or hearing loss. Spondyloepiphyseal dysplasia is not usually apparent in the newborn period. Mutations affecting one of six genes (*COL2A1, COL9A1, COL9A2, COL9A3, COL11A1*, and *COL11A2*) have been associated with Stickler syndrome, and clinical molecular testing by sequence analysis is available for all types. More then 90% of individuals with Stickler syndrome are found to have a mutation in either *COL2A1* (Stickler syndrome type I, Online Mendelian Inheritance in Man [OMIM] 108300) or *COL11A1* (Stickler syndrome type II, OMIM 604841) (Robin et al., 2017). The diagnosis should also be considered in any newborn with a family history of RS or Stickler syndrome features.



• **Fig. 100.2** Infant with Stickler syndrome, showing a flat face, depressed nasal bridge, and epicanthal folds. This infant also has Robin sequence and required tracheostomy.

In addition to appropriate management of feeding, breathing, and growth (as described earlier in RS), management of Stickler syndrome includes active detection of the ocular features of the syndrome, such as myopia. This is because the associated risk of retinal detachment and blindness are preventable. An initial ophthalmology evaluation is recommended for all children with RS aged between 6 and 12 months or at the time of a definitive molecular diagnosis of Stickler syndrome and then routine surveillance thereafter.

Orofacial Clefting

Epidemiology

Orofacial clefts of the primary and secondary palate are among the most common congenital anomalies. Classified as either cleft lip with or without CP (CL±P) or CP only (CPO), these two phenotypes are thought to be distinct in origin. One case of orofacial cleft occurs in approximately every 500 to 550 births, and on an average day in the United States, 20 infants are born with an orofacial cleft (Tolarova and Cervenka, 1998). Cleft lip and palate is the most common type of orofacial clefting, followed by cleft lip, then CPO, and less prevalent are atypical clefts (macrostomia or lateral cleft, oblique and midline clefts). Unilateral CL±P is more common than bilateral involvement (Genisca et al., 2009). A bifid uvula can be a normal variant, found in 2% to 4% of births, but can also be a sign of an associated submucous cleft palate, which can have the same functional impact as an overt CP (Hennekam et al., 2010a, Ch 21).

The causes of most orofacial clefts are unknown and are nonsyndromic (isolated) in 70%–75% of infants with CL±P and approximately 50% of those with CPO (Tolarova and Cervenka, 1998; Leslie and Marazita, 2013). Neonates with orofacial clefting

who are born prematurely or have low birth weight may have a higher incidence of associated congenital malformations (Milerad et al., 1997). Racial and ethnic variation in the prevalence of clefts has been described, with the highest prevalence of CL±P found in Native Americans, followed by whites and Hispanics, and the lowest overall prevalence of CL±P demonstrated in African Americans (Croen et al., 1998). The cause of nonsyndromic clefts is complex and multifactorial, likely resulting from interaction between environmental and genetic factors. Known environmental risk factors include maternal tobacco smoking, alcohol use, anticonvulsant treatment, and nutritional status. Recognition of contributing genetic factors such as a mutation in *IRF6* resulting in Van der Woude syndrome is increasing, and the impact of folate supplementation as an environmental modulator is under investigation (Mossey et al., 2009; Wehby and Murray, 2010). Although many candidate genes have been described, there is no routinely recommended genetic testing for a child with isolated CL±P in the absence of a family history. Recurrence risk information for the parents of a child with CL±P or for the affected individual is dependent either on the specific syndrome/genetic diagnosis or on empiric risks for those with nonsyndromic clefting. For a family with just one child affected with CL±P, the recurrence risk is 2%–5% for a subsequent child, increasing to 10%–15% if there are other family members with clefts. The recurrence risk is slightly less if the child has CPO (Harper, 2011).

Anatomy

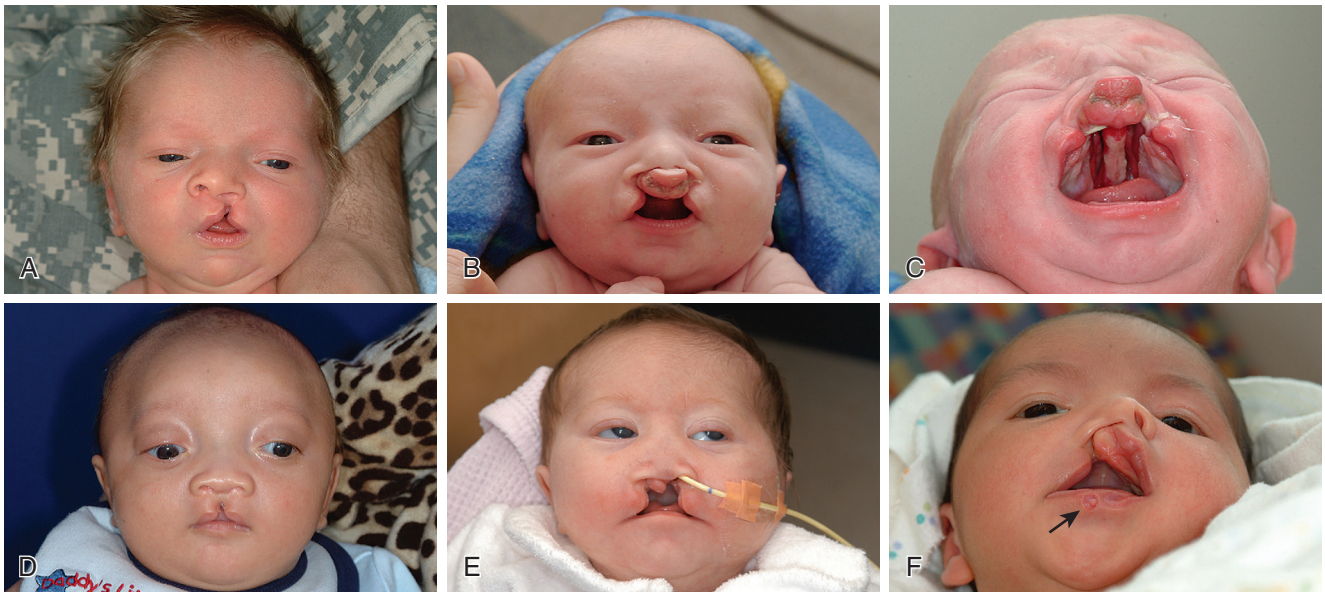
The embryologic development of the primary palate begins very early in gestation, and the upper lip and primary palate have usually fused by the seventh week of gestation. A failure of fusion of the medial and lateral nasal processes with the maxillary process produces CL±P. Clefts can affect the primary palate (lip, alveolus, or anterior portion of the hard palate that extends to the incisive foramen) and secondary palate (posterior hard palate and soft palate). Clefts of the primary and secondary palate can be unilateral or bilateral and complete or incomplete. A complete cleft of the primary palate leaves no residual tissue between the alar base and the lip, whereas an incomplete cleft does not extend through the floor of the nose (Fig. 100.3A–C, F).

Phenotype

The cleft of the primary and secondary palate will affect facial shape and growth (see Fig. 100.3A–C). Children with CP are at increased risk of eustachian tube dysfunction, recurrent otitis media, and acquired hearing loss, as well as speech issues later in childhood. Associated dental findings include hypodontia and, less commonly, natal teeth. Feeding difficulties, nasal regurgitation of feeds, and difficulty gaining weight may occur in infants with a CP (submucous and overt clefts of the palate).

Lateral facial clefting or macrostomia is pathogenically distinct from isolated cleft lip/palate and is often associated with syndromes, including craniofacial microsomia (CFM) and Treacher Collins syndrome (TCS). Amniotic rupture sequence can be associated with oblique facial clefts and may be associated with underlying central nervous system (CNS) malformations and transverse limb anomalies.

A true median cleft of the upper lip is the rarest type of facial clefting (see Fig. 100.3D). Midline clefting can be associated with other congenital defects as can be seen in orofaciodigital syndrome and frontonasal dysplasia (FND), and CNS malformations are common in children with midline clefts. Some midline clefts are not true clefts but represent hypoplasia or agenesis of the primary palate or premaxillary agenesis, which can be associated with holoprosencephaly (HPE) sequence (see Fig. 100.3E). Infants with HPE often have a depressed nasal tip and a short columella and appear hypoteloric (compared with FND or frontonasal encephalocele, where midline clefting may



• **Fig. 100.3** (A) Infant with a unilateral incomplete cleft lip. (B, C) Infant with bilateral complete cleft lip and palate. (D) Infant with midline cleft and hypertelorism. He also has a frontonasal encephalocele. (E) Infant with premaxillary agenesis and holoprosencephaly. (F) Infant with Van der Woude syndrome with unilateral complete cleft lip and a lip pit (*arrow*).

be present, but the infant has a broad nasal tip and/or columella and hypertelorism).

Orofacial clefting is rarely associated with clefting of the airway structures, such as cleft larynx or extension of clefting into the trachea. Opitz G/BBB syndrome is a multiple congenital anomaly syndrome characterized by facial anomalies (100% will be hypertelorism and 50% will have CL±P), genitourinary abnormalities (90% will have hypospadias), and laryngotracheoesophageal (LTE) defects (present in 70%) (Meroni, 2011). Autosomal dominant (OMIM 145410) and X-linked recessive (OMIM 300000) forms of Opitz G/BBB syndrome are recognized. Pallister–Hall syndrome (PHS; OMIM 146510) is characterized by a constellation of findings that include hypothalamic hamartoma (resulting in seizures and pituitary dysfunction), polydactyly, airway clefting, and other anomalies (genitourinary, renal, pulmonary, and imperforate anus). Bifid epiglottis is the most common airway manifestation in PHS, although LTE clefts have been reported. LTE defects may range from LTE dysmotility in mild forms to laryngeal or tracheoesophageal clefts in more severe forms.

ICU Concerns

Most infants with CL±P do not require ICU care. Thus an infant with an apparently isolated cleft who develops significant respiratory or electrolyte abnormalities requiring ICU care should be considered syndromic until proven otherwise. In these infants a genetics consultation should be considered.

The newborn with a midline cleft or premaxillary agenesis is at risk of serious underlying CNS anomalies, including HPE. In the presence of HPE, detection of associated medical issues is important. Endocrine abnormalities can arise because the midline malformation affects the development of the hypothalamus and the pituitary gland. Clinical manifestations can include growth hormone deficiency, adrenal hypoplasia, hypogonadism, diabetes insipidus, and thyroid deficiency. Neurologic manifestations that warrant close attention include seizures, hypotonia, spasticity, autonomic dysfunction, and developmental delays.

With an LTE cleft, there is longitudinal communication between the airway and the esophagus, allowing tracheal aspiration of oral contents, including saliva and feeds. Clefting of the larynx may result in stridor, a hoarse cry, respiratory distress, swallowing dysfunction, feeding difficulties, regurgitation, and aspiration, hypoxia, recurrent pneumonias, and eventually severe respiratory compromise if unrecognized. An infant boy with hypertelorism, hypospadias, orofacial clefting, and symptoms of airway obstruction or aspiration should be evaluated for Opitz syndrome. Infants with PHS may also have respiratory distress due to airway clefting, as well as other potentially life-threatening clinical manifestations such as seizures and severe panhypopituitarism. Genetic evaluation and consideration of molecular testing for Opitz syndrome and PHS can be coordinated through a geneticist.

Management

The specifics of management of orofacial clefting are center specific. Because of the potential impact of the orofacial cleft on breathing, eating, hearing, speech, facial growth, and dental health, it is recommended that infants and children with clefts be referred to a multidisciplinary care team for long-term management. In remote areas, the nearest cleft team may be found through the American Cleft Palate-Craniofacial Association (ACPA) team listings (American Cleft Palate-Craniofacial Association, 2017). Overviews of recommended team care for patients with cleft lip/palate can be accessed electronically (American Cleft Palate-Craniofacial Association, 2009; The Center for Children with Special Needs, 2010).

On the initial assessment, the provider should assess the cleft and examine the infant for dysmorphic features and other anomalies. Hearing should be evaluated by evoked otoacoustic emissions or by brainstem auditory evoked response if the newborn does not pass the initial hearing screen. A neonate with a complete cleft lip should be evaluated by a craniofacial or cleft team in the first 2 weeks of life, and some centers offer taping or presurgical molding (nasoalveolar molding) that can be initiated in this period.

Many mothers will be able to breastfeed an infant born with an isolated cleft lip. Breastfeeding a baby with CP (with or without cleft lip) will prove extremely challenging because the open palate will not generate the negative pressure needed for sucking. Thus infants with CP with or without cleft lip should be offered expressed breast milk or infant formula with use of a specialized cleft feeder. A variety of cleft nipples/bottles have been devised to allow oral feeding, including the CP nurser (squeeze bottle), Haberman feeder, Pigeon bottle, and Dr. Brown bottle with a cleft valve (http://www.cleftline.org/who-we-are/what-we-do/feeding-your-baby/). Infants with CP tend to swallow more air during feedings. The child should feed in an upright position, as gravity will help prevent nasal regurgitation. If the child is still having difficulty feeding, a feeding specialist should be consulted. Adequate weight gain is important for overall health and readiness for the surgical procedures that occur in the first year of life. Newborns with clefts are considered nutritionally high risk, and a dietitian should be consulted to help determine caloric needs and to closely monitor growth.

In general, surgical closure of the lip and nasal deformity is done within the first 6 months of life. Palatoplasty typically occurs between 9 and 12 months of age to optimize speech and language development.

If there are concerns about airway clefting or anomalies of the larynx or trachea, a chest X-ray should be obtained and the airway evaluated, in addition to appropriate evaluation of associated anomalies. Microlaryngoscopy with the patient under general anesthesia remains the gold standard in the diagnosis of a laryngeal cleft (Johnston et al., 2014). Given the risk of gastrointestinal manifestations such as gastroesophageal reflux, dysmotility, and aspiration, antireflux precautions should be initiated in infants with suspected or confirmed LTE defects. Early diagnosis and proper repair of the laryngeal cleft are essential to prevent injury to the lungs. Significant LTE defects will need to be managed surgically, and tracheostomy may be necessary initially to ensure airway stability and safety.

In the presence of a midline cleft, it is important to evaluate the patient for underlying CNS malformations such as HPE. In any child with a midline cleft or facial features consistent with premaxillary agenesis/hypoplasia, CNS imaging (CT or MRI) is recommended. Consultation with a geneticist or genetic counselor may provide insight into the genetics, molecular testing options, and recurrence risk of HPE. Treatment of HPE is supportive and based on symptoms. The outcome depends on the severity of HPE and the associated medical and neurologic manifestations.

Syndromes Associated With Cleft Lip and/or Palate

It is estimated that there are more than 400 syndromes associated with orofacial clefts (Hennekam et al., 2010a). The frequency

with which associated malformations are encountered with CL±P is approximately 25% (Genisca et al., 2009). In approaching diagnosis of a syndrome, one should categorize the type of cleft (CL±P, U-shaped or V-shaped cleft palate, or more atypical orofacial cleft) and look for any other malformations. Table 100.1 describes the syndromes most commonly associated with clefting and the key features, potential ICU issues, and OMIM database classification. The OMIM database at the National Library of Medicine is a comprehensive collection of more than 15,000 human genes and genetic phenotypes. A referral to a clinical geneticist is recommended when an underlying diagnosis is suspected but not established.

22q11.2 Deletion Syndrome

Epidemiology and Genetics

22q11.2 deletion syndrome is a genetic condition with an estimated prevalence of 1 in 1000 births in which affected individuals are missing a region (typically 3 Mb, encompassing approximately 40 genes) on one copy of chromosome 22 (Carlson et al., 1997; McDonald-McGinn et al., 2015). Before the availability of genetic testing for this condition, individuals with clinical features of 22q11.2DS were classified under a range of other clinical syndromes, such as DiGeorge syndrome, velocardiofacial syndrome, and Shprintzen syndrome. Subsequently, a subset of children with overlapping features in these conditions (such as congenital heart disease and cleft palate) were also noted to share a deletion on chromosome arm 22q. It was later discovered that the most children in whom either DiGeorge syndrome or velocardiofacial syndrome has been clinically diagnosed share the deletion on one copy of chromosome 22. It has been estimated that more than 90% of individuals with "classic" features of 22q11.2DS have a detectable 22q deletion (McDonald-McGinn et al., 2013). 22q11.2DS is associated with more than 180 clinical features, and phenotypic variation is a hallmark of this genetic condition (McDonald-McGinn et al., 2015).

Phenotype

In neonates, 22q11.2DS presents in various ways. In some infants this condition is diagnosed prenatally. Testing may occur as part of the evaluation for fetuses with congenital heart disease or because of a parental history of 22q11.2DS. The clinical indications for genetic testing for this condition in neonates frequently include congenital heart malformations (particularly conotruncal anomalies), seizures secondary to hypocalcemia, dysphagia, cleft palate, and/or respiratory distress secondary to upper airway obstruction. 22q11.2DS commonly has multiorgan system involvement, including cardiac and palatal abnormalities, immune differences, endocrine and gastrointestinal problems, and later-onset conditions across the life span, including variable cognitive deficits and psychiatric illness. In this section, we focus on the evaluation of infants with craniofacial characteristics suggestive of 22q11.2DS.

Several craniofacial features have been observed in individuals with 22q11.2DS; however, many of these are subtle and may not be apparent in the newborn period. Common features identified on the newborn physical examination include cleft palate, small, overfolded helices, and tapered fingers. Other clues to the diagnosis include dysphagia and/or nasal regurgitation (even in the absence of an overt cleft palate), congenital heart disease (most commonly conotruncal anomalies), and hypocalcemia.

An estimated 8% of infants with CP have 22q11.2DS (Hennekam et al., 2010b). For this reason, recommendations differ regarding routine testing of infants with isolated cleft palate. Most agree, however, that molecular testing is indicated for children with a CP in combination with any of the other features that can be observed in 22q11.2DS. The accurate identification of 22q11.2-associated disorders impacts medical surveillance, management, and counseling. Clinical testing with chromosomal microarray or multiplex ligation-dependent probe amplification will capture deletions, duplications, and smaller changes including those that would not be detected with fluorescence in situ hybridization for 22q deletion.

Evaluation and Management

Families of infants, for whom there is a high clinical suspicion and those testing positive for this deletion, should receive genetic counseling. Individuals with 22q11.2DS should undergo studies to identify associated health concerns. These screening evaluations include a total lymphocyte count (low absolute lymphocyte count necessitates evaluation of T-cell and B-cell subsets and referral to an immunologist), hematocrit, platelet count, and total and ionized calcium levels to screen the infant for hypocalcemia. Additional studies include echocardiogram to evaluate the infant for congenital heart malformations and renal ultrasonography. Newborns should have a palatal examination to evaluate them for overt or submucous clefting, as well as a diagnostic hearing test. Infants with evidence of dysphagia (even in the absence of a palatal cleft) benefit from an evaluation by a feeding specialist to determine if a swallow study is needed or if a cleft bottle would be helpful. Additional recommendations for screening evaluations and management have been outlined by McDonald-McGinn et al. (2015).

• BOX 100.2 Specialties of the Members of a Craniofacial Team

Pediatrics	Otolaryngology
Nursing	Plastic surgery
Social work	Neurosurgery
Genetics	Ophthalmology
Nutrition	Oral surgery
Feeding	Dentistry
Speech pathology	Orthodontics
Audiology	Psychology

Craniosynostosis

Definitions/Epidemiology

Craniosynostosis refers to the premature fusion of one or more cranial sutures (metopic, sagittal, right or left coronal, or right or left lambdoid) that normally separate the bony plates of the cranium. The birth prevalence of all craniosynostoses is estimated to be 1 in 2500 live births (Boulet et al., 2008).

Typically, patent sutures allow the calvaria to expand as the brain grows, producing the normal head shape and size. If one or more sutures fuse prematurely, there is restricted growth perpendicular to the fused sutures and compensatory growth in the patent sutures, producing an abnormal head shape. Craniosynostosis is a heterogeneous disorder with significant health consequences that range from an abnormal head shape and increased intracranial pressure (ICP) to secondary visual and intellectual impairments. Known causes of primary craniosynostosis include monogenic and chromosomal abnormalities as well as environmental factors. Nonsyndromic single suture craniosynostosis accounts for 85% of patients. Syndromic

TABLE 100.2 Craniosynostosis Syndromes and Potential Airway Compromise

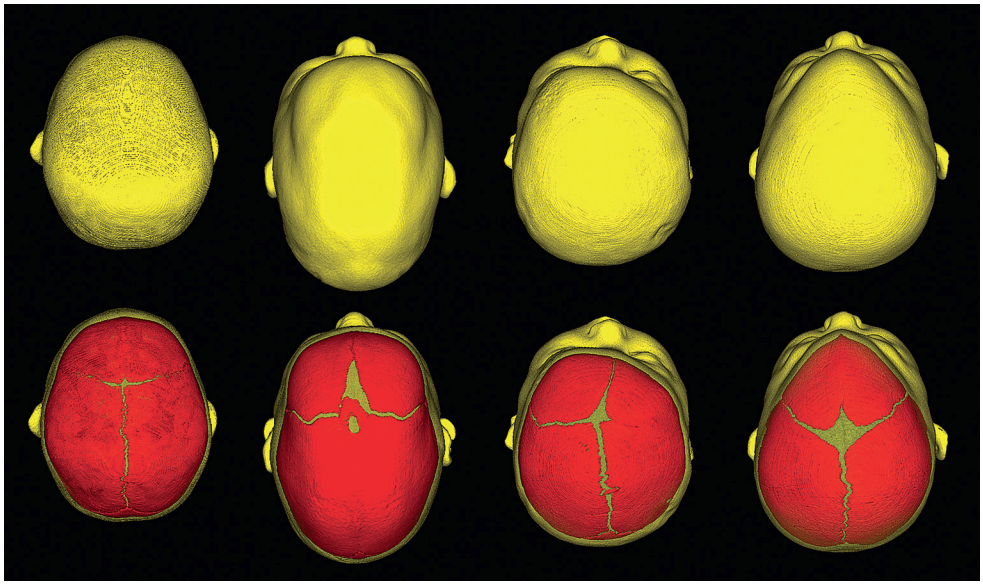
Syndrome	Key Features	Tracheal Abnormalities	Midface Hypoplasia	OMIM
Apert syndrome[a]	Craniosynostosis (coronal > lambdoid > sagittal), acrobrachycephaly (steep, wide forehead and flat occiput), proptosis, hypertelorism, exotropia, trapezoid-shaped mouth, prognathism, invariable symmetric syndactyly of hands and feet, variable elbow fusion, cognitive impairment, narrow palate with lateral palatal swellings, widely patent sagittal suture connecting anterior and posterior fontanels	Tracheoesophageal fistula, tracheal cartilaginous sleeve less common	Significant maxillary hypoplasia, obstructive sleep apnea syndrome	101200
Crouzon syndrome[a]	Craniosynostosis (coronal > lambdoid > sagittal), brachycephaly, prognathism, exophthalmos, papilledema, hypermetropia, divergent strabismus, atresia of auditory canals, Chiari type 1 malformation and hydrocephalus	Solid cartilaginous trachea or tracheal cartilaginous sleeve	Significant maxillary hypoplasia, obstructive sleep apnea syndrome	123500
Pfeiffer syndrome types I, II, and III[a]	Craniosynostosis (coronal > sagittal > lambdoid), brachycephaly, hypertelorism, proptosis, broad first digits with radial deviation, variable syndactyly and elbow fusion, cloverleaf skull	Solid cartilaginous trachea or tracheal cartilaginous sleeve	Significant maxillary hypoplasia, obstructive sleep apnea syndrome	101600
Muenke syndrome	Unilateral or bilateral coronal craniosynostosis, brachydactyly, downslanting palpebral fissures, thimble-like middle phalanges, coned epiphysis, carpal and tarsal fusions, sensorineural hearing loss, Klippel–Feil anomaly		Mild maxillary hypoplasia, no airway compromise anticipated	602849
Saethre-Chotzen syndrome[a]	Unilateral or bilateral coronal craniosynostosis, acrocephaly, brachycephaly, low frontal hairline, hypertelorism, facial asymmetry, ptosis, characteristic ear (small pinna with a prominent crus), fifth finger clinodactyly, partial 2–3 syndactyly of the fingers, duplicated halluces		Maxillary hypoplasia	101400
Carpenter syndrome	Craniosyvnostosis (coronal > lambdoid > sagittal), hypertelorism, proptosis, brachycephaly, brachydactyly, preaxial polysyndactyly, mental retardation		Maxillary hypoplasia	201000
Jackson–Weiss syndrome	Craniosynostosis (coronal), acrocephaly, hypertelorism, proptosis, midface hypoplasia, radiographic abnormalities of the foot including fusion of the tarsal and metatarsal bones, 2–3 syndactyly, broad short first metatarsals and broad proximal phalanges		Maxillary hypoplasia	123150

[a]Significant risk of airway morbidity.
OMIM, Online mendelian inheritance in man.

craniosynostosis may involve single or multiple fused sutures, additional anomalies (such as limb, cardiac, CNS, and tracheal malformations), and developmental delay. Multiple suture involvement is usually considered hereditary even when it does not fit a classic pattern of anomalies. Advances in molecular genetics and next-generation sequencing have led to the identification of causative mutations and genetic pathways in these relatively common congenital anomalies (Twigg and Wilkie, 2015a, 2015b). The genetic cause of craniosynostosis in humans is only partially understood. However, for most syndromic forms, identification of the primary genetic cause and contributing factors is possible with use of clinically available genetic tests (Agochukwu et al., 2012).

Single Suture Synostosis

Sagittal synostosis is the most common single suture synostosis (50%–60%), with a prevalence of 1.5 per 10,000 live births (Boulet et al., 2008). Known risk factors include male sex, intrauterine head constraint, twin gestation, thyroid hormone dysregulation, and maternal smoking. Although uncommon, the most frequently encountered associated anomalies include congenital heart defects and genitourinary tract malformations. Syndromes with synostosis involving only the sagittal suture are rare. Premature union of the sagittal suture hinders normal calvarial expansion, leading to scaphocephaly, an elongated, narrow calvarium, decreased bitemporal diameter, and frontal and occipital bossing (Fig. 100.4). Premature fusion of the suture before birth leads to abnormal head shape in the newborn period. A breech-positioned neonate can have scaphocephaly or dolichocephaly that may mimic sagittal synostosis. However, in sagittal synostosis, frontal bossing and biparietal narrowing progress, whereas the head shape in a breech-positioned infant will normalize in the first month of life. There is a concern that children with single suture synostosis are at risk of elevations in ICP, local brain injury, and later developmental delays. Although school-age children born with single suture craniosynostosis have been found to have evidence of mild developmental delays, the pathogenesis and direct relationship to synostosis have not been determined (Speltz et al., 2015).



• **Fig. 100.4** Head shapes in single suture synostosis. *From left to right:* normal head shape, sagittal synostosis, coronal synostosis, and metopic synostosis.

Coronal synostosis is the second most common single suture synostosis (20%–30%), with a prevalence of 0.7 per 10,000 live births (Boulet et al., 2008). The skull is notable for a flat supraorbital rim and orbit that appears higher on the affected side, with a frontal bulge on the contralateral side (see Fig. 100.4). The nose often appears to twist away from the coronal fusion. Genetic syndromes are more frequently seen in individuals with coronal synostosis, including Saethre–Chotzen syndrome, Muenke syndrome, and craniofrontonasal dysplasia. All families of children with coronal synostosis should be offered genetic consultation and/or genetic testing to include *FGFR2, FGFR3, TWIST1*, *TCF12*, and *EFNB1* on the basis of clinical examination.

Metopic synostosis (15%–20% of single suture craniosynostosis) has a prevalence of 0.8 per 10,000 live births (Boulet et al., 2008), although recent reports suggest that metopic synostosis may be as common as coronal synostosis (Lee et al., 2012). Risk factors include male sex, twin gestation, and in utero exposure to valproate. Syndromes, associated anomalies, and chromosomal abnormalities occur in approximately one-quarter of individuals with metopic synostosis (Lajeunie et al., 1998; Azimi et al., 2003). Premature fusion of the metopic suture results in a triangular head shape, or trigonocephaly, which features a midline forehead ridge, frontotemporal narrowing, pterion constriction, hypotelorism, and an increased biparietal diameter (see Fig. 100.4). Isolated metopic ridging is common in infancy, does not distort forehead shape, and is not associated with metopic synostosis.

Lambdoid synostosis (3% of single suture craniosynostosis) is the least common form of single suture synostosis. It is characterized by flattening of the ipsilateral occiput, posterior–inferior displacement of the ear, bulge of the mastoid process on the fused side, and a skull base tilted downward on the affected side.

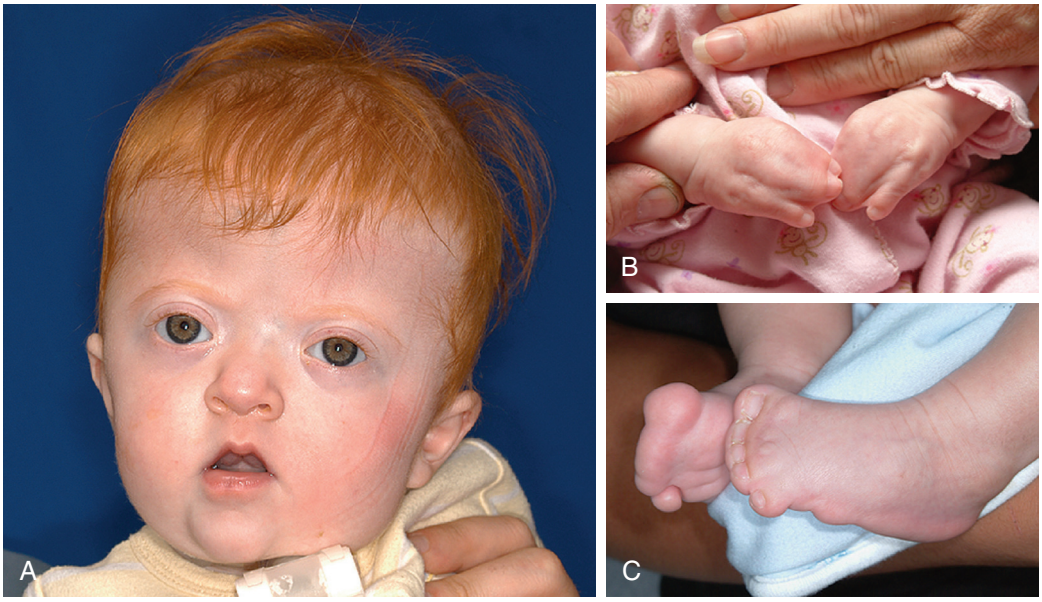
Multiple Suture Synostosis

Multiple suture (or *multisuture*) *synostosis* describes patients who have two or more fused sutures. Although children with multisuture synostosis are more likely to have a known syndromic form of craniosynostosis such as Apert syndrome, Crouzon syndrome, or Muenke syndrome, some have chromosome aberrations or patterns of craniosynostosis with associated anomalies not previously described. With 20 known hereditary forms of craniosynostosis, genetic consultation and counseling are of critical importance in the management of these conditions (Twigg and Wilkie, 2015a, 2015b). Here we briefly discuss select major syndromes with craniosynostosis that may have medical issues in the newborn period. See Table 100.2 for a description of key phenotypic features and potential airway compromise.

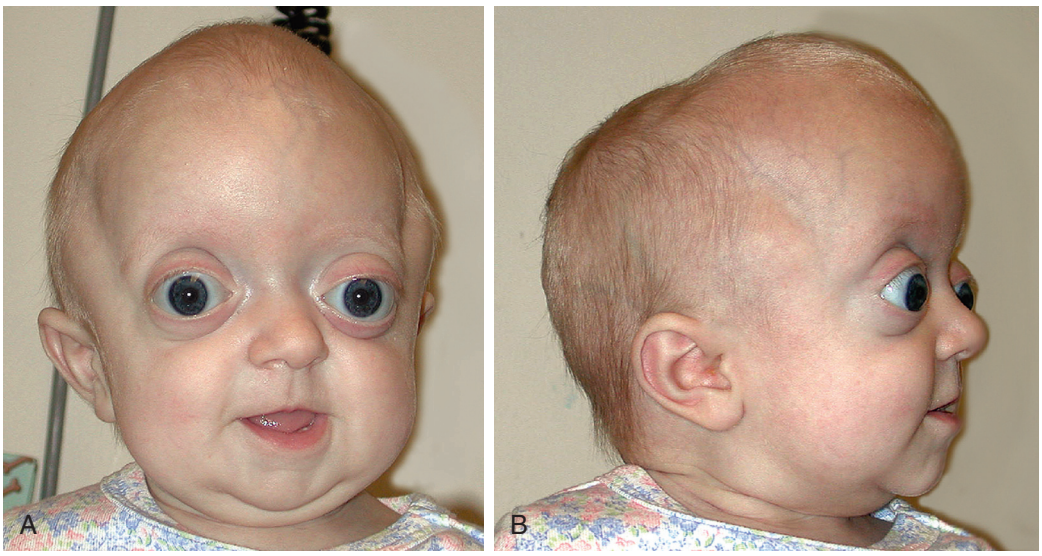
Apert syndrome (OMIM 101200) was initially described as acrocephaly with four-limb syndactyly. It accounts for 4.5% of all craniosynostosis (Hennekam et al., 2010c; Fig. 100.5). It is inherited as an autosomal dominant trait and is associated with advanced paternal age. Neurocognitive outcomes differ, but a moderate to severe degree of cognitive impairment is most common. Four mutations in *FGFR2* causing Apert syndrome have been identified.

Crouzon syndrome (OMIM 123500) is an autosomal dominant condition that demonstrates wide phenotypic variability. Shallow orbits with proptosis are an important diagnostic finding, although this feature may be subtler in the newborn (Fig. 100.6). Significant abnormalities involving the CNS include the frequent presence of a Chiari type 1 malformation, with progressive hydrocephalus resulting in intracranial hypertension. Compared with Apert syndrome, Crouzon syndrome is associated with more extensive suture involvement, smaller cranial volume, and more severe intracranial constraint; however, cognitive development is usually normal. Like Apert syndrome, Crouzon syndrome is caused by mutations in *FGFR2*. A less common form of Crouzon syndrome with acanthosis nigricans skin findings developing in the first 2 years of life is caused by a transmembrane mutation in *FGFR3* (OMIM 612247).

Pfeiffer syndrome (OMIM 101600) is a hereditary craniosynostosis that shares significant overlap, both phenotypically and genetically, with Crouzon syndrome. It is an autosomal dominant inherited disorder with craniosynostosis accompanied by proptosis, broad and deviated thumbs and big toes, and



• **Fig. 100.5** (A) Infant with Apert syndrome, a high and full forehead, proptosis and exotropia, midface hypoplasia, and a trapezoid-shaped mouth. (B, C) Hands and feet in Apert syndrome. Note the syndactyly symmetrically affecting hands and feet. All five digits may be webbed, or a single toe, finger, or thumb may be free.



• **Fig. 100.6** (A) Infant with Crouzon syndrome with brachycephaly. (B) Proptosis is seen in the lateral view.

partial syndactyly of the hands and feet (Fig. 100.7). Mutations in *FGFR1* and *FGFR2* cause Pfeiffer syndrome. Type 1 (i.e., classic) Pfeiffer syndrome involves mild manifestations including brachycephaly, midface hypoplasia, and digital malformations. Type 2 consists of cloverleaf skull, extreme proptosis, digital malformations, elbow ankylosis, developmental delay, and neurologic complications. Type 3 is similar to type 2 but without a cloverleaf skull.

Muenke syndrome (OMIM 602849) is an autosomal dominant syndrome caused by a single P250R mutation in the *FGFR3* gene. Like Apert syndrome, Muenke syndrome is associated with advanced paternal age. Individuals with Muenke syndrome may have coronal craniosynostosis (unilateral or bilateral) or macrocephaly and variable degrees of proptosis, without significant midface hypoplasia (Fig. 100.8).

Saethre–Chotzen syndrome (OMIM 101400) is caused by a mutation in the *TWIST1* gene on chromosome 7. The inheritance is autosomal dominant, and many children with Saethre–Chotzen syndrome will have an affected parent. In addition to craniosynostosis, affected individuals commonly have a low frontal hairline, ptosis, 2–3 syndactyly of the fingers, cervical spine anomalies, and duplicated halluces. Although learning difficulties may be noted, cognitive impairment is not typical of Saethre–Chotzen syndrome caused by intragenic mutations. Children with deletions rather than point mutations often demonstrate significant developmental delays.

• **Fig. 100.7** (A, B) Infant with Pfeiffer syndrome, brachycephaly, a high forehead, midface hypoplasia, proptosis, and ocular hypertelorism. (C) An older child with Pfeiffer syndrome and the typical broad thumbs with radial deviation.

• **Fig. 100.8** (A, B) Infant with Muenke syndrome, acrobrachycephaly due to bicoronal synostosis, and absence of proptosis. (C) Sibling of the infant in (A, B) also with Muenke syndrome; note the downslanting palpebral fissures.

Cloverleaf skull can result from any form of multisuture craniosynostosis. The skull forms a trilobular appearance, as the cerebrum bulges through the sagittal and squamosal sutures, because of craniosynostosis affecting the coronal, metopic, and lambdoid sutures. Cloverleaf skull can be isolated or more commonly associated with a syndrome, and it is estimated that up to 20% of cases represent Pfeiffer syndrome.

ICU Concerns

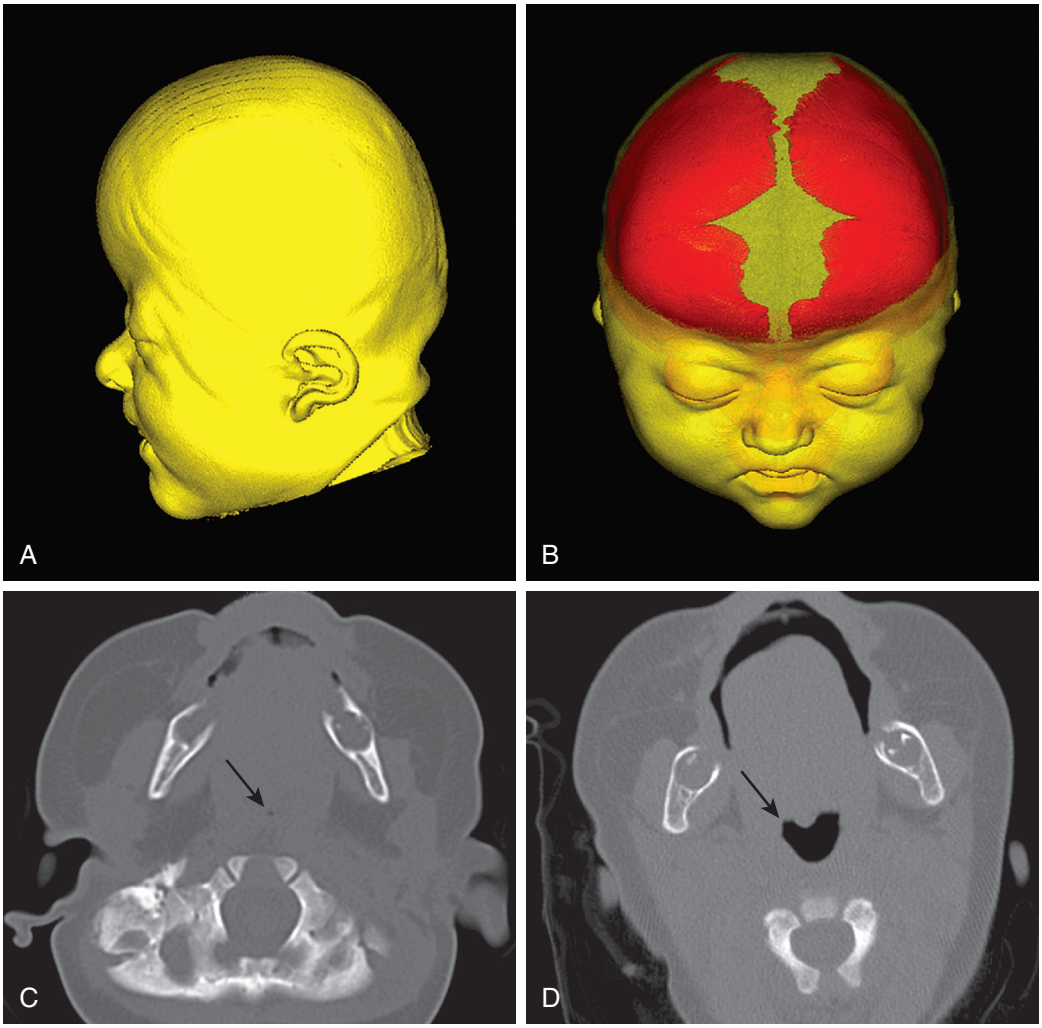
The most significant concerns for the newborn with craniosynostosis are airway compromise (specifically, upper airway obstruction) and intracranial hypertension.

Midface hypoplasia and tracheal anomalies that may be present in syndromic craniosynostosis can lead to significant airway compromise (see Table 100.2). With midface hypoplasia, there is decreased NP/oropharyngeal space because of a small maxilla, narrowing at the level of the posterior choanae and posterior displacement of bony and soft tissue structures, leading to breathing problems, obstructive sleep apnea, asphyxia, and even death (Fig. 100.9). Obstructive sleep apnea is common in Apert, Pfeiffer, and Crouzon syndromes.

Cartilaginous tracheal abnormalities can be present in multisuture craniosynostosis syndromes. Vertically fused tracheal cartilage (also referred to as tracheal cartilaginous sleeve, solid cartilaginous trachea, and stovepipe trachea) in Crouzon and Pfeiffer syndromes may produce a rigid trachea resulting in upper airway stenosis, inability to clear secretions, and increased risk of injury because of decreased distensibility. Characteristic tracheal cartilaginous rings are fused to form a continuous sleeve of cartilage, which may extend from below the subglottis to the carina or bronchus; rarely, the cartilaginous sleeve can begin more proximally, at the level of the cricoid cartilage. Infants with congenital tracheal anomalies may have fixed stridor, apnea, cyanosis, or increased work of breathing because of multilevel airway obstruction.

Neurologic abnormalities such as hydrocephalus and increased ICP may arise, especially in multisuture craniosynostosis. Increased ICP due to constraint of the growing brain within a restricted calvarium is usually of low grade and chronic, causing symptomatic intracranial hypertension when brain growth is rapid during the first 2 years of life. ICP issues in the neonate are not usually life threatening, given the open fontanel and compensatory splaying of normal sutures or erosion of the calvarium, but brain injury and cognitive impairment may result if skull-expanding surgery is not performed.

Hydrocephalus, which is more common in Crouzon and Pfeiffer syndromes compared with other multisuture synostosis syndromes, can occur as a result of obstruction of cerebrospinal fluid at the basal cistern, aqueductal stenosis, or impeded venous flow or when there is an associated Chiari malformation. Hydrocephalus is extremely common in cloverleaf skull. Individuals with multisuture craniosynostosis (particularly Apert syndrome) more commonly have nonprogressive distortion ventriculomegaly or compensated hydrocephalus, which does not require shunting (Collmann et al., 2005). Abnormalities of the corpus callosum and septum pellucidum have been described in Apert syndrome, and neuroimaging and genetic advances will illustrate links between brain architecture, phenotype, and genotype (Fernandes et al., 2016). Seizures presenting in multisuture craniosynostosis syndromes are usually due to encephalopathy rather than increased ICP. Epilepsy is more common



• **Fig. 100.9** (A, B) Three-dimensional reconstruction of a child with Apert syndrome with significant midface hypoplasia, leading to upper airway obstruction. Also notable is acrobrachycephaly due to bicoronal synostosis and the typical pattern of sagittal suture patency. (C) Computed tomography (CT) scan axial slice at the level of the skull base in a newborn with Apert syndrome. The *arrow* pointing to the airway illustrates significant airway obstruction. (D) CT scan of a newborn illustrating a normal airway (*arrow*).

with increasing number of sutures involved, and seizures occur in approximately 10% of individuals with Crouzon syndrome (Cohen, 2000).

Conductive and mixed hearing loss, most commonly due to middle ear disease, ossicular abnormalities, and external auditory canal stenosis or atresia, can be present in syndromic craniosynostosis. Profound sensorineural hearing loss has been described in Saethre–Chotzen syndrome (Lee et al., 2002).

Evaluation

The evaluation of the patient with craniosynostosis includes recognizing and confirming the type of suture fusion, clinical syndrome identification, evaluation for associated anomalies, and preparedness for surgical repair. A craniofacial team made up of the appropriate specialties allows proper planning and coordination so that the patient may receive the best possible care (McCarthy et al., 2012).

The family and prenatal history, including documentation of affected family members, teratogen exposure, maternal thyroid disease, and in utero constraint (oligohydramnios, twins, fetal movement), and the birth history should be ascertained, specifically looking for risk factors.

A detailed physical examination should be performed as part of the initial evaluation, looking for any other anomalies, with specific attention to cleft palate, limb defects, heart defects, and ear anomalies. The assessment of cranial and face shape, mobility of the sutures, presence of sutural ridging, skull base symmetry, and ear position is important. Facial appearance, with particular attention to the degree of maxillary hypoplasia, is important in determining the risk of airway compromise due to midface hypoplasia. If concerning airway symptoms are present, such as snoring, stridor, or apnea, consultation with a sleep specialist and polysomnography may help to quantify the presence and severity of obstructive sleep apnea. Consultation with an otolaryngologist and airway endoscopy may help identify the types and degree of airway narrowing (Wenger et al., 2017). Particular attention to the presence of tracheal malformations, such as vertically fused tracheal cartilage, is crucial in some craniosynostosis syndromes.

With the increased awareness of this condition, the diagnosis of these tracheal malformationsis increasingly made on direct laryngoscopy/bronchoscopy or with MRI.

Neurologic assessment includes ascertaining the history, brain imaging, an audiologic evaluation (early screening for hearing loss in conjunction with regular otologic examinations), ophthalmologic evaluation, and ongoing developmental assessments. In multisuture craniosynostosis, it is important to monitor the patient for any signs or symptoms of increased ICP. Evaluation of the patient for hydrocephalus should be a part of the initial assessment of all children with multisuture craniosynostosis. CT with three-dimensional reconstruction will ultimately confirm the diagnosis of craniosynostosis, delineate the degree of suture involvement, and help with preoperative planning. MRI may be helpful in defining any associated CNS anomalies. Ophthalmology consultation is valuable in management of proptosis, strabismus, or nystagmus and in determining the presence of papilledema or optic atrophy.

In addition to the foregoing general recommendations, syndrome-specific recommendations are outlined as follows. In Apert syndrome a cardiac and genitourinary evaluation is recommended. If proptosis is present, as can occur in Apert, Crouzon, and Pfeiffer syndromes, ocular lubricants may be helpful in prevention of exposure keratopathy. In Apert, Crouzon, Pfeiffer, and Saethre-Chotzen syndromes, associated vertebral anomalies, especially fusions, may be present, detected on spine radiographs, and more accurately visualized with CT imaging. If any limb abnormalities are seen, as in Apert, Jackson–Weiss, Pfeiffer, and Saethre–Chotzen syndromes, radiographs with orthopedic consultation should be obtained.

All individuals with single suture synostosis and developmental delay or associated birth defects should be evaluated by a geneticist to determine association with a clinical syndrome and the role of genetic testing. The families of children with multisuture synostosis caused by known classic craniosynostosis syndromes should be offered appropriate genetic testing and genetic counseling. The remaining children with multisuture synostosis in the absence of a known syndromic form should be offered genetic consultation and possible molecular genetic testing.

Management

Although the specific timing of the surgical treatment may differ between teams, it is generally accepted that individuals with synostosis should undergo cranial surgery in the first year of life. Cranioplasty involves release of fused sutures and repositioning and reconstruction of the calvaria, so as to prevent increased ICP and progressive abnormal craniofacial development. Several techniques, including endoscopic strip craniectomy, calvaria distraction, and traditional cranioplasty, are currently used.

Early recognition of tracheal malformations can be lifesaving (Letsburapa et al., 2010). Awareness of potential airway compromise and proactive airway management are crucial in many craniosynostosis syndromes. Temporizing measures to bypass airway obstruction include placement of nasal stents, endotracheal intubation, and ultimately tracheostomy. Specific airway management in syndromic craniosynostosis will depend on the level and severity of obstruction. Serious caution must be exercised in the placement and care of tracheostomies in patients with tracheal cartilaginous sleeve malformation because of abnormal tissue healing and granulation tissue formation. Midfacial surgery may be necessary in some children who have problems with airway obstruction, swallowing, feeding, and dental malocclusion. This is usually performed later in childhood.

For all individuals with craniosynostosis, we recommend involvement of a craniofacial team, including members specializing in pediatrics, neurosurgery, ophthalmology, oral surgery, orthodontics, otolaryngology, nursing, nutrition, plastic surgery, and social work.

Disorders of the First and Second Branchial Arches

Craniofacial Microsomia

Epidemiology and Genetics

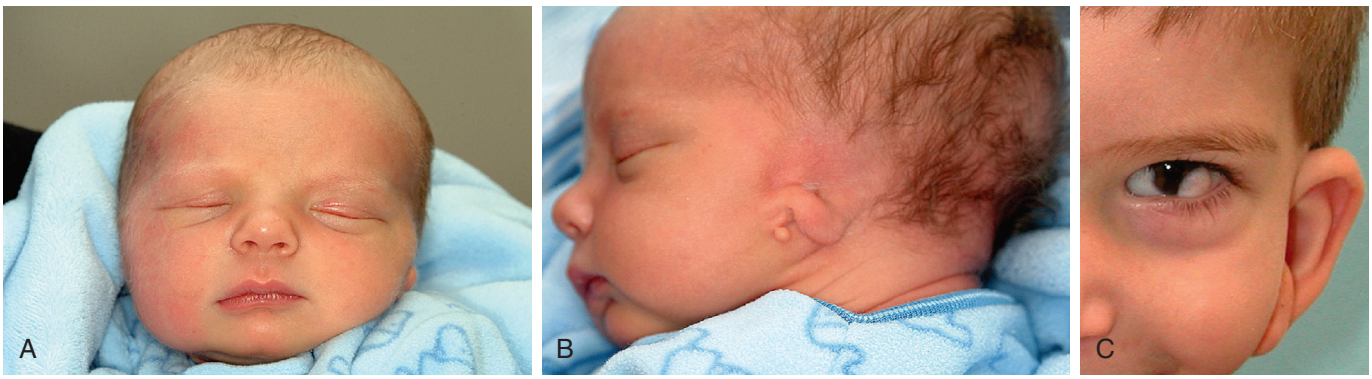
CFM (OMIM 164210), a congenital malformation in which there is asymmetric deficiency in skeletal and soft tissue on one or both sides of the face, is the most frequently encountered form of facial asymmetry. CFM affects approximately 1 in 5600 births (Grabb, 1965). Individuals with features of CFM have been classified under a variety of different diagnoses (hemifacial microsomia, oculoauriculovertebral spectrum, facioauriculovertebral syndrome, first and second branchial arch syndrome, otomandibular dysostosis, Goldenhar syndrome, lateral facial dysplasia) attesting to the phenotypic variability of disorders associated with mandibular hypoplasia. Most often CFM is a sporadic condition with a recurrence risk of approximately 2% for future pregnancies, unless there is a known family history of microtia or CFM (Beleza-Meireles et al., 2014; Heike et al., 2014). Various causes, both environmental and heritable, have been studied, and for most, the cause is thought to be multifactorial.

Phenotype

CFM is primarily a syndrome of the first or second branchial arches, resulting in underdevelopment of the ear, temporomandibular joint, mandibular ramus and body, and mastication muscles. The affected ear may have an external soft-tissue malformation with or without preauricular tags and may be lower in position compared with the ear on the contralateral side. Hearing loss may result from maldevelopment of the ossicular chain and a stenotic or atretic external auditory canal. Second branchial arch defects can involve the facial nerve and muscles of facial expression, which can exacerbate the appearance of facial asymmetry. Even with bilateral facial involvement, there is usually asymmetry (Fig. 100.10A). The presence of microtia can be associated with significant risk of hearing loss on the affected side and increased risk of hearing loss in the contralateral ear (see Fig. 100.10B). Infants with CFM are often born small for their gestational age, and the perinatal history may include polyhydramnios due to fetal swallowing dysfunction.

A common classification system for CFM is the OMENS system, which characterizes the degree of involvement of facial structures: *o*rbital distortion, *m*andibular hypoplasia, *e*ar anomaly, *n*erve involvement, *s*oft tissue deficiency (Gougoutas et al., 2007; Birgfeld et al., 2011). Extracraniofacial anomalies associated with CFM, including renal, cardiac, and vertebral anomalies, are common and will affect recommendations for screening and surveillance.

There can be extreme variability of phenotypic expression, ranging from isolated microtia to significant mandibular hypoplasia, bilateral microtia, clefting, and extracranial involvement. Isolated microtia may represent a forme fruste of CFM. Other craniofacial features include external auditory canal stenosis or atresia, unilateral



• **Fig. 100.10** (A, B) Infant with craniofacial microsomia, mandibular asymmetry, and left-sided microtia. (C) Child with an epibulbar lipodermoid and craniofacial microsomia.

macrostomia (transverse facial cleft leading to lateral displacement of the oral commissure and the most common form of orofacial clefting in CFM), cleft lip and/or palate, temporomandibular joint ankylosis, ankyloglossia, preauricular or facial pits (most common in the distribution of the facial nerve), midface hypoplasia and malocclusion, epibulbar lipodermoids (see Fig. 100.10C), microphthalmia, eyelid and ocular colobomas, facial palsy, and seventh nerve paresis and other cranial nerve palsies. Goldenhar syndrome has historically been described as a subgroup variant of CFM characterized by vertebral anomalies and epibulbar dermoids in addition to the ear and jaw findings. In CFM, deficient growth of the hypoplastic mandible and the compensatory growth of the contralateral maxilla and zygoma contribute to significant facial asymmetry that progresses with growth. Conversely, facial and skull asymmetry caused by deformation (intrauterine or postnatally with plagiocephaly and torticollis) will often reduce with time, repositioning, and treatment of torticollis.

Other Branchial Arch Malformations

Moebius Syndrome

Moebius syndrome (OMIM 157900) is a rare congenital condition affecting approximately 2000 people worldwide (Broussard and Borazjani, 2008). The sixth and seventh cranial nerves are universally affected. Sixth nerve palsy leads to inability to abduct the eyes beyond the midline. This is usually bilateral but may be unilateral or asymmetric. Paralysis of facial muscles results from the seventh nerve palsy. While newborns may have a "masklike facies," the presentation may not be recognized in the newborn period (McKay et al., 2016). Feeding difficulties may result from swallowing and sucking problems, aspiration, and palatal weakness related to more widespread cranial nerve involvement. There have been associations with chest wall abnormalities, including absence of the pectoralis muscle, suggesting a pathogenic relationship with the Poland anomaly (OMIM 173800). Exposure conjunctivitis and keratopathy can occur in children with facial paralysis and lagophthalmos and should be prevented with ocular lubricants. Limb defects occur in half of children with Moebius syndrome, most commonly talipes deformity; however, transverse limb anomalies are also seen. Individuals with hypoglossia–hypodactylia or Hanhart syndrome can have severe limb deformities, ankyloglossia, and temporomandibular joint ankylosis, in addition to Moebius syndrome–like features and micrognathia, and are at risk of significant swallowing dysfunction and airway compromise (Yasuda et al., 2003).

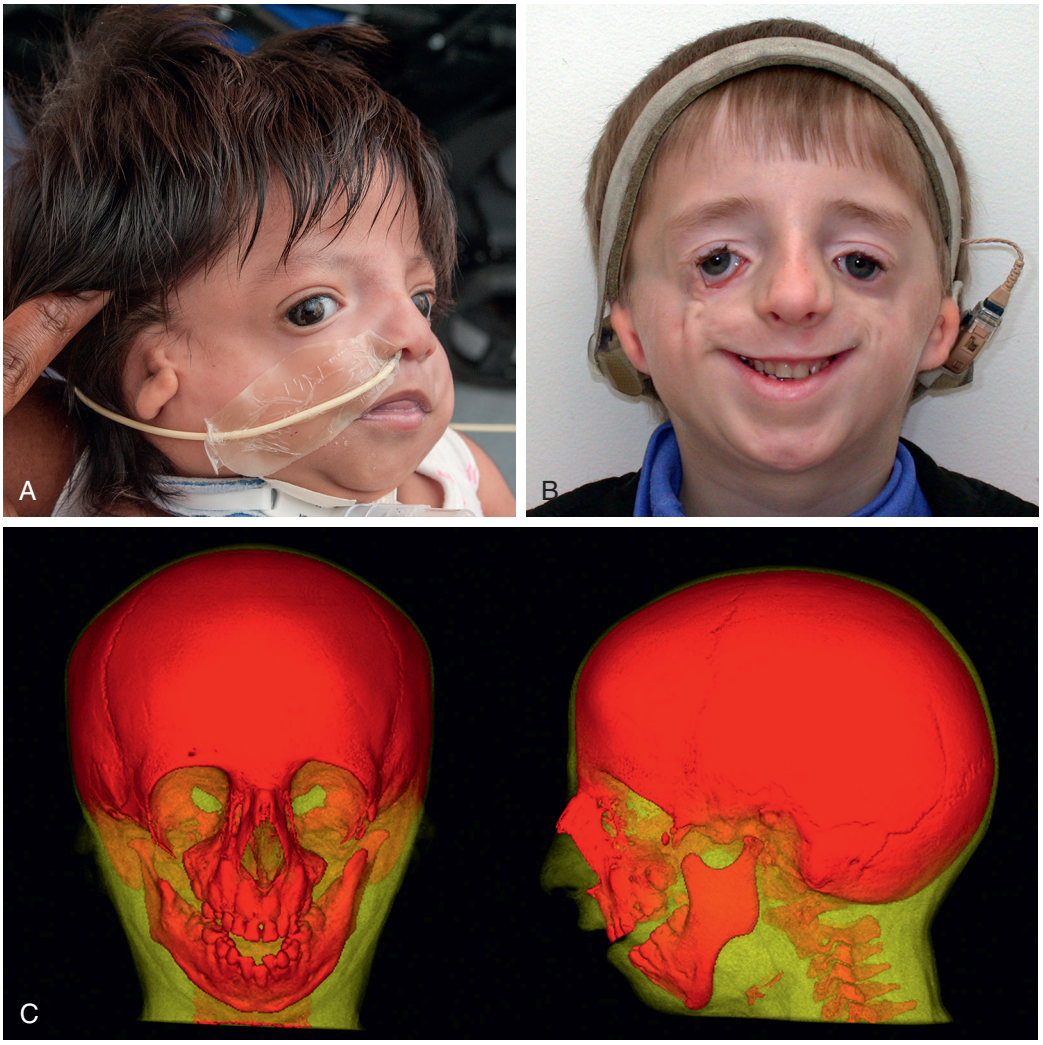
Treacher Collins Syndrome

TCS is most commonly an autosomal dominant disorder of craniofacial development that affects approximately 1 in 50,000 live births (Rovin et al., 1964). As in CFM, the tissues affected in TCS arise from the first and second branchial arches. The major clinical features of TCS include hypoplasia of facial bones (particularly the mandible and zygoma), external ear anomalies or microtia, external auditory canal atresia, bilateral conductive hearing loss, lateral downward sloping palpebral fissures, and lower eyelid colobomas (Fig. 100.11A–B). Hearing loss is present in up to 50% of individuals with TCS (Dixon et al., 2007). In severe cases the zygomatic arch may be absent and CP may occur. Extracraniofacial features are rare in TCS. Mutations in one of three genes *TCOF1, POLR1C*, and *POLR1D* are causative of TCS, and mutations in the *TCOF1* gene account for 71%–93% of affected individuals (OMIM 154500). Diagnosis of TCS is usually made clinically and can be confirmed with genetic testing (Katsanis and Jabs, 2012). In newborns with TCS, airway management may be required to address narrowing of the airway or extreme shortening of the mandible (see Fig. 100.11C). When compared with that in CFM, the mandibular hypoplasia in TCS is usually bilateral and symmetric, leading to increased risk of upper airway obstruction, increased need for tracheostomy, and risk of death in the neonatal period. Choanal atresia or stenosis and severe micrognathia with glossoptosis can lead to airway obstruction in the infant with TCS (Katsanis and Jabs, 2012).

Intensive Care Unit Concerns

Mandibular hypoplasia in CFM can lead to upper airway obstruction that may be obvious on physical examination, presenting with stertor or stridor and increased work of breathing, or may be more subtle, as with snoring obstructive sleep apnea. Bilateral severe mandibular and malar involvement in TCS leads to airway obstruction at the level of nasopharynx and base of the tongue and substantial respiratory compromise.

Infants with CFM may have feeding difficulties that may be related to macrostomia affecting lip seal, palate dysfunction, or more commonly swallow coordination issues and dysphagia related to hypoglossal dysfunction and muscular and bony underdevelopment. Infants with Moebius syndrome may have cranial nerve palsies that affect swallow and oral coordination. These infants are at higher risk of aspiration and should be monitored clinically,



• **Fig. 100.11** (A) Infant with Treacher Collins syndrome (TCS), microtia, severe mandibular and zygomatic hypoplasia, and airway obstruction requiring tracheostomy. (B) An older child with TCS, downslanting palpebral fissures, eyelid colobomas, and bilateral microtia wearing a hearing augmentation device. (C) Three-dimensional reconstruction of TCS. Note the severe mandibular and zygomatic hypoplasia, which may lead to significant airway compromise. Also notable are the orbital defects seen in TCS.

especially if they are failing to thrive or developing any concerns for aspiration or lower respiratory tract disease.

Management

In newborns with suspected CFM, an evaluation for any associated anomalies should be undertaken. All children with external ear anomalies or any evidence of first or second branchial arch abnormalities should undergo a diagnostic hearing evaluation in the newborn period, with follow-up audiometry in the first year of life. If there is any hearing loss, ongoing monitoring of hearing is routine. It is also important to monitor ear health and eustachian tube function in the patent/hearing ear. CT to assess middle and inner ear anatomy is not recommended in the neonatal period. Consultation for ear reconstruction and atresia repair should occur by 4 years of age, although hearing amplification and aural habilitation in hearing loss can be initiated earlier.

Renal ultrasonography and cardiac examination (echocardiogram) should be undertaken in infancy to identify any serious structural malformations. Ophthalmology consultation should be sought for appropriate management of epibulbar lipodermoids, colobomas (if present), and risk of exposure keratopathy. Malocclusion and dental issues will need to be addressed as the child gets older. Children should undergo cervical spine screening radiographs to identify vertebral defects in segmentation. If the newborn has no symptoms of cervical spine abnormality, screening four-view cervical spine radiographs can be deferred until the child is 2 to 3 years old, when cervical vertebrae are more easily imaged. Appropriate cervical spine imaging is recommended in children undergoing surgery before 2 years of age and children with head tilt or signs of vertebral anomalies.

Mild airway obstruction in CFM may be reduced or minimized with prone positioning. However, infants with severe bilateral mandibular hypoplasia may have significant airway compromise and require tracheostomy placement. In cases with significant airway compromise, referral to a craniofacial center to determine optimal and safe airway management should be pursued. For treatment of mandibular underdevelopment, surgery timing is dependent on

the degree of mandibular hypoplasia, mandibular growth, occlusion, and airway involvement. For children with severe hypoplasia of the mandible, bone grafting may be necessary for jaw reconstruction before mandible distraction. Oral feeding should be introduced when the airway is stable. Oral stimulation is important to prevent oral aversion. Given the risk of feeding difficulty and aspiration in infants with malformations of the first and second branchial arches, early consultation with both a dietitian and a feeding therapist is recommended.

CHARGE Syndrome

Epidemiology and Genetics

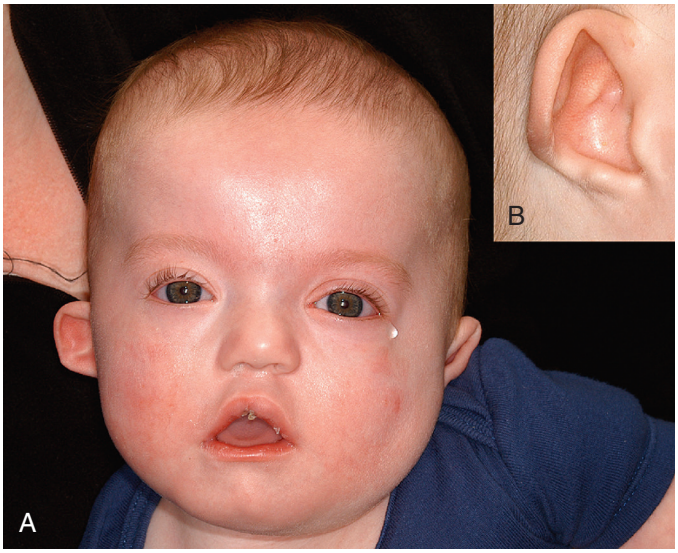
The term *CHARGE* (*c*oloboma, *h*eart defect, *a*tresia choanae, *r*etarded growth and development, *g*enital hypoplasia, *e*ar anomalies/deafness) was first coined by Pagon, given the observation that the associated malformations occurred more frequently together than one would expect on the basis of chance (Pagon et al., 1981). Over time, the facial features and associated malformations were better characterized as a syndrome, with mutations in at least one major gene described (OMIM 214800).

This multiple malformation condition has a prevalence of approximately 1 in 10,000 births (Blake and Prasad, 2006). Although multiple chromosomal aberrations have been reported in children with the phenotype of CHARGE syndrome, mutations in the *CHD7* gene account for 65%–70% of cases. When the diagnosis of CHARGE syndrome is suspected, molecular testing for mutations in the *CHD7* gene can be performed to confirm the diagnosis and provide more information to assist in counseling for the parents and the patient. For children in whom *CHD7* gene testing results are normal, evaluation for chromosomal abnormalities and copy number variants is possible with use of comparative genomic hybridization and single-nucleotide polymorphism array technology (Lalani et al., 2012).

Phenotype

The diagnosis of CHARGE syndrome is based on a combination of major and minor clinical criteria, but the diagnosis should be suspected in any neonate with any of the major characteristics: ocular coloboma (80%–90%), choanal atresia or stenosis (50%–60%), cranial nerve dysfunction or facial palsy (40%–90%, depending on which cranial nerve is involved), or characteristic CHARGE ears (90%–100%) (Lalani et al., 2012). As in other conditions with severe airway obstruction or swallowing dysfunction, polyhydramnios is commonly present prenatally when bilateral choanal atresia is present.

Distinctive ear anomalies (hypoplastic lobes, cupped or lop, position is often low set and posteriorly rotated) or deafness occurs in most individuals with CHARGE syndrome (Fig. 100.12). Hearing loss can be a combination of conductive and sensorineural hearing loss. Other craniofacial features include square face with malar flattening, broad forehead, facial asymmetry, pinched nostrils, full nasal tip, long philtrum, and CP (40%). Ocular colobomas can range from a coloboma of the iris to anophthalmia. Cardiac defects can be a major source of morbidity in infants with CHARGE syndrome and are found approximately 80% of the time. Conotruncal and aortic arch anomalies are the most common congenital heart defects, but atrioseptal defects, ventriculoseptal defects, patent ductus arteriosus, hypoplastic left-sided heart, and vascular rings have also been described.



• **Fig. 100.12** (A) Child with CHARGE syndrome with (B) classic ear malformation—hypoplastic lobes, cupped and low set.

Intensive Care Unit Concerns

The most important postnatal emergency in CHARGE syndrome is bilateral posterior choanal atresia (Blake et al., 2009). Neonate with bilateral choanal atresia will have breathing difficulty and cyanosis within the first hour of life. As with all forms of nasal obstruction, crying relieves the cyanosis because it allows the obligate nose breather to take in air through the mouth; feeding exacerbates respiratory distress. Left untreated, the newborn with bilateral choanal atresia can asphyxiate and die. Symptoms of bilateral choanal stenosis or unilateral atresia may not present until after the newborn period with chronic rhinorrhea or breathing problems associated with respiratory infections. Respiratory distress in a newborn with CHARGE syndrome is usually due to choanal atresia, but other features, including swallowing dysfunction and reflux, can contribute to aspiration and lower respiratory tract disease. These infants may also have micrognathia and glossoptosis, putting them at risk of airway obstruction at the level of the pharynx/hypopharynx. Infants with CHARGE syndrome may require multiple surgical procedures during the first year of life and are at increased risk of postoperative airway events (Blake et al., 2009; Bergman et al., 2010).

Cyanotic heart disease may present in the immediate newborn period because of tetralogy of Fallot, outflow tract anomalies, and interrupted aortic arch. Awareness and recognition of the association of CHARGE syndrome and congenital heart defects are crucial.

A significant cause of morbidity is feeding difficulty. Feeding and secondary growth problems are common in early infancy and may be attributed to swallowing dysfunction, pharyngeal incoordination, gastroesophageal reflux, and aspiration. Cranial nerve palsies (specifically cranial nerves V, IX, and X) may contribute to swallowing dysfunction, and tracheoesophageal fistula (TEF) contributes to aspiration risk. Although it is well described that infants with CHARGE syndrome who survive the newborn period are more likely to survive childhood, the risk of death in infancy remains. Male sex, bilateral choanal atresia, TEF, cyanotic heart disease, atrioventricular septal defects, CNS malformations, and ventriculomegaly have all been associated with reduced life expectancy in individuals with CHARGE syndrome (Tellier et al., 1998; Issekutz et al., 2005; Blake et al., 2009). A study of 77

individuals with CHARGE syndrome found mortality to be 13% (Issekutz et al., 2005).

Management

While the clinical needs will differ, some children with CHARGE syndrome will require intensive medical management and undergo multiple surgical interventions in infancy and early childhood. Early management targets airway stabilization and circulatory support. With this in mind, neonates with CHARGE syndrome require immediate evaluation of their airway and cardiac structure and function. An oral airway should be placed if bilateral choanal atresia is suspected. This can stabilize the airway by bypassing the choanal obstruction. Once the airway has been secured, a confirmatory CT scan of the nasal passages can be obtained; a CT of the temporal bones can be included in conjunction with the facial CT and may reveal the characteristic inner ear findings (Mondini malformation of the cochlea and/or absent or hypoplastic semicircular canals) of CHARGE syndrome. If the oral airway does not allow adequate air entry, endotracheal intubation may be required. In consultation with a pediatric otolaryngologist, transnasal stents may be placed to keep the nasal passages patent in choanal stenosis (and postoperatively after choanal atresia repair). Given the significant risk of cyanotic heart defects, an echocardiogram and cardiology consultation should be obtained to assist in management.

Infants with CHARGE syndrome or suspected CHARGE syndrome should also have audiologic and ophthalmologic evaluations in the neonatal period and should be referred to Birth to Three/early intervention services. Consultation with an immunologist and immune evaluation should occur for the individual with CHARGE syndrome and recurrent infections (Wong et al., 2015). Underdevelopment of the genitals and genitourinary anomalies may be present. If there is a concern for hypogonadism, the pituitary–gonadal axis can be evaluated in infancy and will help determine the option for sex steroid therapy. Screening renal ultrasonography should also be performed (Blake and Prasad, 2006).

Consultations with both a feeding specialist and a dietitian are recommended in the newborn period. If the findings of an oral feeding evaluation or videofluoroscopic swallow study are concerning for swallowing dysfunction or aspiration, supplemental tube feeding should be initiated. With prolonged feeding issues, gastrostomy tube feeding is often necessary. Infants with severe gastroesophageal reflux and/or aspiration risk may be candidates for Nissen fundoplication at the time of gastrostomy tube placement.

Macroglossia/Beckwith–Wiedemann Syndrome

Epidemiology and Genetics

The true prevalence of Beckwith–Wiedemann syndrome (BWS; OMIM 130650) is unknown, but it has been estimated that BWS affects 1 in 13,700 births (Thorburn et al., 1970). This is probably an underestimate, given that there are mild cases of BWS that go undetected. The genetics of BWS is complex and variable. Most cases are sporadic and may result from chromosomal rearrangement, mutations, or epigenetic effects (DNA methylation changes) affecting imprinted genes on chromosome band 11p15.5. Approximately 80% of individuals with features of BWS are found to have an 11p15.5 abnormality by clinically available testing (Shuman et al., 2016). Although there are no consensus criteria for diagnosis of BWS, the presence of macroglossia, overgrowth, and abdominal wall defects suggests the diagnosis of BWS. As children with BWS are at risk of neoplasms in early childhood, recognition and diagnosis of BWS are consequential. Data suggest a possible link between imprinting disorders and assisted reproduction, and thus infants conceived by in vitro fertilization may be at higher risk of BWS (Maher et al., 2003). If there are features of BWS present or a family history of BWS, geneticists may recommend 11p15 methylation studies and chromosome microarray analysis to identify abnormalities of the 11p15 region. Although genetic testing can provide confirmation of diagnosis in 80% of individuals, clinical suspicion of the diagnosis is sufficient for initiation of medical management and tumor surveillance studies. Currently, the frequency of screening study recommendations is independent of the underlying molecular cause; however, this will likely change in the future as children with BWS due to a gain of methylation at imprinting center 1 and paternal 11p15 uniparental disomy have a higher risk of developing tumors (Mussa et al., 2016). At this time, initiation of screening studies and consultation with genetics are recommended (Brioude et al., 2013).

Phenotype

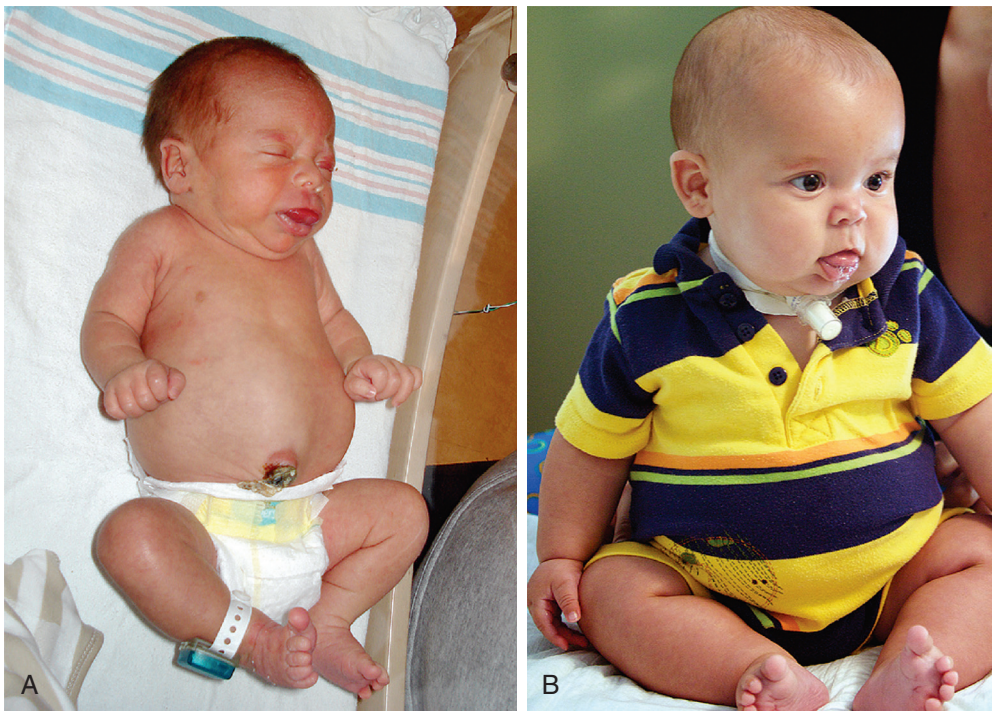
BWS is a disorder of overgrowth with multiple features, including macrosomia, macroglossia, visceromegaly (involving the kidneys, pancreas, liver, spleen, or adrenal glands), abdominal wall defects (including rectus diastasis, umbilical hernia, and omphalocele), hemihypertrophy (asymmetric overgrowth of one or more regions of the body), renal anomalies (structural anomalies and nephrocalcinosis), and adrenocortical cytomegaly (Fig. 100.13). Macroglossia is the most frequent and most obvious manifestation of BWS (present more than 95% of the time) (Elliott et al., 1994). Other craniofacial features include capillary nevus flammeus, metopic ridge, large fontanel, mandibular prognathism, prominent eyes, anterior earlobe linear creases, and posterior helical pits. Less common findings in BWS include CP, cryptorchidism, and cardiac defects (isolated cardiomegaly is more common than cardiomyopathy). The risk of embryonal tumors (Wilms tumor, hepatoblastoma, neuroblastoma, or rhabdomyosarcoma) in childhood is estimated to be 7.5%, of which 95% present in the first 8 years of life, leading to recommendations for tumor surveillance (Firth and Hurst, 2005).

Some features suggestive of BWS may be present prenatally, including polyhydramnios (caused by swallowing dysfunction), preeclampsia, fetal macrosomia, and a large placenta. Prematurity has been reported in 50% of births (Elliott et al., 1994), and in addition to complications of prematurity, the neonate with BWS may develop hypoglycemia and polycythemia.

Intensive Care Unit Concerns

Hypoglycemia due to hyperinsulinemia and islet cell hyperplasia occurs in up to 50% of neonates with BWS and usually develops in the first few days of life (Munns and Batch, 2001). It is critical to detect and treat hypoglycemia in any neonate with features of BWS to prevent seizures and brain injury. Polycythemia can occur and may need to be treated in the early neonatal period.

Obstructive airway symptoms may present in the newborn period if macroglossia is severe. However, airway obstruction more commonly presents later in infancy, outside the newborn period. The enlarged tongue can occlude the upper airway, leading to respiratory distress, apnea, and hypoxia. A large tongue can also contribute to feeding issues, dysphagia, and aspiration. Upper airway endoscopic evaluation by an otolaryngologist and an



• **Fig. 100.13** (A) Premature newborn with Beckwith–Wiedemann syndrome, macroglossia, and rectus diastasis. (B) Same child at 6 months of age. Macroglossia has increased, and he now has a tracheostomy.

overnight sleep study may help understand the severity of airway compromise and guide airway treatment.

Mortality among infants with BWS has been reported to be as high as 21% and is related to complications of prematurity and macroglossia (Shuman et al., 2010).

Management

Hypoglycemia in newborns should be managed according to standard protocols for treating neonatal hypoglycemia. If hypoglycemia persists or is refractory to therapy, additional biochemical testing and consultation with an endocrinologist should be considered (Roženková et al., 2015). Neonates with an omphalocele may require surgery in the first few days of life.

There is no definitive approach to the management of macroglossia. Airway obstruction may be lessened by the placing of the baby on the side or prone. If the infant requires endotracheal intubation, it is important to exercise caution, because macroglossia can affect visibility of airway structures. If macroglossia results in significant airway obstruction or prolonged intubation, tracheostomy may be needed as a temporizing measure to bypass the obstruction. Tongue growth will slow over time, and as jaw growth accelerates, airway compromise should decrease. Some children may benefit from surgical reduction of the tongue, which is usually performed between 2 and 4 years of age, but may be offered as early as 3 to 6 months at some centers.

Referrals to an infant feeding specialist and dietitian are recommended in the infant with severe macroglossia or if the infant is not gaining weight. Although some infants are able to feed orally, others will benefit from supplemental tube feeding.

Although cardiac defects are rare, it is important to perform a thorough cardiac evaluation, including electrocardiogram and echocardiogram if any cardiac abnormalities are suspected.

Surveillance for tumors begins in the neonate with BWS or at the time of diagnosis. Abdominal ultrasonography to assess the patient for organomegaly and baseline CT or MRI of the abdomen should be performed. Abdominal ultrasonography every 3 months is recommended through 8 years of age. In conjunction, staggered serial serum alpha fetoprotein measurements (every 6 to 12 weeks) are recommended through 4 years of age to assist early identification of hepatoblastomas before detection by screening ultrasonography.

Referral to a craniofacial team may be helpful in the management of the airway obstruction in BWS, including evaluation for tongue reduction and facial hemihypertrophy. A geneticist and genetic counselor may recommend genetic testing for confirmation of the diagnosis and/or recurrence risk counseling.

Frontonasal Dysplasia, Hypertelorism, Encephalocele

Embryology

Frontonasal dysplasia (FND; also known as *frontonasal malformation, median cleft face syndrome*, and *frontal nasal syndrome*) is a malformation resulting from abnormal morphogenesis of the frontonasal process. The development of the facial midline is abnormal, leading to ocular hypertelorism and associated craniofacial features. Most cases of FND are sporadic.

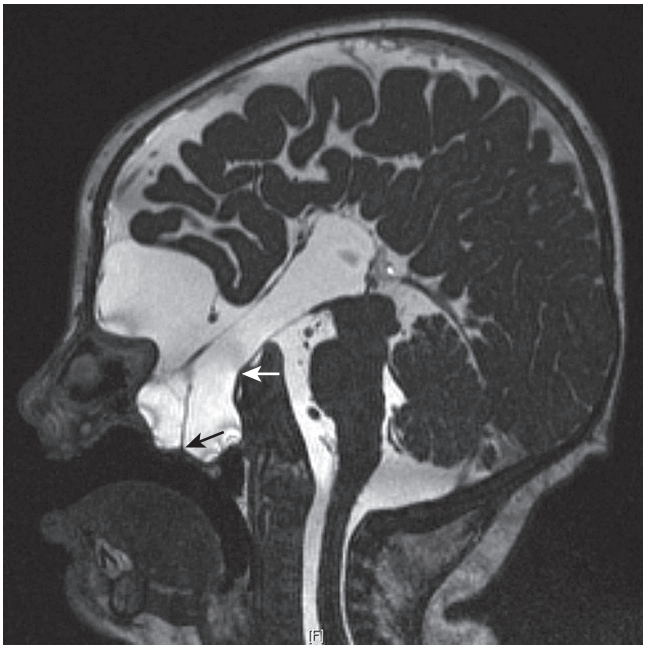
Phenotype and Genetics

FND has been defined phenotypically as containing two or more of the following craniofacial features: ocular hypertelorism; broadening of the nasal root; midline facial cleft affecting the nose, lip, or palate; unilateral or bilateral clefting of the alae nasi; hypoplastic nasal tip; anterior cranium bifidum; and a V-shaped frontal hairline

(Wu et al., 2007). Grading of hypertelorism is best achieved by measurement of the interpupillary distance. In a term newborn an interpupillary distance greater than 4.5 cm is considered hyperteloric (Jones et al., 2013). FND is a heterogeneous condition with genetic forms (OMIM 136760, OMIM 613451, OMIM 613456, associated with mutations in three *ALX* genes), sporadic forms without associated anomalies, and FND phenotype with associated pattern of malformations (subtype of FND) or known genetic syndrome such as craniofrontonasal syndrome (Wu et al., 2007; van den Elzen et al., 2014).

In addition to hypertelorism, eye anomalies, including epibulbar dermoids, colobomas, ptosis, nystagmus, or cataracts, may be present in FND and are associated with a more severe phenotype and an increased incidence of CNS abnormalities (Wu et al., 2007). Associated CNS manifestations include encephalocele, agenesis of the corpus callosum, and abnormal neuronal migration. Developmental delay is a significant risk, especially when there are CNS malformations. When FND is associated with extracephalic anomalies or when ocular hypertelorism is more severe, there is an increased association with cognitive impairment (Hennekam et al., 2010d). Frontonasal encephaloceles (and meningoceles) are the most common encephaloceles in FND (Fig. 100.14).

A subpopulation of patients with frontonasal malformation also have coronal craniosynostosis and variable skeletal and ectodermal defects and have an X-linked condition termed *craniofrontonasal syndrome* (CFNS, OMIM 304110). Similarly to FND, facial features include hypertelorism, frontal bossing, broad nasal bridge, and a bifid nasal tip. Children with CFNS often have significant facial asymmetry due to unicoronal synostosis. In this X-linked condition, females are affected more severely than males (and typically have hypertelorism and grooved nails), and mutations are detected in the *EFNB1* gene. Affected individuals usually have normal intelligence.



• **Fig. 100.14** Magnetic resonance imaging of an infant with frontonasal dysplasia and a midline cleft lip. The scan reveals a moderate-sized meningocele extending into the posterior nasopharynx. The *white arrow* points to midbrain meningocele coming through the cribriform plate; the *black arrow* points to the intraoral meningocele.

Intensive Care Unit Concerns

Intracranial abnormalities associated with FND may put the infant at risk of CNS manifestations such as hydrocephalus or seizures. If the pituitary gland is involved or deficient, as can be seen with HPE sequence, there can be serious endocrine abnormalities (as discussed in Orofacial Clefting). Also, frontonasal encephalocele may contribute to upper airway compromise at the level of the nasopharynx.

Management

In any infant with hypertelorism or features that raise suspicion for FND, awareness of potential underlying malformations is critical, and cranial imaging by CT scan or MRI should be considered. Instrumentation of the nose and mouth, including placement of a nasogastric tube or suction catheter, should be avoided or used with caution until the CNS anatomy has been delineated. Because infants with FND have a high incidence of frontonasal encephalocele or meningocele, placement of these catheters could lead to brain injury. If an infant with FND needs urgent or emergent endotracheal intubation, intraoral structures should be examined carefully to prevent injury to herniating CNS structures if they are present. Management of seizures or any electrolyte derangements should be managed as per the neonatal ICU standard protocol. Consultation with a craniofacial team, including specialists in ophthalmology, can be helpful in understanding the work-up and management (including potential surgical interventions) for individuals with FND.

Prenatal Screening for Fetal Face Anomalies

The exact role of fetal face examination with ultrasonography in a low-risk pregnancy is under evaluation. Routine obstetric surveillance includes a midtrimester anatomic ultrasound examination at 18 to 22 weeks' gestation. Most studies looking at the recognition rate and incidence of ultrasonographic diagnosis of orofacial clefting focus on this anatomic examination. Adequate evaluation of the facial structures with ultrasonography can be achieved by 16 to 17 weeks' gestation. The following facial features can be visualized with two-dimensional routine ultrasonography at 18 weeks' gestation with standard facial views (which include coronal images of the nose, lips, and orbits and sagittal profile views): orbital size and position, eye size, including microphthalmia and anophthalmia, shape of nose, nasal hypoplasia, length of the philtrum, clefts of the upper lip, frontal bossing, retrognathia, micrognathia, macroglossia, and soft tissue abnormalities. Cleft lip with or without CP can be detected by prenatal ultrasonography, whereas isolated CP, which is not typically associated with a cleft of the alveolus, may be obscured by the tongue, which has the same echogenicity as the secondary palate, thus making prenatal diagnosis of CPO more difficult. A retrospective study in a low-risk population demonstrated that routine prenatal ultrasonography with standard facial views performed at 18 weeks' estimated gestational age detected 93% of cases of cleft lip and palate, 67% of cases of isolated cleft lip, and 22% of cases of CPO (Cash et al., 2001). New and increasingly sensitive methods for identifying craniofacial differences prenatally are emerging (Tonni et al., 2015; Rubio et al., 2016). Although the diagnosis is not definitive, prenatal diagnosis is particularly valuable in allowing appropriate prenatal counseling (Maarse et al., 2015). Families who have the opportunity to meet members of a craniofacial team before delivery often appreciate having some understanding of what to

expect in the newborn period and are armed with knowledge to help their new baby receive the best care possible.

Suggested Readings

Agochukwu NB, Solomon BD, Muenke M. Impact of genetics on the diagnosis and clinical management of syndromic craniosynostoses. *Childs Nerv Syst*. 2012;28(9):1447-1463.

Blake KD, Prasad C. CHARGE syndrome. *Orphanet J Rare Dis*. 2006;1:34.

Breugem CC, Evans KN, Poets CF, et al. Best practices for the diagnosis and evaluation of infants with Robin sequence: a clinical consensus report. *JAMA Pediatr*. 2016;170(9):894-902.

Cielo CM, Montalva FM, Taylor JA. Craniofacial disorders associated with airway obstruction in the neonate. *Semin Fetal Neonatal Med*. 2016;21(4):254-262.

Elliott M, Bayly R, Cole T, et al. Clinical features and natural history of Beckwith-Wiedemann syndrome: presentation of 74 new cases. *Clin Genet*. 1994;46:168-174.

Heike CL, Luquetti DV, Hing AV. Craniofacial microsomia overview. *GeneReviews* (Internet). Available from: http://www.ncbi.nlm.nih.gov/books/NBK5199/. Posted March 19, 2009. updated October 9, 2014.

Johnston DR, Watters K, Ferrari LR, Rahbar R. Laryngeal cleft: evaluation and management. *Int J Pediatr Otorhinolaryngol*. 2014;78:905-911.

Katsanis SH, Jabs EW. Treacher Collins syndrome. *GeneReviews* (Internet). http://www.ncbi.nlm.nih.gov/books/NBK1532/.

McCarthy JG, Warren SM, Bernstein J, et al. Parameters of care for craniosynostosis. *Cleft Palate Craniofac J*. 2012;49(S1):1S-24S.

McDonald-McGinn DM, Sullivan KE, Marino B, et al. 22q11.2 deletion syndrome. *Nat Rev Dis Primers*. 2015;1:15071.

Robin NH, Moran RT, Ala-Kokko L. Stickler syndrome. *GeneReviews* (Internet). http://www.ncbi.nlm.nih.gov/books/NBK1302. Posted June 9, 2000. Updated March 16, 2017.

The Center for Children with Special Needs, Washington State Department of Health and Seattle Children's Hospital, Seattle, WA. *Cleft Lip and Palate: Critical Elements of Care*. ed 5, 2010. http://www.doh.wa.gov/YouandYourFamily/InfantsandChildren/HealthandSafety/ChildrenwithSpecialHealthCareNeeds/Partners/MaxillofacialTeams. The booklet can be accessed here: http://cshcn.org/wp-content/uploads/files/CriticalElementsofCare-CleftLipandPalate.pdf.

Complete references used in this text can be found online at www.expertconsult.com

References

Abel F, Bajaj Y, Wyatt M, Wallis C. The successful use of the nasopharyngeal airway in Pierre Robin sequence: an 11-year experience. *Arch Dis Child*. 2012;97:331-334.

Agochukwu NB, Solomon BD, Muenke M. Impact of genetics on the diagnosis and clinical management of syndromic craniosynostoses. *Childs Nerv Syst*. 2012;28(9):1447-1463.

American Cleft Palate-Craniofacial Association. *Parameters for Evaluation and Treatment of Patients with Cleft Lip/Palate or Other Craniofacial Anomalies*. Revised edition, November 2009. http://acpa-cpf.org/team-care/standardscat/parameters-of-care/.

American Cleft Palate-Craniofacial Association. *Team Listings*. 2017. http://acpa-cpf.org/team-care/team-listings/.

Azimi C, Kennedy SJ, Chitayat D, et al. Clinical and genetic aspects of trigonocephaly: a study of 25 cases. *Am J Med Genet A*. 2003;117A:127-135.

Beleza-Meireles A, Clayton-Smith J, Saraiva JM, Tassabehji M. Oculo-auriculo-vertebral spectrum: a review of the literature and genetic update. *J Med Genet*. 2014;51(10):635-645.

Bergman JE, Blake KD, Bakker MK, et al. Death in CHARGE syndrome after the neonatal period. *Clin Genet*. 2010;77(3):232-240.

Birgfeld CB, Luquetti DV, Gougoutas AJ, et al. A phenotypic assessment tool for craniofacial microsomia. *Plast Reconstr Surg*. 2011;127:313-320.

Blake K, MacCuspie J, Hartshorne TS, et al. Postoperative airway events of individuals with CHARGE syndrome. *Int J Pediatr Otorhinolaryngol*. 2009;73:219-226.

Blake KD, Prasad C. CHARGE syndrome. *Orphanet J Rare Dis*. 2006;1:34.

Bookman LB, Melton KR, Pan BS, et al. Neonates with tongue-based airway obstruction: a systematic review. *Otolaryngol Head Neck Surg*. 2012;146(1):8-18.

Boulet SL, Rasmussen SA, Honein MA. A population-based study of craniosynostosis in metropolitan Atlanta, 1989–2003. *Am J Med Genet A*. 2008;146A:984-991.

Breugem CC, Evans KN, Poets CF, et al. Best practices for the diagnosis and evaluation of infants with Robin sequence: a clinical consensus report. *JAMA Pediatr*. 2016;170(9):894-902.

Brioude F, Lacoste A, Netchine I, et al. Beckwith-Wiedemann syndrome: growth pattern and tumor risk according to molecular mechanism, and guidelines for tumor surveillance. *Horm Res Paediatr*. 2013;80(6):457-465.

Broussard AB, Borazjani JG. The faces of Moebius syndrome: recognition and anticipatory guidance. *MCN Am J Matern Child Nurs*. 2008;33:272-280.

Bush PG, Williams AJ. Incidence of the Robin anomalad (Pierre Robin syndrome). *Br J Plast Surg*. 1983;36:434-437.

Caouette-Laberge L, Bayet B, Larocque Y. The Pierre Robin sequence: review of 125 cases and evolution of treatment modalities. *Plast Reconstr Surg*. 1994;93:934-942.

Carlson C, Sirotkin H, Pandita R, et al. Molecular definition of 22q11 deletions in 151 velo-cardio-facial syndrome patients. *Am J Hum Genet*. 1997;61:620-629.

Cash C, Set P, Coleman N. The accuracy of antenatal ultrasound in the detection of facial clefts in a low-risk screening population. *Ultrasound Obstet Gynecol*. 2001;18:432-436.

Cielo CM, Montalva FM, Taylor JA. Craniofacial disorders associated with airway obstruction in the neonate. *Semin Fetal Neonatal Med*. 2016;21(4):254-262.

Cohen MM. Crouzon syndrome. In: Cohen MM, Maclean RE, eds. *Craniosynostosis: Diagnosis, Evaluation, and Management*. 2nd ed. New York, NY: Oxford University Press; 2000:362.

Collmann H, Sorensen N, Krauss J. Hydrocephalus in craniosynostosis: a review. *Childs Nerv Syst*. 2005;21:902-912.

Costello BJ, Hueser T, Mandell D, et al. Syndromic micrognathia and peri-natal management with the ex-utero intra-partum treatment (EXIT) procedure. *Int J Oral Maxillofac Surg*. 2010;39:725-728.

Croen LA, Shaw GM, Wasserman CR, Tolarova MM. Racial and ethnic variations in the prevalence of orofacial clefts in California, 1983-1992. *Am J Med Genet*. 1998;79:42-47.

Denny AD, Amm CA, Schaefer RB. Outcomes of tongue-lip adhesion for neonatal respiratory distress caused by Pierre Robin sequence. *J Craniofac Surg*. 2004;15:819-823.

Dixon J, Trainor P, Dixon MJ. Treacher Collins syndrome. *Orthod Craniofac Res*. 2007;10:88-95.

Elliott M, Bayly R, Cole T, et al. Clinical features and natural history of Beckwith-Wiedemann syndrome: presentation of 74 new cases. *Clin Genet*. 1994;46:168-174.

Evans KN, Sie KC, Hopper RA, et al. Robin sequence: from diagnosis to development of an effective management plan. *Pediatrics*. 2011;127:936-948.

Fernandes MB, Maximino LP, Perosa GB, et al. Apert and Crouzon syndromes—cognitive development, brain abnormalities, and molecular aspects. *Am J Med Genet A*. 2016;170(6):1532-1537.

Firth HV, Hurst JA. *Oxford Desk Reference. Clinical Genetics*. New York, NY: Oxford University Press; 2005.

Genisca AE, Frias JL, Broussard CS, et al. Orofacial clefts in the National Birth Defects Prevention Study, 1997-2004. *Am J Med Genet A*. 2009;149A:1149-1158.

Gomez-Ospina N, Bernstein JA. Clinical, cytogenetic, and molecular outcomes in a series of 66 patients with Pierre Robin sequence and literature review: 22q11.2 deletion is less common than other chromosomal anomalies. *Am J Med Genet A*. 2016;170(4):870-880.

Gougoutas AJ, Singh DJ, Low DW, Bartlett SP. Hemifacial microsomia: clinical features and pictographic representations of the OMENS classification system. *Plast Reconstr Surg*. 2007;120:E112-E120.

Grabb WC. The first and second branchial arch syndrome. *Plast Reconstr Surg*. 1965;36:485-508.

Harper PS. Oral and craniofacial disorders. In: Harper PS, ed. *Practical Genetic Counseling*. 7th ed. London: Hodder Arnold; 2011.

Heike CL, Luquetti DV, Hing AV. Craniofacial microsomia overview. *GeneReviews* (Internet). http://www.ncbi.nlm.nih.gov/books/NBK5199/. Posted March 19, 2009. Updated October 9, 2014.

Hennekam RCM, Krantz ID, Allanson JE. Chapter 21: Orofacial clefting syndromes: general aspects. In: *Gorlin's Syndromes of the Head and Neck*. 5th ed. New York, NY: Oxford University Press; 2010a:943-971.

Hennekam RCM, Krantz ID, Allanson JE. Chapter 22: Orofacial clefting syndromes: common and well-known syndromes. In: *Gorlin's Syndromes of the Head and Neck*. 5th ed. New York, NY: Oxford University Press; 2010b:973-1010.

Hennekam RCM, Krantz ID, Allanson JE. Chapter 15: Syndromes with craniosynostosis: general aspects and well-known syndromes. In: *Gorlin's Syndromes of the Head and Neck*. 5th ed. New York, NY: Oxford University Press; 2010c:732-748.

Hennekam RCM, Krantz ID, Allanson JE. Chapter 16: Syndromes with craniosynostosis: miscellaneous syndromes. In: *Gorlin's Syndromes of the Head and Neck*. 5th ed. New York, NY: Oxford University Press; 2010d:750-791.

Issekutz KA, Graham JM Jr, Prasad C, et al. An epidemiological analysis of CHARGE syndrome: preliminary results from a Canadian study. *Am J Med Genet A*. 2005;133A:309-317.

Izumi K, Konczal LL, Mitchell AL, Jones MC. Underlying genetic diagnosis of Pierre Robin sequence: retrospective chart review at two children's hospitals and a systematic literature review. *J Pediatr*. 2012;160(4):645-650.

Johnston DR, Watters K, Ferrari LR, Rahbar R. Laryngeal cleft: evaluation and management. *Int J Pediatr Otorhinolaryngol*. 2014;78:905-911.

Jones KL, Jones MC, Del Campo M. *Smith's Recognizable Patterns of Human Malformations*. 7th ed. Philadelphia, PA: Saunders; 2013.

Katsanis SH, Jabs EW. Treacher Collins syndrome. *GeneReviews* (Internet). http://www.ncbi.nlm.nih.gov/books/NBK1532/. Posted July 20, 2004. Updated August 30, 2012.

Lajeunie E, Le Merrer M, Marchac D, Renier D. Syndromal and non-syndromal primary trigonocephaly: analysis of a series of 237 patients. *Am J Med Genet*. 1998;75:211-215.

Lalani SR, Hefner MA, Belmont JW, et al. CHARGE syndrome. *GeneReviews* (Internet). http://www.ncbi.nlm.nih.gov/books/NBK1117/. Posted October 2, 2006. Updated February 2, 2012.

Lee HQ, Hutson JM, Wray AC, et al. Changing epidemiology of non-syndromic craniosynostosis and revisiting the risk factors. *J Craniofac Surg*. 2012;23(5):1245-1251.

Lee S, Seto M, Sie K, Cunningham M. A child with Saethre-Chotzen syndrome, sensorineural hearing loss, and a TWIST mutation. *Cleft Palate Craniofac J*. 2002;39:110-114.

Leslie EJ, Marazita ML. Genetics of cleft lip and cleft palate. *Am J Med Genet C Semin Med Genet*. 2013;163C(4):246-258.

Letsburapa K, Schroeder JW, Sullivan C. Tracheal cartilaginous sleeve in patients with craniosynostosis syndromes: a meta-analysis. *J Pediatr Surg*. 2010;45:1438-1444.

Maarse W, Boonacker CW, Breugem CC, Kon M, Manten GT, Mink van der Molen AB. A practical prenatal ultrasound classification system for common oral clefts. *Prenat Diagn*. 2015;35(9):894-900.

Maher ER, Brueton LA, Bowdin SC, et al. Beckwith-Wiedemann syndrome and assisted reproduction technology (ART). *J Med Genet*. 2003;40:62-64.

McCarthy JG, Warren SM, Bernstein J, et al. Parameters of care for craniosynostosis. *Cleft Palate Craniofac J*. 2012;49(S1):1S-24S.

McDonald-McGinn DM, Emanuel BS, Zackai EH. 22q11.2 Deletion Syndrome. *GeneReviews* (Internet). http://www.ncbi.nlm.nih.gov/books/NBK1523/. Posted September 23, 1999. Updated February 28, 2013.

McDonald-McGinn DM, Sullivan KE, Marino B, et al. 22q11.2 deletion syndrome. *Nat Rev Dis Primers*. 2015;1:15071.

McKay VH, Touil LL, Jenkins D, Fattah AY. Managing the child with a diagnosis of Moebius syndrome: more than meets the eye. *Arch Dis Child*. 2016;101:843-846.

Meroni G. X-Linked Opitz G/BBB syndrome. *GeneReviews* (Internet). http://www.ncbi.nlm.nih.gov/books/NBK1327/. Posted December 17, 2004. Updated July 28, 2011.

Milerad J, Larson O, Hagberg C, Ideberg M. Associated malformations in infants with cleft lip and palate: a prospective, population-based study. *Pediatrics*. 1997;100(2 Pt 1):180-186.

Mossey PA, Little J, Munger RG, Dixon MJ, Shaw WC. Cleft lip and palate. *Lancet*. 2009;374:1773-1785.

Munns CF, Batch JA. Hyperinsulinism and Beckwith-Wiedemann syndrome. *Arch Dis Child Fetal Neonatal Ed*. 2001;84:F67-F69.

Mussa A, Di Candia S, Russo S, et al. Recommendations of the Scientific Committee of the Italian Beckwith-Wiedemann Syndrome Association on the diagnosis, management and follow-up of the syndrome. *Eur J Med Genet*. 2016;59(1):52-64.

Paes EC, Mink van der Molen AB, Muradin MS, et al. A systematic review on the outcome of mandibular distraction osteogenesis in infants suffering Robin sequence. *Clin Oral Investig*. 2013;17:1807-1820.

Pagon RA, Graham JM Jr, Zonana J, Yong SL. Coloboma, congenital heart disease, and choanal atresia with multiple anomalies: CHARGE association. *J Pediatr*. 1981;99:223-227.

Parhizkar N, Saltzman B, Grote K, et al. Nasopharyngeal airway for management of airway obstruction in infants with micrognathia. *Cleft Palate Craniofac J*. 2011;48(4):478-482.

Persson M, Sandy J, Kilpatrick N, et al. Educational achievements in Pierre Robin sequence. *J Plast Surg Hand Surg*. 2013;47:36-39.

Printzlau A, Andersen M. Pierre Robin sequence in Denmark: a retrospective population-based epidemiological study. *Cleft Palate Craniofac J*. 2004;41:47-52.

Robin NH, Moran RT, Ala-Kokko L. Stickler Syndrome. *GeneReviews* (Internet). http://www.ncbi.nlm.nih.gov/books/NBK1302/. Posted June 9, 2000. Updated March 16, 2017.

Rovin S, Dachi SF, Borenstein DB, Cotter WB. Mandibulofacial dysostosis, a familial study of five generations. *J Pediatr*. 1964;65:215-221.

Roženková K, Güemes M, Shah P, Hussain K. The diagnosis and management of hyperinsulinaemic hypoglycaemia. *J Clin Res Pediatr Endocrinol*. 2015;7(2):86-97.

Rubio EI, Blask A, Bulas DI. Ultrasound and MR imaging findings in prenatal diagnosis of craniosynostosis syndromes. *Pediatr Radiol*. 2016;46(5):709-718.

Schaefer RB, Gosain AK. Airway management in patients with isolated Pierre Robin sequence during the first year of life. *J Craniofac Surg*. 2003;14:462-467.

Shuman C, Beckwith JB, Smith AC, et al. Beckwith-Wiedemann syndrome. *GeneReviews* (Internet). http://www.ncbi.nlm.nih.gov/books/NBK1394/. Posted Narch 3, 2000. Updated August 11, 2016.

Speltz ML, Collett BR, Wallace ER, et al. Intellectual and academic functioning of school-age children with single-suture craniosynostosis. *Pediatrics*. 2015;135(3):e615-e623.

Tan TY, Kilpatrick N, Farlie PG. Developmental and genetic perspectives on Pierre Robin sequence. *Am J Med Genet C Semin Med Genet*. 2013;163C:295-305.

Tellier AL, Cormier-Daire V, Abadie V, et al. CHARGE syndrome: report of 47 cases and review. *Am J Med Genet*. 1998;76:402-409.

The Center for Children with Special Needs, Washington State Department of Health and Seattle Children's Hospital, Seattle, WA. *Cleft Lip and Palate: Critical Elements of Care*. ed 5, 2010. http://www.doh.wa.gov/YouandYourFamily/InfantsandChildren/HealthandSafety/ChildrenwithSpecialHealthCareNeeds/Partners/MaxillofacialTeams. The booklet can be accessed here: http://cshcn.org/wp-content/uploads/files/CriticalElementsofCare-CleftLipandPalate.pdf.

Thorburn MJ, Wright ES, Miller CG, Smith-Read EH. Exomphalos-macroglossia-gigantism syndrome in Jamaican infants. *Am J Dis Child*. 1970;119:316-321.

Tolarova MM, Cervenka J. Classification and birth prevalence of orofacial clefts. *Am J Med Genet*. 1998;75:126-137.

Tonni G, Martins WP, Guimarães Filho H, Araujo Júnior E. Role of 3-D ultrasound in clinical obstetric practice: evolution over 20 years. *Ultrasound Med Biol*. 2015;41(5):1180-1211.

Twigg SR, Wilkie AO. A genetic-pathophysiological framework for craniosynostosis. *Am J Hum Genet*. 2015a;97(3):359-377.

Twigg SR, Wilkie AO. New insights into craniofacial malformations. *Hum Mol Genet*. 2015b;24(R1):R50-R59.

van den Elzen ME, Twigg SR, Goos JA, et al. Phenotypes of craniofrontonasal syndrome in patients with a pathogenic mutation in EFNB1. *Eur J Hum Genet* 2014;22(8):995-1001.

Wagener S, Rayatt SS, Tatman AJ, et al. Management of infants with Pierre Robin sequence. *Cleft Palate Craniofac J*. 2003;40:180-185.

Wehby GL, Murray JC. Folic acid and orofacial clefts: a review of the evidence. *Oral Dis*. 2010;16(1):11-19.

Wenger TL, Dahl J, Bhoj EJ, et al. Tracheal cartilaginous sleeves in children with syndromic craniosynostosis. *Genet Med*. 2017;19(1):62-68.

Wong MT, Lambeck AJ, van der Burg M, et al. Immune dysfunction in children with CHARGE syndrome: a cross-sectional study. *PLoS ONE*. 2015;10(11).

Wu E, Vargevik K, Slavotinek AM. Subtypes of frontonasal dysplasia are useful in determining clinical prognosis. *Am J Med Genet A*. 2007;143A:3069-3078.

Yasuda Y, Kitai N, Fujii Y, et al. Report of a patient with hypoglossia-hypodactylia syndrome and a review of the literature. *Cleft Palate Craniofac J*. 2003;40:196-202.