Chapter 40: Syndromes

Laura Rhee

INTRODUCTION

FOCUS POINTS

1. Trisomy 21 (Down syndrome): Congenital heart disease, sleep apnea, and subglottic stenosis.
2. Trisomy 13 and 18: High infant mortality rate, apnea, and airway challenges.
3. Turner syndrome: Cardiac evaluation, webbed neck with limited mobility, and difficult IV access.
4. VACTERL: Three defining features for diagnosis, cardiac evaluation, and spontaneous ventilation for TEF.
5. CHARGE: Major features include choanal atresia, coloboma, cranial nerve dysfunction, and characteristic ear anomalies.
6. 22q11 deletion syndrome: Cardiac abnormalities, abnormal facies, thymic hypoplasia, cleft palate, hypocalcemia.
7. Muscular dystrophy does not increase the risk of malignant hyperthermia (MH).
8. Williams syndrome: “Cocktail-party” personality, supravalvar aortic stenosis at high risk for perioperative myocardial ischemia.

With advances in the field of molecular cytogenetics, more genetic syndromes are being formally diagnosed than ever before. Likewise, further innovations in medical care have fostered the survival of children with multiple congenital malformations further into adulthood. Children with a chronic underlying disorder of genetic origin account for over two-thirds of hospital admissions[1]—and are consequently quite likely to require (anesthesia for) diagnostic imaging or procedures. While syndromes do not account for all “disorders of genetic origin,” they are collectively common (albeit individually rare) and likely to be encountered with regularity by the anesthesiologist caring for pediatric patients.

Children with genetic dysmorphic conditions are at greater risk for perioperative morbidity and mortality with multiple organ systems often affected.[1] While neurologic and developmental abnormalities are frequent and can impact perioperative care, many are also associated with cardiovascular disease, and various craniofacial abnormalities that may affect airway management. To successfully anticipate perioperative challenges and provide safe and effective care, it is imperative that pediatric anesthesiologists are aware of potential congenital anomalies and their associated anatomic and physiologic disturbances. This chapter reviews the major features and perioperative implications of common syndromes that are pertinent to the pediatric anesthesiologist.

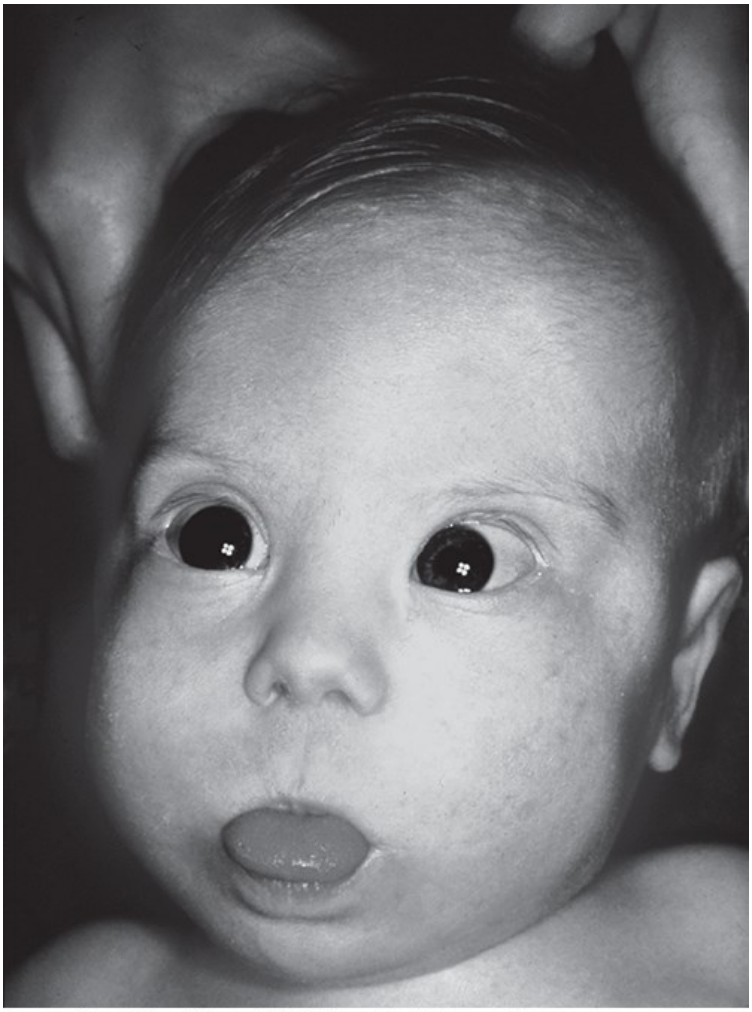
TRISOMY 21 (DOWN SYNDROME)

Trisomy 21 or down syndrome (DS) (see Figure 40-1), which is caused by an extra 21st chromosome, is the most common autosomal chromosomal disorder in humans, with an incidence of 1:700 live births.[2,3] The characteristic phenotypic features of these patients include brachycephaly, oblique palpebral fissures, epicanthal folds, small low-set ears, midfacial and mild mandibular hypoplasia, and a short neck.[3] Individuals with DS may have multiple reasons of airway obstruction such as protruding tongue and adenotonsillar hypertrophy, in combination with pharyngeal hypotonia, which frequently contribute to upper airway obstructive symptoms and obstructive sleep apnea (OSA). Subglottic stenosis, cleft palate, and choanal atresia are also more frequently seen in DS. There is a high rate (40% to 50%) of congenital heart disease, particularly endocardial cushion defects, such as

ASD, VSD, and atrioventricular canal defects (though PDA and TOF are also common).[3] There is a higher incidence of pulmonary hypertension in children with DS; coexisting congenital heart disease, higher rates of persistent pulmonary hypertension of the newborn, and predisposition to upper airway obstruction (leading to chronic hypoxemia) may all contribute.[4] GI malformations detected in the neonatal period (duodenal atresia, annular pancreas, tracheo-esophageal fistula, Hirschsprung disease, imperforate anus) are common as well.[4] Growth delay, obesity, and thyroid disease frequently occur in patients with DS and 1% of individuals with DS are diagnosed with leukemia.[5] Musculoskeletal abnormalities may include polydactyly, recurrent joint dislocation, and extreme joint laxity, in addition to generalized hypotonia.[5]

Figure 40-1

Trisomy 21 features. (Reproduced with permission, from Bissonnette B, Luginbuehl I, Marciniak B, et al., eds. *Syndromes: Rapid Recognition and Perioperative Implications.* 2006. https://accessanesthesiology.mhmedical.com. Copyright © McGraw Hill LLC. All rights reserved.)



Source: Herodotos Ellinas, Kai Matthes, Walid Alrayashi, Aykut Bilge: *Clinical Pediatric Anesthesiology*

Because of ligamentous laxity and bony anomalies in the cervical vertebrae, patients with DS are prone to atlanto-occipital (occiput-C1) and (more commonly) atlanto-axial (C1-C2) instability.

Anterior subluxation of C1-C2 may lead to spinal cord compression and rotary subluxation of C1-C2 may lead to neck pain, immobility, and kinking of the ipsilateral vertebral artery.[6] Both clinical and radiologic assessments of cervical spine instability (CSI) are challenging in this patient population. While the frequency of atlanto-occipital and atlanto-axial instability is estimated at 15%, only 1% to 2% of individuals will present with overt symptoms.[4] Radiologic assessment is typically measured by the atlanto-dens interval on plain cervical spine radiographs, which changes with neck

position. Prior guidelines from the American Academy of Pediatrics recommended obtaining cervical spine films to assess for CSI in all patients 3 to 5 years of age with DS but more recent evidence suggests no routine radiographs in asymptomatic children: “Plain radiographs do not predict well which children are at increased risk of developing spine problems, and normal radiographs do not provide assurance that a child will not develop spine problems later.”[6]

A variety of neuropsychiatric features are common in individuals with DS. Intellectual disability of varying degrees and developmental delay are ubiquitous; achievement of all developmental milestones in the early years lags behind that of their unaffected peers. Individuals with DS are frequently affected by autism spectrum disorders, behavioral disorders, depression and early-onset Alzheimer’s disease.[5]

Perioperative Implications

Particular care should be given to the maintenance of airway patency and airway management in patients with DS. Their high risk for airway obstruction (subglottic stenosis, narrowed nasopharynx, upper airway obstruction secondary to macroglossia, and adenotonsillar hypertrophy) and for OSA render them a higher risk perioperatively thus requiring closer monitoring. Endotracheal tubes should be downsized given the likelihood of subglottic narrowing. Discretion should be used with placement of nasal endotracheal tubes, especially if there is a history of choanal atresia or stenosis. Because of the risk of cervical spine instability, a thorough preoperative history and physical should be performed to elicit any signs or symptoms of cord compression. As clinical assessment is still somewhat unreliable, even asymptomatic children should be considered at risk of acute dislocation and special attention should be given to positioning during intubation and surgery to maintain a neutral cervical spine position (consider avoiding the typical headrest).

Patients with congenital heart disease and/or pulmonary hypertension may require a cardiac evaluation (depending on severity of lesion and status of the repair). Caution should be used during inhaled induction as individuals with DS are known to have a higher prevalence and degree of bradycardia during sevoflurane induction.[7] Given the high incidence of hypothyroidism in this patient population, recent thyroid function testing should be reviewed prior to major procedures. Lastly, due to obesity, obtaining vascular access (venous and arterial) in these children can be challenging.[8]

TRISOMY 13 (PATAU SYNDROME) AND TRISOMY 18 (EDWARD SYNDROME)

Trisomy 13 (Patau syndrome) is caused by an additional 13th chromosome. The incidence of trisomy 13 is approximately 1:5000 births and it is associated with a high infant mortality rate (over 90% of patients die by one year of age).[9] Common features include microcephaly, cleft lip and/or palate, ocular hypertelorism, microphthalmia, low-set ears, and polydactyly. CNS defects may include holoprosencephaly (most common), seizures, deafness, and significant neurodevelopmental delay. Cardiac malformations are frequent as are visceral and genital anomalies.[10,11]

Trisomy 18 (Edward syndrome) is caused by an additional 18th chromosome. The incidence of trisomy 18 is approximately 1:6–8000 live births, with a predisposition toward females.[12,13] Prognosis is similar to that of trisomy 13. Children with trisomy 18 commonly have microcephaly with a prominent occiput, a small mouth, microretrognathia, short sternum, and positional foot deformities. Clenched fists with overlapping digits are a distinctive feature of this syndrome. CNS abnormalities include cerebellar hypoplasia, agenesis of corpus callosum, polymicrogyria, hydrocephalus, seizures, and myelomeningocele.[13] Cardiac malformations occur in over 95% of patients.[14] Renal anomalies are quite common. Like patients with trisomy 13, these patients also suffer intellectual disability and neurodevelopmental delay.[13]

Perioperative Implications for Trisomy 13 and Trisomy 18

While the prognosis for these two disorders is very poor, those children that do survive often require many hospitalizations, interventions, and surgical procedures. Preoperative assessment should include a discussion with parents to discern the best interests of the patient and quality of life that is desired.[14] Consideration should be given to the fact that the child may not survive long enough to benefit from a particular procedure. Once the surgical procedure is deemed necessary or beneficial, the anesthesia provider should anticipate potential difficulties with direct laryngoscopy (especially due to a small mouth opening and micrognathia in trisomy 18). For those patients with congenital heart disease, cardiac evaluation is important. Children with both syndromes are prone to apnea and this should be taken into consideration during the perioperative period.

TURNER SYNDROME

Turner syndrome (TS) is caused by the absence of all or part of a normal second sex chromosome (46, XO). While it is the single most common chromosomal abnormality, the incidence is only approximately 1:3000 live (female) births due to a high rate of spontaneous abortion.[14] The syndrome is characterized by a constellation of physical findings that includes congenital lymphedema, short stature, and gonadal dysgenesis. Approximately 20% to 30% of TS cases are diagnosed in the newborn period (with findings of congenital lymphedema), 30% in mid childhood (presenting with growth delay), and the remainder of cases in adolescence or adulthood (failure to enter puberty or inability to conceive).[15]

These patients can be identified by their short stature, broad chest, low-set ears, and short, webbed neck (often with limited range of motion). Airway exam may reveal micrognathia and a high arched palate.[16,17] Cardiovascular anomalies are present in a large percentage (17% to 45%) of patients. The most frequent cardiovascular anomalies include aortic coarctation and bicuspid aortic valve; however, hypertension, mitral valve prolapse, and conduction defects (including QTc prolongation) can also occur.[16,18] In addition, 15% to 30% of girls and women with TS have ascending aortic dilation and there are numerous case reports that describe spontaneous aortic dissection.[19] The tracheal bifurcation has been reported to be higher than the general population, which can increase the risk of mainstem intubation.[18] Structural renal malformations are relatively common (up to 40%), as are skeletal deformities (such as scoliosis). Because patients with TS have impaired growth, the administration of recombinant human growth hormone is now standard. Due to gonadal dysgenesis, most patients require hormone replacement therapy to enter puberty and continue appropriate growth. While most patients with TS will have normal intelligence, learning disabilities are quite prevalent. Hypothyroidism is more prevalent in adults with TS but also does occur in a small percentage of patients before puberty.[16]

Perioperative Implications

Due to possible micrognathia, a high arched palate, and short neck with limited mobility, tracheal intubation may be difficult in individuals with TS. A supraglottic airway and a difficult airway cart (i.e., video laryngoscope and fiberoptic scope) should be readily available. A short neck and higher tracheal bifurcation can easily lead to endobronchial intubation. A cardiac workup in these patients is mandatory and an echocardiogram and baseline ECG should be obtained preoperatively. Renal function should be evaluated (electrolytes, BUN/Cr) if renal anomalies are suspected or known. *One should confirm the presence of a euthyroid state if the patient is being treated for hypothyroidism.* If congenital lymphedema is present, peripheral vascular access may be difficult to obtain.

VACTERL ASSOCIATION

VACTERL association was originally described in 1972 as VATER association—**V**ertebral defects, **A**nal atresia, **T** **E** fistula, and **R**enal & **R**adial dysplasia—but has since been broadened to include **V**ascular anomalies, **C**ardiac malformations, and **L**imb anomalies (not limited to radial dysplasia). VACTERL association is a clinical definition, as a distinct pattern or mode of inheritance has not yet been identified (though several signaling pathways and genes have been implicated, such as the Sonic hedgehog signaling pathway, WNT signaling, and the HOX gene clusters). The incidence of VACTERL is estimated to be around 1:10,000–40,000 live births.[19]

While the phenotypic spectrum varies and is broad, the diagnosis of VACTERL typically requires three of the following defining features to be present.

V*ertebral* anomalies (which affect 60% to 90%) may include segmentation defects (such as dysplastic or fused vertebrae) affecting one or more levels, sacral agenesis/dysgenesis, or rib anomalies.

Abnormal spinal curvatures (causing lordosis, kyphosis, or scoliosis) secondary to these vertebral anomalies may occur. Tethered spinal cord is another finding that may be present.[20]

A*nal atresia* (anorectal malformations) which occur in 55% to 90% of patients include imperforate anus or anal atresia, perineal and/or gastrocutaneous fistulas. Patients with such anomalies often also have accompanying genitourinary malformations (such as hypospadias, cryptorchidism, and cloacal malformations).[21]

C*ardiac* malformations affect 40% to 80% of individuals and may vary in complexity from a minor anatomic defect to complex congenital heart disease.[21] Vascular anomalies may be cardiac (such as a right-sided aortic arch, anomalous SVC, or vascular rings) or extracardiac (such as a single umbilical artery, which may be the first clue to a diagnosis antenatally).[21]

T*racheo-***E***sophageal fistula* with or without esophageal atresia may be diagnosed if neonates demonstrate difficulty with oral secretions or feeds or when a gastric feeding tube cannot be passed. These anomalies affect 50% to 80% of individuals and will require surgical repair.[21] **R***enal* abnormalities such as horseshoe kidney, renal agenesis, or cystic and/or dysplastic kidneys affect 50% to 80% of individuals and may be accompanied by ureteral and genitourinary anomalies.

L*imb* anomalies, while initially thought isolated to the radius, may affect any limb and are found in 40% to 55% of individuals. Polydactyly, limb length discrepancy, or limb hypoplasia may be present.[21]

Perioperative Implications

If VACTERL association is suspected, a cardiac evaluation (with echocardiogram) should be performed prior to any surgical intervention. It is important to obtain imaging studies to evaluate for spinal deformities if neuraxial anesthetic is planned. If significant scoliosis is present, tracheal intubation may be challenging and restrictive lung disease (if severe) may affect oxygenation and ventilation. Special considerations for TEF, if present and unrepaired, apply: beware of the propensity of these patients to aspirate and maintain spontaneous ventilation until fistula ligation is confirmed (or endotracheal tube has been placed beyond fistula). If renal anomalies exist, dosing of renally excreted drugs and fluid management should be tailored accordingly. Obtaining vascular access may be challenging if significant limb anomalies are present.

CHARGE SYNDROME

This syndrome, first described in 1979, was given the acronym CHARGE (**C**oloboma, **H**eart defect, **A**tresia choanae, **R**etarded growth/development, **G**enital hypoplasia, **E**ar anomalies/deafness) shortly thereafter, which described an association of various anomalies.[22] CHARGE is now recognized as a syndrome, and a (de novo) mutation of the *CHD7* gene is thought to be responsible for the majority of cases.[23] Its incidence is estimated at 1:8500–10,000 live births.[24] While the clinical phenotype may be quite heterogeneous, a set of diagnostic criteria have been outlined to aid in diagnosis. The presence of any major feature in a neonate should trigger suspicion and investigation into a diagnosis of CHARGE. A diagnosis of CHARGE is highly likely if an individual has either four of the major characteristics or three major and three minor characteristics. **Major features** (4 C's) of CHARGE are as follows: Choanal atresia, Coloboma, Cranial nerve dysfunction, and Characteristic ear anomalies. **Minor features** are as follows: Cardiovascular malformations, Genital hypoplasia, Cleft lip/palate, TE fistula, Distinctive CHARGE facies, Growth deficiency, and Developmental delay.[23]

Eye malformations, which may range from **colobomas** to microphthalmia to anophthalmos, affect up to 80% of patients.[23] Congenital **heart defects** affect 75% to 80% of patients, the most common types of large-level defects being conotruncal defects, septal defects, and atrioventricular septal defects.[25] Tetralogy of Fallot (a conotruncal defect) is the most frequent (33%). **Choanal atresia** may be bilateral or unilateral, membranous or bony, and is associated with polyhydramnios antenatally on ultrasound. Because neonates are obligate nose breathers, those with bilateral choanal atresia must undergo surgical correction. **Growth retardation** may be secondary to respiratory or cardiac comorbidities, growth hormone deficiency, or feeding difficulties. While most neonates with CHARGE have normal birth weights, by school age these children are often underweight. Developmental delays may include motor and language and/or intellectual disability that can range from mild to profound. Autism spectrum disorder may also be present. **Genital hypoplasia** is easier to recognize and more common in males. Occasionally renal anomalies may also occur. **Ear anomalies,** which affect 80% to 100% of individuals, include abnormally shaped ears as well as sensorineural hearing loss often accompanied by facial nerve palsies.[23]

Cranial nerve anomalies are evident in over 75%[26] and may cause anosmia (CN I), facial nerve palsy (CN VII), and swallowing problems and/or aspiration (CN IX/X/XI) which cause feeding difficulties and/or recurrent respiratory infections. Multiple cranial neuropathies may be present and in general are often asymmetric.[23,27]

While not described in the acronym, there is a higher documented incidence of upper airway abnormalities in patients with CHARGE syndrome.[27] In addition to cleft lip and palate, individuals may have a short neck, micrognathia, and laryngomalacia,[28] all of which may contribute to upper airway obstruction or difficult tracheal intubation. Many patients will require tracheostomy placement secondary to upper airway obstruction.[27]

Perioperative Implications

Individuals with special needs may require premedication and/or child behavioral support perioperatively. Many are affected by intellectual disability

or autism spectrum disorder and 80% to 90% have at least mild *dual* sensory loss (deafblindness)[28] which can impair perioperative communication. Cardiac evaluation should be performed to identify any congenital heart defects. The presence of choanal atresia or stenosis precludes placement of nasogastric tube or nasal airway. Mask ventilation on induction may require CPAP if laryngomalacia is present and tracheal intubation may be challenging if anatomic airway abnormalities (cleft lip/palate, micrognathia, short neck) are present. Laryngeal discoordination from cranial nerve palsies may contribute to pooling of oral secretions, aspiration, and airway obstruction. As these patients are at higher risk of postoperative airway events (airway obstruction and need for reintubation),[29] intensive care unit monitoring with or without postoperative ventilation should be considered.

22Q11 DELETION SYNDROME (22Q11DS)

This syndrome is a major cause of developmental delay and major congenital heart disease second only to trisomy 21. 22q11DS occurs in approximately 1:4,000 births (Bassett).[30] The most common cause is a deletion of a segment of 35 genes on chromosome 22 (though this is usually a de novo event, this mutation can be inherited in an autosomal dominant fashion).[31] The constellation of clinical findings are the result of aberrant migration of neural crest cells during embryonic development which leads to abnormal development of the pharyngeal arches (which form the aortic arch and its branches, cardiac outflow tract, the thymus, the parathyroid, parts of the palate, pharynx, and face).[32] There is significant variability in the severity and extent of phenotypic expression. 22q11DS encompasses three syndromes with overlapping phenotypic features: DiGeorge syndrome, velocardiofacial syndrome, and conotruncal anomaly face syndrome (historically these were described as three separate entities but it is now known that most cases of these syndromes are caused by the 22q11 deletion).[31] Some of the more prominent clinical features of 22q11DS may be recalled using the "**CATCH-22**" mnemonic: **C**ardiac abnormalities, **A**bnormal facies, **T**hymic hypoplasia, **C**left palate, **H**ypocalcemia.

Cardiac anomalies are present in approximately 75% of patients, with conotruncal defects being the most prevalent: tetralogy of Fallot, truncus arteriosus, interrupted aortic arch, and pulmonary atresia with VSD.[32,33] Aberrant vascular anomalies, such as vascular rings or medial carotid arteries, are often identified in these patients.[33,34] Characteristics that contribute to the **dysmorphic facial features** in this syndrome include a long face, ocular hypertelorism, narrow palpebral fissures, a squared nasal root, narrow nares, low-set ears, small mouth, and retrognathia. A small percentage (11% to 17%) of patients have Pierre Robin sequence.[35] While the original description by DiGeorge included an absent thymus, **thymic aplasia** and hypoplasia are far less common than low T-cell counts which affect 75% to 80% of infants (<1% have no T cells). Impaired immunity may lead to recurrent infections (especially upper respiratory infections) in affected patients. **Abnormalities of the palate**, pharynx, and trachea affect three-fourths of patients: bifid uvula, cleft palate, tracheo- and laryngomalacia, and laryngeal webs may be present.[32,35] A short trachea has also been reported in these patients.[35] Velopharyngeal insufficiency (present in 70%) quite commonly contributes to feeding difficulties and speech delays.[35] **Hypocalcemia** secondary to hypoparathyroidism is common, and although it tends to resolve with age, hypocalcemia may recur during periods of increased metabolic demand.[36] Approximately ⅓ of patients have a structural genitourinary tract abnormality but generally these require no intervention.[32] Scoliosis affects nearly half of individuals with 22q11DS and may require surgical intervention. Learning disabilities affect over 90% of patients and approximately 35% of patients have cognitive delays. Behavioral and psychiatric disorders are also very common, both in children and adults.[31]

Perioperative Implications

Palatal defects, micrognathia, and a small mouth opening can make direct laryngoscopy and tracheal intubation difficult (especially if Pierre Robin sequence is present). Beyond direct visualization of the glottic opening, the potential for a shorter trachea, laryngeal web, and/or vascular rings may hinder endotracheal tube advancement. Evaluation for potential congenital heart disease should be performed to determine the severity of a lesion and status of a repair if present. Anatomy of vascular structures (carotid and subclavian arteries) should be confirmed prior to central line insertion (or velopharyngoplasty) given the potential presence of major arterial malformations. In case of impaired immune function, administration of irradiated blood may be necessary and strict aseptic technique should be followed during placement of lines or other invasive monitors or regional anesthetic technique. Symptomatic hypocalcemia, which can be aggravated by hyperventilation (alkalosis) and citrate-containing blood products, should be monitored and corrected perioperatively.

BECKWITH–WIEDEMANN SYNDROME

Beckwith–Wiedemann syndrome (BWS) is an overgrowth syndrome, characterized by pre- and post-natal macrosomia, various malformations, and an elevated risk of embryonal tumors.[37] It is caused by an alteration in chromosome 11p15, which is usually sporadic but can be inherited.[38] It occurs at a rate of approximately 1:13,700 births and its clinical picture is extremely variable.[39]

While patients with BWS often exhibit macrosomia and are large for gestational age, the syndrome is also frequently associated with prematurity (and its associated comorbidities).[40]

Macroglossia, which may contribute to chronic upper airway obstruction, is one of the more distinguishing features of this syndrome. Occasionally the obstruction may become so severe leading to alveolar hypoventilation and cor pulmonale; some patients may require tracheostomy or partial glossectomy.[41,42] Hemihypertrophy and visceromegaly (disproportionately oversized organs—adrenals, kidneys, pancreas, gonads) are major findings as are abdominal wall defects (omphalocele and umbilical hernia).[39] Cardiac anomalies (particularly cardiomegaly, which usually spontaneously regresses) have been reported in some children.[42] Children with BWS are at much greater risk of developing childhood malignancies, particularly Wilms tumor, hepatoblastoma, neuroblastoma, rhabdomyosarcoma, as well as some benign tumors.[38,39] Severe neonatal hypoglycemia (related to pancreatic islet cell hypertrophy) may occur, though hypoglycemic episodes usually spontaneously resolve with growth.[42]

Perioperative Implications

Macroglossia usually regresses as the patient grows (as facial bones grow more, room is available in the oral cavity). In the neonatal period, macroglossia can be a source of significant upper airway obstruction and cause difficulty visualizing the glottis during direct laryngoscopy. Preoperative sedation is best avoided. Awake direct laryngoscopy can aid in detecting visualization of the glottis.[42] Fiberoptic intubation may be necessary. Intubation via video laryngoscopy and placement of supraglottic devices have both been successful in these patients.[43] A preoperative echocardiogram may be indicated. Close monitoring of blood glucose in the neonatal period is warranted and may necessitate a bolus and infusion of dextrose.

MUSCULAR DYSTROPHINOPATHIES

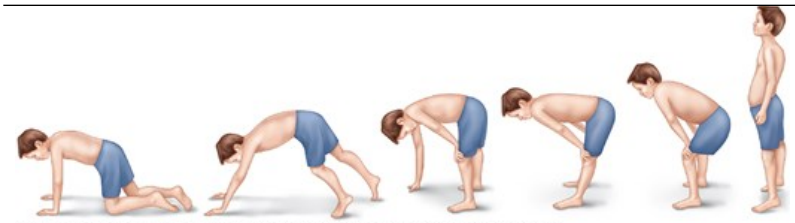
Duchenne and Becker muscular dystrophy (together) are the most common forms of muscular dystrophy found in children,[44] with an incidence of approximately 1:3500 live male births. Both are the result of X-linked recessive mutations in the dystrophin gene; a mutation resulting in a partially functional dystrophin protein causes Becker muscular dystrophy (BMD), while a mutation resulting in complete absence of dystrophin causes Duchenne muscular dystrophy (DMD).[45]

Both DMD and BMD are characterized by progressive (skeletal and cardiac) muscle degeneration and weakness, though BMD is less severe and progression of the disease is much slower than DMD. Due to such severe muscle breakdown, serum CK in DMD may be 50 to 100 times normal.[46]

Individuals with DMD are asymptomatic in infancy, but generally begin walking later than their peers and have a waddling gait with toe-walking. Pseudohypertrophy, especially of the calf muscles, is characteristic and because of proximal muscle (pelvic muscle) weakness, individuals may exhibit the Gower maneuver (see Figure 40-2). As lower extremity muscles deteriorate before upper extremity muscles, the ability to ambulate is generally lost around age 10,[47] after which nearly all boys will rapidly develop scoliosis.

Figure 40-2

Gower sign. (Reproduced with permission, from Kline MW. eds. *Rudolph's Pediatrics*. 23rd ed. 2018. https://accesspediatrics.mhmedical.com. Copyright © McGraw Hill LLC. All rights reserved.)



Initially boys have increased chest wall compliance and increased forced vital capacity (FVC) for their age. Deterioration of pulmonary function and decreased compliance begin at around 10 years of age, with a gradual decline in FVC[47] and the development of restrictive lung disease.

The ability to cough and clear secretions likewise worsens, and pneumonia is frequent in these patients. Nocturnal hypoventilation may require assisted ventilation by the late teenage years.

Cardiomyopathy presents on echocardiography earlier in life, and is often asymptomatic until the early teenage years.[48] Left ventricular hypertrophy is commonly found on electrocardiograms of younger patients. A progressive decline in LV ejection fraction leads to LV failure and the development of a dilated cardiomyopathy. Resting sinus tachycardia is common and may be present prior to the development of impaired systolic function;[49] the incidence of arrhythmias, however, has been shown to correlate with a decrease in ejection fraction.[49]

Glucocorticoid administration has been shown to delay the overall progression of muscle weakness in DMD and advances have been made in management of the respiratory component of this disease. As such, the longevity of these patients has improved into the third and fourth decades and cardiomyopathy has emerged as the major cause of morbidity and mortality.[50]

Perioperative Implications

Patients with BMD and DMD often present for procedures such as scoliosis surgery, and release of contractures, gastric tube placement, or tracheostomy. A thorough preoperative evaluation should take place prior to any surgical procedure. Cardiology consultation is a must prior to any major procedure (i.e., scoliosis) and a baseline ECG, and either echocardiogram or cardiac MRI should be reviewed. Dobutamine stress echocardiogram or Holter monitor may be warranted (upon evaluation by the child's cardiologist).[49] Consultation with pulmonologist should occur to assess the degree of respiratory insufficiency. A decline in FVC may predict moderate (FVC <50% predicted) or high (FVC <30% predicted) risk of respiratory complications perioperatively.[48]

Caution should be exercised with administration of preoperative anxiolysis or sedation which can further compromise existing respiratory insufficiency. Potential airway involvement should be considered: fibrosis of masseter muscles may lead to limited mouth opening and involvement of neck muscles may restrict cervical range of motion. These factors combined with tongue hypertrophy and high rates of obesity may contribute to difficulty with direct laryngoscopy, the incidence of which has been higher in DMD, especially in older patients.[50] Nondepolarizing neuromuscular blocking agents (such as rocuronium) may be safely used in muscular dystrophy, though prolongation of time to peak blockade and recovery should be expected.[49,51]

If cardiomyopathy exists, abrupt changes to CO may occur with patient position (supine to prone), institution of positive pressure ventilation, or abdominal insufflation during laparoscopy.[49] Likewise, the presence of cardiomyopathy should guide fluid management perioperatively (in any type of procedure) to avoid fluid shifts that may promote heart failure.[48] The presence of contractures in the extremities may make peripheral arterial or venous cannulation challenging and also impact positioning.

Significantly higher amounts of blood loss and "impaired hemostatic function" have been documented in patients with DMD undergoing spinal surgery; preoperative planning should focus on ways to minimize homologous transfusion but also avoid hypovolemia in the setting of potential cardiovascular impairment (use of antifibrinolytics or cell salvage with intraoperative autotransfusion).[49,51]

Patients with DMD are at increased risk of acute rhabdomyolysis and subsequent hyperkalemic cardiac arrest. Succinylcholine is a known trigger for this reaction and should be avoided; however, volatile anesthetics are also associated with this reaction, and their use in this patient population is controversial. Many advocate for a nontriggering anesthetic technique (total intravenous anesthetic, or TIVA) to avoid rhabdomyolysis, though

reactions have been reported with nontriggering anesthetic agents as well. Acute rhabdomyolysis from triggering agents may cause a hypermetabolic state that can mimic malignant hyperthermia (MH), but it is not caused by MH nor does muscular dystrophy increase the risk of MH.[46]

Postoperatively, patients may require extubation to noninvasive PPV (especially if required at baseline).[49] Prolonged intubation and mechanical ventilatory support may be required after more extensive procedures (such as posterior spine fusion).

SYNDROMES WITH SPECIFIC CARDIAC CONSIDERATIONS

In addition to Down syndrome, 22q11 deletion syndrome, Turner syndrome, CHARGE syndrome, and VACTERL association, the following syndromes merit special attention because of their high incidence of cardiac involvement and its impact on perioperative planning.

Noonan syndrome is an autosomal dominant genetic disorder with an incidence of approximately 1:1000–2500 live births.[51] A mutation in the RAS/MAPK signaling pathway can be identified in many but not all patients with Noonan syndrome. Many phenotypic features may overlap with those of Turner syndrome, including short stature, webbed neck, broad chest with wide spaced nipples, lymphatic issues, and renal malformations. Cardiac anomalies affect 80% of individuals with pulmonary stenosis (valvar or supravalvar) being the most common defect.

Other frequent anomalies include ASD, partial atrioventricular canal defect, and hypertrophic cardiomyopathy. Bleeding diatheses have been reported in a large proportion of individuals, and may be secondary to platelet dysfunction, thrombocytopenia, or factor deficiencies.[52] Spinal anomalies such as scoliosis, kyphosis, spina bifida, and vertebral or rib abnormalities may be present.[52]

Perioperative Implications

An airway evaluation should be performed preoperatively; like individuals with Turner syndrome, those with Noonan may have a high arched palate and micrognathia. This facial feature combined with a short neck and limited extension may contribute to difficulty with direct laryngoscopy and tracheal intubation. Preoperative assessment should include echocardiography; imaging should be included to evaluate for spinal deformities if neuraxial anesthetic is planned. Coagulation studies and platelet function tests should be performed prior to procedures with potential for significant blood loss.

Williams syndrome (WS) (or Williams–Beuren syndrome) is caused by a contiguous gene deletion on chromosome 7 (usually sporadic but it may be inherited in an autosomal dominant fashion).[53] Its incidence is estimated at 1:20,000 live births.[54] Of primary concern for the anesthesiologist is the potential for cardiovascular disease, but this syndrome like others has a multisystem involvement. Patients may be distinguished by characteristic facies such as midfacial flattening, mandibular hypoplasia, and dental malocclusion, all contributing to difficulty with tracheal intubation.[54] Intellectual disability and developmental delay are also typical. While individuals with WS are known for their unique outgoing “cocktail party” personality, anxiety and ADHD are common.[54,55] Endocrine disease may include hypercalcemia (primarily affecting infants and resolved by age 4 years), hypercalciuria, hypothyroidism, and early puberty. Failure to thrive with feeding difficulties commonly affects infants with WS.[54] Renal or genitourinary involvement incorporates anatomic renal abnormalities, nephrocalcinosis, or bladder diverticuli.[55] Because part of the region of deleted genes on chromosome 7 includes the elastin gene, connective tissue abnormalities may be present, and may manifest as joint laxity or more importantly, as elastin arteriopathy, the cause of cardiovascular pathology in these individuals.[55]

Cardiovascular disease affects 80% of individuals, with most diagnosed by one year of age.[54] Supravalvar aortic stenosis (SVAS) is the most common lesion, present in 45% to 75% of individuals.[54,55] Pulmonary artery stenosis is also quite common and peripheral stenosis is more frequently encountered than central;[54] these lesions typically improve as children age.[56] Coronary anomalies are frequently encountered resulting in coronary artery disease in 5% to 9% of patients. Left or right ventricular hypertrophy caused by outflow obstructive lesions may be present. Hypertension affects over half of individuals with WS and may be secondary to renal artery stenosis; vascular stenoses secondary to elastin arteriopathy are common and may be seen at the thoracic aorta (causing middle aortic syndrome), or mesenteric, carotid, or peripheral arteries. Prolonged QTc has also been observed in WS.[54]

Perioperative Implications

Individuals with WS are at a high risk of sudden cardiac death, and the literature abounds with case reports of anesthesia-related cardiac arrest.[57] Most are secondary to myocardial ischemia. Therefore, a very thorough preoperative evaluation should precede sedation or general anesthesia for any type of diagnostic imaging or surgical procedure. The necessity of the procedure should be determined (given the high risk in the perioperative setting) as should the location—ideally any elective procedure should occur at a tertiary care facility where a pediatric anesthesia team can be involved, and where ECMO is readily available.[57] A cardiologist should be consulted preoperatively and the patient's most recent ECG, ECHO, and cardiac catheterization (if applicable) should be reviewed. Screening for hypercalcemia and hypothyroidism should occur in frequent intervals and calcium/creatinine ratio annually.[56] An airway exam should be performed to assess for potential indicators of difficult airway.

Since anxiety is common in patients with WS, the perioperative hospital setting may exacerbate such behavior; premedication may aid in a smoother induction. Preoperative hydration should be stressed to maintain adequate preload, and scheduling should attempt to minimize prolonged NPO times. Intraoperatively, a five-lead ECG should be utilized to monitor for ischemia, and a lower threshold should exist for placing invasive monitors. According to Burch, "All patients with SVAS should be considered at risk for myocardial ischemia."[57] Anesthetic goals should reflect this and should include maintenance of an age-appropriate heart rate and sinus rhythm, maintenance of preload, contractility and SVR (with vasopressors if needed), and avoidance of increased PVR.[57] Attempts to stratify perioperative risk in individuals with WS indicate that children with biventricular outflow tract obstruction and age <3 years are at highest risk of cardiac arrest,[57] although the potential for perioperative cardiac complications should not be underestimated in any child with WS.

SYNDROMES WITH AIRWAY MANAGEMENT CONCERNS

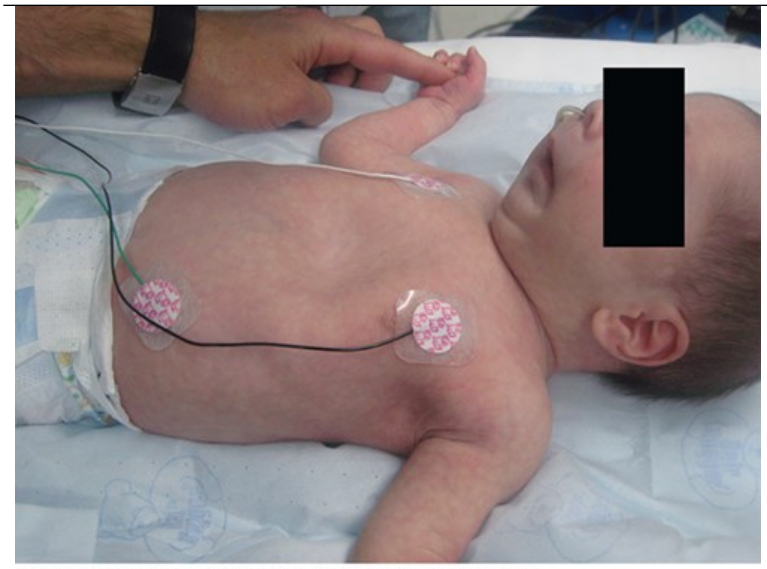
Several syndromes are of interest to the pediatric anesthesiologist because of potential difficulty with ventilation or tracheal intubation. Airway concerns for the following syndromes are outlined below.

Micrognathia or Mandibular Hypoplasia

Pierre Robin Sequence (PRS) is defined by the triad of micrognathia, glossoptosis, and airway obstruction (see Figure 40-3). An underlying genetic abnormality has not been identified and PRS may occur in isolation or in association with a syndrome (commonly Stickler syndrome, 22q11DS, fetal alcohol syndrome, and Treacher–Collins syndrome). Its incidence ranges from 1:5000 to 1:85,000.[58] In non-syndromic PRS, jaw size may increase (and airway difficulty may improve) with age.[43,59] Symptoms in PRS may range from mild to severe, with severe airway obstruction causing respiratory distress and failure to thrive. Affected infants may require various interventions to relieve airway obstruction, including prone positioning, nasopharyngeal airway placement, tongue lip adhesion, mandibular distraction osteogenesis, and/or tracheostomy. Cleft palate is common among individuals with PRS. Due to severe micrognathia and airway obstruction, airway management may be quite challenging. Maintenance of spontaneous ventilation should be emphasized and specialized airway equipment (fiberoptic bronchoscopy, video laryngoscopy) and adjuncts (nasopharyngeal and oropharyngeal airways) should be available. Awake supraglottic device placement (with subsequent fiberoptic intubation) is a well-known successful technique in patients with severe airway obstruction.[60]

Figure 40-3

Pierre Robin neonate. Note the micrognathia and resultant sternal retraction. (Reproduced with permission, from Hung OR, Murphy MF. eds. *Hung's Difficult and Failed Airway Management*. 3rd ed. 2018. https://accessanesthesiology.mhmedical.com. Copyright © McGraw Hill LLC. All rights reserved.)



Source: Herodotos Ellinas, Kai Matthes, Walid Alrayashi, Aykut Bilge: *Clinical Pediatric Anesthesiology*

Treacher-Collins syndrome (or mandibulofacial dysostosis) is caused by a mutation of the *TCOF1* gene and is inherited in an autosomal dominant manner (though 60% arise from new mutations). Its incidence is estimated at 1:50,000 live births. Craniofacial features affecting the airway include maxillary, zygomatic, and mandibular hypoplasia combined with small mouth opening, high arched palate, and temporomandibular joint abnormalities. These features may contribute to airway obstruction hindering bag mask ventilation and difficult direct laryngoscopy and intubation.[60] Unlike individuals with PRS, airway management in Treacher-Collins may increase in difficulty with patient age.[43,61] Airway devices such as nasopharyngeal airways and supraglottic devices should be readily available as should specialized intubating equipment (fiberoptic bronchoscopy, video laryngoscopy) as conventional direct laryngoscopy is often insufficient in these patients.

Craniofacial Microsomia

Hemifacial microsomia is caused by a derangement in the development of the first and second pharyngeal arches during embryogenesis; its cause is unknown, but is thought to be multifactorial (most cases are sporadic, with few inherited; maternal exposure and environmental factors may play a role).[61] Its incidence ranges from 1: 3500 to 1: 27,000 live births.[62] This malformation results in unilateral cranial bone abnormalities, microtia/anotia with preauricular skin tags/pits, microphthalmia, and, most significantly, mandibular hypoplasia which may cause difficulties in direct laryngoscopy and intubation (bilateral microsomia does occur in approximately 20% and may resemble Treacher–Collins syndrome in both clinical phenotype and level of airway difficulty).[63]

Goldenhar syndrome is considered a variant of hemifacial microsomia that, in addition to unilateral cranial and soft tissue deformities, also includes vertebral anomalies and epibulbar dermoids (benign eye cysts).[63] Vertebral anomalies may include fused or hemivertebrae which may limit neck flexion and extension and worsen intubating conditions.[43]

Limited Cervical Mobility

Klippel-Feil syndrome occurs in 1:42,000 births and its etiology is yet unknown. Individuals with Klippel–Feil syndrome have a short neck, low posterior hairline and severe limitation in cervical motion. The *limitation in cervical motion* is caused by congenital fusion of two or more cervical vertebrae (and may be classified into Types I to III based on degree of fusion on radiographic examination). Cervical fusion typically worsens with age.[64] Bag mask ventilation is not typically difficult,[43] but severe restriction of range of cervical motion may make direct laryngoscopy very difficult, and fiberoptic intubation or supraglottic airway device is often the preferred route of airway instrumentation. In addition, individuals with Klippel–Feil syndrome are more likely to have additional skeletal abnormalities, such as atlanto-occipital abnormalities, spinal canal stenosis, and scoliosis.[65] As such, caution with head and neck positioning is advised to avoid neurologic injury during airway manipulation.

Turner, **Noonan**, and **Goldenhar** syndromes are also known for limited cervical mobility, which can hinder tracheal intubation by direct

laryngoscopy.

Craniofacial Synostosis

Apert syndrome (AS), **Crouzon syndrome** (CS), and **Pfeiffer syndrome** (PS) are three of several common genetic syndromes associated with craniosynostosis. All are caused by (usually) de novo mutations in the *FGFR1-3* genes, though these can be inherited in an autosomal dominant fashion. Their incidence ranges from 1:100,000 (Pfeiffer syndrome) to 6–16:1,000,000 (Apert and Crouzon syndromes). In addition to craniosynostosis, all have flat foreheads, proptosis, and midfacial hypoplasia with narrowed nasopharynx or choanal atresia. Individuals with **Apert syndrome** frequently have bilateral symmetrical syndactyly of upper and lower extremities, cleft palate, and fusion of the cervical spine at C5-6.[65,66] **Pfeiffer syndrome** can be differentiated by the presence of broad, radially deviated thumbs or big toes and occasional partial syndactyly. Patients with **Crouzon syndrome** typically have normal hands and feet and may have fusion of the cervical spine at C2-3.[66,67] Learning disability or delayed development are common in AS and PS but individuals with CS usually have normal intelligence.[68]

These individuals are often prone to upper airway obstruction because of midfacial hypoplasia, and many develop OSA. Those with severe respiratory distress often require tracheostomy. Bag mask ventilation may be challenging not only because of upper airway obstruction but also because of insufficient mask fit secondary to midfacial hypoplasia and proptosis. Direct laryngoscopy, however, is not typically difficult unless cervical spine abnormalities are present.[43]

Tracheal cartilaginous sleeve is associated with syndromic craniosynostosis; lower airway stenosis may result and a smaller endotracheal tube than expected may be necessary.[68]

Mucopolysaccharidoses

The mucopolysaccharidoses are a group of hereditary multisystem disorders that lead to cognitive impairment, organ failure, and shortened lifespan.[69] Except MPS II (Hunter syndrome; X-linked recessive) inheritance is autosomal recessive; their incidence ranges from 1:100,000 (MPS I) to 1:2,000,000 (MPS VI).[70] They are caused by deficiencies of different lysosomal storage enzymes creating progressive buildup of glycosaminoglycans (GAGs) in various tissues throughout the body. These diseases are heterogenous and the severity of phenotype varies.

MPS I (**Hurler syndrome**) and MPS II (**Hunter syndrome**) have very similar clinical features, which include progressive development of coarse facial features, corneal clouding, hearing loss, short stature, hepatomegaly and splenomegaly, communicating hydrocephalus, and spinal cord compression with cognitive impairment.[70]

Clinical features of individuals with MPS IV (**Morquio syndrome**) include those for MPS I and II, but these individuals also exhibit skeletal dysplasia, ligamentous laxity and joint hypermobility (rather than stiff joints with decreased mobility in MPS I/II), and odontoid hypoplasia leading to potential cervical spine instability.[70] Individuals also may develop kyphoscoliosis with subsequent restrictive pulmonary defects. Tracheal collapse has also been reported with flexion of the head (which causes buckling of the posterior tracheal wall).[71] In contrast to MPS I and II, these patients typically do not have cognitive impairment.

Airway management is a primary concern in patients with MPS. Submucosal GAG deposition in the tongue, nasopharynx, oropharynx, and larynx leads to progressive upper airway obstruction;[72] mask ventilation can be very challenging or impossible. Additionally, a short neck with limited range of motion and limited mobility of the temporomandibular joint (combined with narrowed and rigid airway anatomy) contribute to difficult direct laryngoscopy and intubation.[71] Incidence of difficult airway in MPS patients has been reported at around 25%;[73] preoperative airway examination is critical as is careful preparation for airway instrumentation. Fiberoptic intubation or video laryngoscopy is often needed and a supraglottic device should be available as a rescue device. As would be expected with progressive GAG buildup, airway difficulty worsens with age.

Secondarily, GAG deposition in the heart can lead to valve thickening and subsequent dysfunction (insufficiency more commonly than stenosis). Generally mitral and aortic valves are affected more frequently; valvular disease can progress to LV volume overload, LVH, or dilation, followed by ventricular dysfunction. Coronary artery narrowing secondary to GAG deposition has also been described.[74]

Enzyme replacement therapy and hematopoetic stem cell transplant are therapies that have been instituted and if initiated early on, they may alter

progression of the disease.

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