The syndromic child and anaesthesia

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Abstract:

Many systems that are relevant to anaesthetists may be affected in syndromic children. These include the spine, airway, respiratory, cardiovascular, genitourinary and neuromuscular systems, as well as coagulation, endocrine and metabolic functions. Embryological development may explain some co-existing anomalies. Although each syndromic child must be managed individually, an approach to evaluating syndromic children and knowledge of common syndromes may be useful.

Keywords: anaesthesia, syndrome, atlantoaxial joint, branchial arches, Down's syndrome, 22q11 deletion syndrome

Introduction

When faced with a syndromic child presenting for surgery, the anaesthetist has to ensure that he or she is familiar with potential issues relating to the specific syndrome. This article will attempt to highlight some of the ways in which systems can be affected. The systems most relevant to anaesthetists are listed in Table 1. Since both the heart and great vessels, and the airways, are often involved in syndromes, it is interesting to note commonalities to the embryology of the two systems.

Embryology

Structures of the mandible, ear and neck develop from the pharyngeal (branchial) arches. The embryo has six pharyngeal arches, and these are in close proximity to the heart field. Each pharyngeal arch contains an artery, nerve and cartilage. The six "arch arteries" are precursors of (among others) the aorta, pulmonary arteries, right subclavian artery, and common and internal carotid arteries (Table 2).[1] The arches are separated by invaginations which are called "pouches" on the endodermal side and "clefts" on the ectodermal side.

The first three arches give rise to structures above the larynx, the fourth and sixth arches give rise to the larynx and trachea, and the fifth arch regresses in humans without contributing to any structure (Table 3).[2]

The term "first arch syndrome" applies to conditions with coexisting abnormalities of the eyes, ears, palate and jaw, and include Treacher Collins and Pierre Robin syndromes.[3]

Neural crest cells

Neural crest cells are stem and progenitor cells that migrate early during embryogenesis from the neural crest into the pharyngeal arches. Here, they form many of the tissues in the head and face, and organise the differentiation of tissues.[4] Abnormalities in their formation, migration or differentiation can lead to defects.

First arch syndrome results from a defect in neural crest cell migration.[4]

The neural crest cells migrate toward the heart via the third, fourth and sixth pharyngeal arches. They interact with the second heart field, which is involved in the formation of the right ventricle, conotruncus and parts of the atria. The neural crest

Table 1: Relevant systems affected by the syndromes

Spine
Atlantoaxial instability
Kyphoscoliosis
Airway
Micrognathia
Midface hypoplasia
Macroglossia
Obstructive sleep apnoea
Cleft lip and palate
Choanal atresia
Abnormal tracheobronchial tree
Pulmonary
Reflux and aspiration
Scoliosis
Alveolar hypoplasia
Cardiac
Cyanotic
Cyanotic
Renal
Coagulation
Metabolic and endocrine
Thyroid function
Calcium
Glucose
Neuromuscular

Table 2: Some structures formed by the pharyngeal arches

Arch	Arteries	Some muscles	Bones
I	Mainly lost, and forms part of the maxillary artery	Mastication	Mandible malleus and incus
II	Stapedial arteries	Facial expression	Part of hyoid stapes and the styloid process
III	Common and internal carotid arteries	Stylopharyngeus	Part of the hyoid process
IV	The left forms part of the aortic arch, and the right forms part of the right subclavian artery	Pharyngeal and laryngeal	Laryngeal cartilage
VI	Form part of the left and right pulmonary arteries		

Table 3: Atlantoaxial instability and cervical spine abnormalities

Down syndrome
Morquio syndrome
Ehlers-Danlos syndrome
Noonan syndrome
Klippel-Feil syndrome
Vertebral fusion
Goldenhar syndrome
Osteogenesis imperfecta
Fracture
Achondroplasia
Arnold-Chiari malformation
Bony defect in the posterior fossa and upper cervical spine
Respiratory depression

Table 4: Conditions with micrognathia or microstomia

Pierre Robin sydnrome
Treacher Collins syndrome
Goldenhar syndrome
Moebius sequence
Osteogenesis imperfecta
King-Denborough (myopathy and malignant hyperthermia)
Noonan syndrome
Turner's syndrome
Trisomy 18
Dandy-Walker malformation (cerebellar hypoplasia and cystic fourth ventricle)

cells are also responsible for the septation of the conotruncus and patterning of the arch arteries.[5]

From what has been mentioned, it is clear how defective neural crest cell migration, through the pharyngeal apparatus, can be responsible for the phenotype of 22q11 deletion (including Di George syndrome), namely a shortened mandible (the first arch), ear defects (the first and second arches), parathyroid and thymic defects (the third and fourth pouches), and cardiac, particularly conotruncal, defects (the third, fourth and sixth arches).[6]

Spine

Many conditions are associated with abnormalities of the spine, which may cause scoliosis, or may be concerning when regional anaesthesia is being considered. Atlantoaxial instability can

have life-threatening implications. Table 3 lists some syndromes associated with this problem.

Achondroplasia is an autosomal dominant condition that causes disproportionate dwarfism.[7] Patients may present with airway and ventilation difficulties owing to their large head, midface hypoplasia and macroglossia (which may cause upper airway obstruction), reflux disease and hypotonia (during infancy).[8] Spinal abnormalities include thoracolumbar gibbus, an exaggerated lumbar lordosis, kyphosis with restrictive lung disease and spinal stenosis, which makes for many controversies regarding regional anaesthesia.[9] Foramen magnum stenosis or atlantoaxial instability may also be present, with or without central sleep apnoea, which may be fatal.

Morquio syndrome is a glycogen storage disorder and is associated with a short trunk and neck, midface hypoplasia, obstructive sleep apnoea and kyphoscoliosis, leading to life-threatening *cor pulmonale*.

Airway

The airway and respiratory system are frequently involved in syndromes (Table 1). Because of the common embryological origin, it should be expected that patients with abnormalities of the ears might have upper airway anomalies.[2]

Congenital micrognathia is much more commonly associated with a syndrome (Table 4), than being an isolated anomaly.[10] Obstructive sleep apnoea is a common complication, especially when micrognathia is associated with glossoptosis.[2] Three conditions, namely Pierre Robin, Treacher Collins and Goldenhar, syndromes, are particularly well known for their potential with regard to difficult intubation.

Pierre Robin syndrome consists of severe micrognathia, posterior displacement of the tongue, and cleft lip and palate.[11] Those affected may also have vagal hyperactivity and central apnoea, and Pierre Robin syndrome can be part of a syndrome, e.g. 22q11 deletion or Down's syndrome.[12]

Treacher Collins syndrome is an autosomal dominant disorder consisting of hypoplasia of the facial bones, down-slanting eyes, ear abnormalities, cleft lip and palate, and coloboma of the lower eyelids.[4]

Goldenhar syndrome (oculoauriculovertebral dysplasia and hemifacial microsomia) results in facial asymmetry, owing to the classical triad of mandibular hypoplasia, ear and/or eye deformities and vertebral anomalies. Cardiac, renal, gastrointestinal and central nervous system involvement, as well as cleft lip or palate and temperomandibular joint anomalies, are also possible.[13] Atlantoaxial instability is also a significant risk.[14]

Macroglossia, which may cause airway difficulty, is associated with conditions involving dwarfism, Down's syndrome, Apert and Crouzon syndromes (craniosynostoses, which may also have vertebral fusion), Beckwith-Wiedemann syndrome, and the mucopolysaccharidoses, Hunter's and Hurler's syndromes.[15]

When encountering a patient with a cleft lip and/or palate, it is useful to know that only 10% of isolated cleft lips are associated with other abnormalities, whereas the incidence of associated anomaly is 25% for cleft lip and palate and 45% for isolated cleft palate. Also, a bilateral cleft is more often associated with other anomalies than a unilateral cleft.[16]

Heart

Cardiac lesions can be congenital or acquired. These acquired lesions may be secondary to the primary condition, as is the case with connective tissue disorders, osteogenesis imperfecta (OI) and mucopolysaccharidosis. A study of children who presented with surgically correctable congenital anomalies (of whom 46% were cleft lip or palate patients) found that on echocardiography, up to 35% of the children had cardiac anomalies. These were mostly atrial septal defects, followed by ventricular septal defects. The majority of these lesions were not detected clinically.[17]

With cardiac embryology in mind, it is interesting to note that some syndromes are associated with heart defects specifically involving the outflow tract and great vessels, i.e. conotruncus (Table 5).

Those with Williams syndrome (partial deletion of chromosome 7) can also have coronary and other arterial stenoses, hypercalcaemia, hypothyroidism and developmental delay. The combination of obstruction of ventricular outflow and coronary disease can lead to sudden death, which may happen during anaesthesia.[18,19]

Noonan syndrome has much the same phenotype as Turner's syndrome, with a webbed neck, low hairline, hypertelorism, short stature, micrognathia and kyphosis. In contrast to Turner's syndrome, it is an autosomal dominant disorder. It may be associated with significant vertebral anomalies including spina bifida, hemivertebrae and a narrow spinal canal. Coagulation defects may be present.

Apart from cardiac involvement and a cleft palate, those with Turner's syndrome may have renal defects and endocrine dysfunction. Patients are also prone to osteoporosis.

Table 5: Syndromes with defects of the outflow tract and great vessels

Syndrome	Cardiac lesion
Williams	Supravalvular aortic stenosis
	Supravalvular pulmonary stenosis
	Aortic coarctation
	Aberrant coronary vessels
Noonan	Pulmonary stenosis
Turner's	Aortic stenosis
	Aortic coarctation
22q11 deletion (includes di George syndrome)	Truncus arteriosus
	Tetralogy of Fallot

Coagulation

As mentioned above, patients with Noonan syndrome may have coagulation disorders. Patients with conditions involving connective tissue may also manifest with clotting abnormalities.

OI is a disorder of connective tissue, usually transmitted as an autosomal dominant trait.[20] Defective collagen formation places such patients at risk of fractures (even with positioning or inflation of a blood pressure cuff). They also suffer from micrognathia, abnormal teeth, a short neck, pectus excavatum, scoliosis and joint laxity. Conductive hearing loss may be present, as well as blue discolouration of the sclera. There are four recognisable types of OI of varying severity, from fatal (intrauterine or immediately postnatal), to mild disease with risk of fracture due to mild trauma, and osteoporosis. Cardiac lesions may be acquired (aortic root dilatation). Coagulation disorder can be ascribed to a combination of capillary fragility, decreased factor VIII production and decreased platelet aggregation. Fifty per cent of patients with OI have elevated thyroxine levels, and many OI patients have a heart rate, respiratory rate and temperature above that in the normal range. A hypermetabolic reaction to anaesthesia has been described, but in most circumstances the cause of the rise in temperature during anaesthesia is unclear.[20]

Metabolic and endocrine derangements

Beckwith-Wiedemann syndrome is characterised by macroglossia, omphalocele or umbilical hernia, gigantism, visceromegaly and cryptorchidism.[21] Patients have a predisposition to developing malignancies, and may have cardiac and skeletal anomalies, hypoglycaemia, hypercholesterolaemia and congenital hypo-thyroidism.

Hypothyroidism is also a well-known risk for patients with Down's syndrome, and can develop at any stage. Their thyroid functions should be tested at birth, at six months, and then annually.[22]

Hypercalcaemia and hypothyroidism can be features of Williams syndrome,[19] and hypocalcaemia due to hypoparathyroidism can be a feature of 22q11 deletion (Di George syndrome).

Neuromuscular disorders

Apart from the highly prevalent disorders of cognitive and behavioural function in children with syndromes, a number of patients may have myopathies. Concerns with regard to patients with myopathies include the airway, bulbar muscle function, respiratory and cardiac function,[23] as well as sensitivity to anaesthetic agents. The latter may result in a hypermetabolic crisis, acute rhabdomyolysis or malignant hyperthermia. Data are still equivocal in this regard, but certain patients are definitely at increased risk.

Those with the dystrophinopathies (Duchenne and Becker muscular dystrophy) may develop acute rhabdomyolysis, especially in younger children where less muscle fibrosis is present.[24] Those with the enzymopathy, carnitine palmitoyltransferase II deficiency, may have acute rhabdomyolysis in response to exercise, fasting, stress and infection. Therefore, it is prudent to avoid inhalational agents and succinylcholine in these patients.[25] Of the familial periodic paralyses, only those with hypokalaemic periodic paralysis may present with hypermetabolic crisis or malignant hyperthermia. Two congenital myopathies, namely central core disease and a subset

of multiminicore myopathy, have an increased risk of malignant hyperthermia.[24]

King-Denborough syndrome has a similar phenotype to Noonan syndrome, with the addition of congenital myopathy which causes proximal weakness and a high risk of malignant hyperthermia.[24,25] Native American myopathy has a similar phenotype, whereby patients present with a cleft palate, a high-arched palate, micrognathia, myopathic facies, a short stature, scoliosis, cryptorchidism, arthrogryposis and clubbed feet. Those affected are also at high risk of developing malignant hyperthermia.[26]

Since Down's syndrome is the most common chromosomal disorder, and 22q11 deletion is currently the most common deletion syndrome known,[6] these will be discussed in further detail.

Down's syndrome

Down's syndrome (trisomy 21) occurs in 1 in 800 live births. Macroglossia, hypotonia, midface hypoplasia and a short neck may result in obstructive sleep apnoea, and can cause airway difficulty on induction of anaesthesia. Other reported airway abnormalities include laryngomalacia, tracheomalacia, bronchomalacia, a narrow trachea and a tracheal bronchus.[27] Because of an increased incidence of subglottic stenosis, a smaller-than-expected endotracheal tube is often required. Patients with Down's syndrome have an overactive vagal tone, and are prone to bradycardia. A review of anaesthesia-related complications in patients with Down's syndrome found severe bradycardia, natural airway obstruction, difficult intubation, post-intubation croup and bronchospasm to be the most frequent problems.[28] Airway concerns are compounded by the risks of atlantoaxial subluxation (which has an incidence of 1%) and alveolar hypoplasia.

Forty to 50% of patients with Down's syndrome have cardiac abnormalities,[29] of which 80% are either atrioventricular septal defects or ventriculoseptal defects. Mitral valve prolapse or aortic incompetence may be acquired later in life, and patients with Down's syndrome have a tendency to develop pulmonary hypertension rapidly.[30] Therefore, their atrioventricular canal defects are often associated with cyanosis. Abnormalities of radial arteries may cause difficulties when placing arterial cannulas.

Apart from hypothyroidism, hyperthyroidism may also occur. Immunosuppression, autoimmune disorders, diabetes and an increased incidence of leukaemia are all potential problems in patients with Down's syndrome. Up to 30% of neonates with duodenal atresia have Down's syndrome.[31]

22q11 deletion

Between 1968 and 1978, three syndromes were described with overlapping features: Di George, velocardiofacial (Shprintzen's) and conotruncal anomaly face. By 1993, genetic investigations found 22q11 deletions in 80–90% of these patients, and it is now estimated that 22q11 deletion has an incidence of 1:4 000–1:6 000.[6] The phenotype and severity of the syndrome is variable, but common features are listed in Table 6. The pneumonic, "catch 22", is often used to describe these features, i.e. cardiac abnormalities, abnormal facies, thymic hypoplasia, cleft palate and hypocalcaemia.

Table 6: Common features of 22q11 deletion

Cardiac abnormalities (typically conotruncal)
Tetralogy of Fallot
Interrupted aortic arch
Perimembranous ventricular septal defects
Truncus arteriosus
Dysmorphic facies
Microcephaly
Retrognathia
Dysplastic ears
Hypertelorism
Hypocalcaemia
Immune deficiency
Palate anolmalies
Velopharyngeal dysfunction
Speech disorders
Feeding disorders
Cognitive disorders
Behavioural or psychiatric disorders

Airway abnormalities include a short trachea, laryngomalacia, tracheomalacia and bronchomalacia. Pierre Robin syndrome is present in 11–17% of patients. Obstructive sleep apnoea and velopharyngeal dysfunction (the latter is present in 80% of patients) predispose patients to complications relating to the airway and respiratory systems.

Only 20% of patients have normal hearts. If the following cardiac lesions are diagnosed, testing for 22q11 deletion should be performed: Tetralogy of Fallot (especially if associated with pulmonary atresia), truncus arteriosus, interrupted aortic arch, isolated aortic arch anomalies and a perimembranous ventriculoseptal defect with concurrent aortic arch anomaly.

Immune deficiency, comprising *T*-cell deficiency due to thymic hypoplasia, is present in up to 80% of patients, with varying degrees of severity.[32] Recurrent infections and autoimmune diseases may result. These patients are at risk of developing graft-versus-host disease when receiving blood transfusions, and irradiated blood should be used.

Parathyroid hypoplasia leads to hypocalcaemia. 22q11 deletion is one of a limited number of causes of neonatal hypocalcaemia. While it generally improves over the first year of life, there have been case reports of new-onset hypocalcaemia in adults.[32]

Speech delay is a common feature. Neurocognitive disorders include learning disabilities, attention-deficit/hyperactivity disorder and autism. Schizophrenia develops in up to 25% of patients.[6]

Conclusion

Although there are a multitude of syndromes, it is useful for the anaesthetist who is assessing a syndromic child to actively search for specific anomalies that might potentially impact on the provision of anaesthesia. Systems that may be affected include cardiac, airway and neck, and respiratory, as well as coagulation, metabolic and endocrine (less commonly considered).

Issues that may impact on perioperative care should be actively sought in order to manage a syndromic patient safely. Careful planning includes selecting an appropriate location for the procedure. The need for maintenance fluids should be considered during preoperative starvation, and problems with behaviour and obstructive sleep apnoea must be considered when deciding on premedication. An appropriate anaesthetic technique needs to be selected, taking into consideration risks such as acute rhabdomyolysis. Patients must also be positioned carefully. Postoperative care has to be individualised. Underlying disorders may increase the need for a higher level of care after anaesthesia. Analgesic techniques should be tailored to maximise treatment while minimising the risks relating to cardiorespiratory depression and anatomical defects, e.g. scoliosis.

Conflict of interest

There was no conflict of interest to declare.

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