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REVIEW

22q11.2 deletion syndrome: an anaesthetic perspective

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Owing to the increased sensitivity and availability of molecular testing, the last decade heralded a new understanding of 22q11.2 deletion syndrome. An awareness of the clinical significance of this syndrome is increasing across medical specialties.

22q11.2 deletion syndrome is the most common microdeletion syndrome. It affects most organ systems but, due to poor phenotypical recognition, it is still vastly underdiagnosed. The incidence of confirmed cases is 1 in 3 000 live births, and it is estimated that the actual incidence among the general population might be much higher than recognised.

Several syndromes previously classified according to phenotypical expression, such as DiGeorge syndrome, velocardiofacial syndrome, conotruncal anomaly face syndrome, Cayler cardiofacial syndrome, CATCH 22 and several psychiatric abnormalities due to a deletion on the long arm of chromosome 22, are now known to be part of a single syndrome.

Pathological features of the syndrome extend beyond the better known conotruncal cardiac defects. Knowledge of the spectrum of the disease is paramount to delivering safe anaesthesia to this cohort of patients.

Anaesthetists have the opportunity to improve recognition and diagnosis of 22q11.2 deletion syndrome and all its clinical manifestations which will allow for multidisciplinary intervention and improve patient outcome and quality of life.

Keywords: DiGeorge syndrome, congenital heart disease, airway abnormalities, anaesthesia syndromes, transfusion-associated graft-versus-host disease

Introduction

Most clinicians are familiar with DiGeorge syndrome and its hallmarks of congenital heart defects, hypoparathyroidism and thymic hypoplasia. Dr DiGeorge, a paediatric endocrinologist from Philadelphia, received international recognition in the mid-1960s for his discovery of a disorder which is characterised by a hypoplastic thymus and parathyroid glands, conotruncal heart defects and specific facial features. This syndrome is but one of multiple syndromes and clinical associations which are now linked to a microdeletion on the long arm of chromosome 22.

Pathophysiology and genetics

Historically, syndromes were defined based on prominent phenotypical features as well as the subspecialties where patients presented during a lengthy ordeal of their diagnostic odyssey.[1] Considerable overlap of diagnostic criteria between syndromes suggested a similar cause and, with the availability of cytogenetic studies in the early 1980s, 22q11.2 deletion was found to be the common denominator. The development of fluorescence in situ hybridization (FISH) probes in the early 1990s allowed for several syndromes and clinical associations to be defined by their common molecular etiology. 22q11.2 deletion syndrome (22q11DS) is now known as the most common microdeletion syndrome with an incidence of 1 in 1 000 in unselected fetuses and 1 in 3 000–6 000 live births.[2]

Deletions of 22q11.2 include a range of phenotypes previously classified as DiGeorge syndrome, velocardiofacial syndrome, conotruncal anomaly face syndrome, Opitz G/BBB syndrome, Cayler cardiofacial syndrome, CATCH 22 and more.

The microdeletion is associated with abnormalities in multiple organ systems. The large variety of symptoms stemming from a small genetic deletion suggests a strong argument for regulatory protein abnormality involved in embryological development and gene expression.

Most deletions occur de novo and only 7% of patients have a family member with the deletion. Phenotypical expression is unrelated to the size or exact position of the deletion. Not all deletions can be diagnosed with FISH probes, as deletions can be smaller nested deletions. These deletions can be diagnosed with chromosomal microarray or multiplex ligation-dependent probe amplification.[3]

Clinical features pertinent to anaesthetic management

Most of the features of importance to anaesthetists are those involving the airway, cardiovascular system, blood transfusions, immune system and gastrointestinal tract. Typical facial features include abnormalities of the auricular helix, like a thick overfolded helix, eye hooding, protuberant ears, epicanthal folds and micrognathia.[3]

Congenital heart disease

Congenital heart disease is the leading cause of mortality in patients with 22q11DS and exceeds the mortality of non-syndromic individuals with comparable cardiac defects according to a study by Carotti et al.[4] In contrast, O'Byrne et al.[5] found no difference in mortality between patients with and those without 22q11DS undergoing surgery for truncus

arteriosus and interrupted aortic arch. They did, however, find a statistically significant increase in ventilator days, length of stay in an intensive care unit and reoperation rates in patients with 22q11DS.[5]

Of the 22q11DS patients on the database of the dedicated 22q11DS centre at The Children's Hospital of Philadelphia, 64% have a cardiac defect.[3] This percentage may be much higher in centres where 22q11DS is vastly underdiagnosed, as the diagnosis is often limited to patients who present with congenital cardiac defects.

The most common cardiac defects are interrupted aortic arch, aorta coarctation, truncus arteriosus, Tetralogy of Fallot, atrial septal defect/ventricular septal defect (ASD/VSD), hypoplastic left heart syndrome and transposition of the great arteries. Conotruncal defects are the result of malalignment and incomplete septation of structures developing from the fourth and sixth branchial arches.[3]

Truncus arteriosus and interrupted aortic arch are lesions that require surgery in the neonatal period and as such the genotype should be taken into account as part of the preoperative risk assessment.[5] Congenital heart defects with 22q11DS are frequently associated with additional cardiovascular anomalies that will complicate cardiac surgery. These anomalies can be found at the aortic arch, pulmonary arterial tree, infundibular septum or semilunar valves.[6] In order to anticipate potential complex cardiac and vascular anatomy, cardiologists and surgeons need to be aware of the 22q11DS diagnosis, and they have to have a low threshold for cardiac catheterisation if echocardiography is insufficient. Magnetic resonance imaging can also be used to delineate vascular defects.

Electrolytes require close scrutiny. Calcium levels must be tested regularly (even if calcium levels were previously normal) and hypocalcaemia should be suspected when there is a reduced response to inotropic support. A respiratory alkalosis must be prevented as it can lower serum calcium.[6] Blood products require gamma irradiation to prevent transfusion-associated graft-versus-host disease (TA-GVHD). Strict asepsis must be adhered to for all invasive procedures.

Transfusion

The risk of TA-GVHD is related to the amount of viable donor T lymphocytes transfused, the human leukocyte antigen (HLA) disparity between donor and recipient, and the ability of the host immune system to eliminate donor lymphocytes.[7]

Patients with 22q11DS are at higher risk of TA-GVHD even when an initial immunological screen is normal. The stress of cardiopulmonary bypass may unmask subtle immune deficiencies. Even though the risk of TA-GVHD is very low, the resulting mortality approaches 100%. All patients with suspected 22q11DS should receive gamma irradiated cellular blood products. This includes red cells, platelets and fresh frozen plasma. Freeze-dried plasma and cryoprecipitate do not need to be irradiated. Leukocyte filtration is not effective at preventing TA-GVHD. Some centres routinely irradiate all blood products for cardiac surgery in patients under the age of six months. Yet, the criticism for the wide-scale irradiation of blood products include cost, reduced shelf life and accelerated potassium efflux.[7]

First-degree family member donor transfusion might exhibit minimal HLA disparity and counterintuitively increases the risk of TA-GVHD. Nonetheless, this risk will also be eliminated with gamma irradiation.

Airway abnormalities

Airway abnormalities are underdiagnosed, yet it is an important and common feature of 22q11DS. Common facial features involving the airway include narrow nares, a small mouth and retrognathia.

Structural airway abnormalities occur in up to 70% of 22q11DS patients that present for otolaryngological assessment. It is possible that a large number of children who present for assessment of stridor, sleep apnoea, speech abnormalities or feeding difficulties have undiagnosed 22q11DS.[8]

Sacca et al.[8] analysed 74 known 22q11DS patients from The Children's Hospital of Philadelphia who underwent otolaryngological assessment. They found that the most common structural abnormalities, in descending order of frequency, were tracheomalacia, subglottic stenosis, laryngomalacia, glottic webs and bronchomalacia. Other airway abnormalities included tracheo-oesophageal fistula, laryngeal clefts, cleft palate and choanal atresia. Velopharyngeal insufficiency is present in at least a third of patients with 22q11DS and can be due either to a cleft palate or to hypotonia.[9]

Polyhydramnios was found to be a good predictor of structural airway abnormalities. Patients with severe structural abnormalities will often require a tracheostomy and possible laryngotracheal reconstruction.[8]

The majority of patients known to have 22q11DS who have airway anomalies also had a congenital cardiac defect (91%). This could be ascribed to the fact that congenital heart disease is the clinical entity that first leads to genetic testing and diagnosis.

Airway abnormalities can lead to high morbidity in patients, especially when associated with congenital heart disease. Therefore, all patients with confirmed 22q11DS should have a thorough airway assessment. The diagnosis of 22q11DS should be considered in patients with unexplained airway abnormalities.

Difficulty with both laryngoscopy and laryngeal mask placement should be anticipated. A smaller endotracheal tube and advanced airway management cart should be readily available. The patient's tracheal length can be shorter with a reduced number of tracheal rings, so the depth of the endotracheal tube must also be considered to avoid endobronchial placement.[9] Patients are at higher risk of gastro-oesophageal reflux secondary to pharyngeal and oesophageal dysmotility.

Owing to chronic otitis media and sinusitis, 22q11DS patients might also present more frequently for otolaryngology procedures. This relates to an underlying immune deficiency, eustachian tube dysfunction and velopharyngeal incompetence.[9]

Immunodeficiency

Immune dysfunction affects up to 75% of patients with 22q11DS.[9] Immunodeficiency ranges from complete thymic aplasia to mild T cell dysfunction. Typical abnormalities include low T cell numbers, low levels of immunoglobulin, and decreased T cell and humoral function.[10]

The degree of immunodeficiency is unrelated to the size of the deletion or the phenotypical expression.[10] Thymus imaging is of little value as neither the size nor the absence of thymic tissue correlates with individual immune function. It is therefore recommended that all patients with 22q11DS should have an immunological screen.[7]

Patients are at increased risk of infection from immune dysfunction but also contract sinopulmonary infections more frequently, secondary to velopharyngeal insufficiency, eustachian tube dysfunction and gastro-oesophageal reflux. Aseptic technique must be strictly adhered to with vessel cannulation, intravenous infusions, airway manipulation or any other invasive procedure.

The use of cytalomegalovirus (CMV) seronegative blood products should be considered in severe immunocompromised patients.[7] Preventative treatment includes pneumococcal immunisation and pneumocystis prophylaxis, and some centres also include an antifungal and aminoglycoside for cardiac surgery prophylaxis. Immunoglobulin replacement is indicated for specific immunoglobulin deficiencies. Patients with athymia can be considered for thymus transplantation as survival without intervention is extremely poor.[9]

Immunodysregulation increases the risk of autoimmune disease and is present in approximately 30% of patients with 22q11DS. Juvenile rheumatoid arthritis, idiopathic thrombocytopenia, hemolytic anaemia and thyroid disease are commonly seen in 22q11DS.[11]

Malignancy rates are higher in 22q11DS and includes hepatoblastoma, Wilms tumour, renal cell carcinoma, thyroid carcinoma, melanoma and leukaemia in the Children's Hospital of Philadelphia cohort.[3]

Endocrine abnormalities

22q11DS is associated with hypoparathyroidism, growth hormone deficiency and hypo- and hyperthyroidism.

Hypocalcaemia secondary to parathyroid aplasia or hypoplasia is a cardinal feature of DiGeorge syndrome and can be life-threatening.[11] The prevalence is lower for other clinical presentations of 22q11DS but should certainly always be considered. Neonatal hypocalcaemia can present as seizures, tetany or tremors. Seizures during the neonatal period are associated with intellectual disability in later life and calcium levels have been shown to influence neurodevelopment.[12] Calcium levels should be maintained in the low normal range (total serum concentration 2–2.25 mmol/L). This will avoid renal calculi, as, in the absence of the parathyroid hormone, renal excretion of calcium will remain high.[13] Severe symptomatic hypocalcaemia should be treated with an intravenous infusion of 10% calcium gluconate at a dose of 0.5 ml/kg (0.11 mmol/kg) to a maximum of 20 ml over 10 minutes. This can be followed by a continuous infusion over 24 hours of 0.5–1.0 mmol/kg. Calcium gluconate should be diluted 1:5 with 0.9% sodium chloride or 5% glucose if it is given in a peripheral line. Central venous administration is advised.[14] Hypocalcaemia may be unmasked during a cardiopulmonary bypass with the infusion of citrate containing blood products.[7] Hypocalcaemia improves with age.

Growth retardation, even in those without associated congenital heart defects, is more prevalent in children with 22q11DS. Some children have a growth hormone deficiency and respond well to recombinant growth hormone therapy.[3,14]

Unsurprisingly, disorders of the thyroid gland are occasionally found in patients with 22q11DS, as the deletion syndrome is partly associated with developmental defects of cranial neural crest cells of the fourth and fifth pharyngeal pouches. Thyroid hormone abnormalities can also be secondary to autoimmune disease.

Regular clinical endocrine evaluation and calcium levels should form part of the long-term care of 22q11DS patients, and the latest results should be evaluated prior to the administration of any anaesthetic.

Gastrointestinal and renal involvement

The majority of patients with 22q11DS will have gastrointestinal involvement. Chronic constipation, dysphagia and feeding problems are commonly observed; some may also require nasogastric feeding or gastrostomy tube placement.[3] Structural bowel disease such as intestinal malrotation, imperforate anus and congenital diaphragmatic hernia occur more frequently in patients with 22q11DS.[8] Oesophageal atresia occasionally occurs in patients with 22q11DS but is more frequently associated with 16q deletion disorders.

Approximately one-third of patients have genitourinary abnormalities such as renal agenesis, dysplastic or cystic kidneys, a duplicated collecting system, hydronephrosis and hypospadias.[3]

Skeletal abnormalities

22q11DS has a scoliosis risk of 50% by the age of 16. Cardiothorasic surgery before the age of 12 compounds this risk.[15] 22q11DS is also associated with polydactyly, camptodactyly, arachnodactyly and radial ray defects in the upper limbs. Lower limb involvement includes 2–3 syndactyly, overlapping toes, hammer toes, postaxial polydactyly and clubfoot.[16]

Neurodevelopmental and neuropsychiatric involvement

Patients with 22q11DS commonly suffer from neonatal seizures, developmental delay, or speech, language and hearing impairment. Seizures are sometimes caused by hypocalcaemia and should be corrected immediately. Attention deficit hyperactivity disorder, autism spectrum disorder and anxiety also occur frequently: neurodevelopmental disorders should be considered during preoperative planning and choice of premedication.[17]

Schizophrenia, depression and early-onset Parkinson's disease are associated with 22q11DS in later life.[18]

Table I: Tests to be considered for evaluation of patients with 22q11DS[20]

- Echocardiogram to evaluate conotruncal abnormalities
- Complete blood count with differential
- T and B lymphocyte subset panels
- Flow cytometry to assess T cell repertoire
- Immunoglobulin levels
- Vaccine titers for evaluation of response to vaccines
- Serum ionised calcium and phosphorus levels
- Parathyroid hormone level
- Chest X-ray for thymic shadow evaluation
- Renal ultrasound for possible renal and genitourinary defects
- Serum creatinine
- TSH
- Testing for growth hormone deficiency

The anaesthetist's role beyond theatre

It has been more than 20 years since the introduction of molecular testing but, despite 22q11DS frequency, its variable clinical presentation continues to be a significant diagnostic challenge. A Canadian study[1] found that the median time from first clinical contact to molecular diagnosis was 4.7 years.

Diagnosis and multidisciplinary team involvement from an early age would not only improve the long-term outcome and quality of life, but also reduce healthcare cost.[1] Early neurodevelopmental assessment and educational support, such as speech therapy, could improve cognitive outcome and facilitate attendance to mainstream schools. Continued screening and neuropsychiatric involvement in later life will also allow for better management of these conditions.

The South African healthcare system is currently vastly underdiagnosing and consequently mismanaging patients with 22q11DS. This is due to lack of awareness, the inability to recognise the variable phenotypical expression and the unavailability of a multidisciplinary care package to address this common syndrome.[19]

Recognition of 22q11DS is of the utmost clinical importance for anaesthetists and will guide the management with regard to possible multisystem involvement, sterility practice for the prevention of infection in a potentially immunocompromised patient, blood product management, the anticipation of a difficult intubation, behavioural challenges and hypocalcaemia.

Conclusion

The anaesthetist's role in addressing the gap in the South African healthcare setting should extend beyond their clinical practice. This is because anaesthetists work across a multitude of surgical and medical disciplines. With recognition of phenotypical clues in one surgical discipline, the opportunity is offered to encourage further diagnosis and invite further screening from other disciplines.

Anaesthetists often wade through a lengthy history of seemingly unrelated medical problems, yet focus on the current surgical dilemma. Instead, they could recognise that the early feeding problems, the tonsillectomy at a young age that did not resolve the upper airway obstruction, and the multiple admissions for chest infections, are not all merely "a case of bad luck" in the teenager currently presenting for scoliosis surgery.

Table II: Abnormalities associated with 22q11DS pertinent to the perioperative period

Potential abnormalities	Implication for perioperative care
Airway abnormalities	
Small mouth Retrognathia Tracheomalacia Subglottic stenosis Glottic webs Bronchomalacia Trachea oesophageal fistula Laryngeal clefts Velopharyngeal insufficiency Cleft palate Reduced number of tracheal rings Choanal atresia	Challenging airway Need for advanced airway equipment Increased risk of aspiration May require smaller endotracheal tube Endobronchial intubation due to shorter trachea High incidence of associated cardiac defects
Congenital cardiac defects	
Interrupted aortic arch Coarctation Truncus arteriosus Tetralogy of Fallot Ventricular septal defect Atrial septal defect Hypoplastic left heart syndrome Transposition of the great arteries	Complex cardiac surgery during the neonatal period Intraoperative consideration of airway, endocrine and immune challenges Difficult anatomical correction Potential complicated postoperative course
Immune system	
Complete thymic aplasia Partial T cell dysfunction Autoimmune disease Increased incidence of malignancy	Increased risk of infection – maintain aseptic technique TA-GVHD – use irradiated blood products
Endocrine abnormalities	
Hypoparathyroidism Hypo- or hyperthyroidism	Hypocalcaemia with risk of seizures Increased sensitivity to anaesthetic drugs and decreased response to inotropes with hypothyroidism
Psychiatric/developmental involvement Developmental delay Speech and hearing difficulty Attention deficit hyperactivity disorder Autism spectrum disorder Anxiety	Will need preoperative assessment for individualised premedication and preoperative environment needs

The opportunity to invite multidisciplinary screening should never be missed, especially for known 22q11DS patients already sedated in the intensive care unit after cardiac surgery.[7] It affords the ideal opportunity to do a thorough airway examination. The opportunity should rather be used to educate parents with regard to future expectations and to establish a follow-up plan, especially for neurodevelopmental assessment.

There is a worldwide drive to increase the awareness surrounding 22q11.2 deletion syndrome. One organisation that aids such education and awareness is The International 22q11.2 Foundation (https://www.22q.org/). Also, support groups are available in some countries such as Max Appeal in the United Kingdom (https://www.maxappeal.org.uk/).

Conflict of interest

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