Managing congenital heart disease and comorbidities – opening a pandora's box?

Congenital heart disease can be a scary scenario when other pathologies are present.

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A common scenario

Mrs Smith brings you her son, John, aged 3 weeks. He has become very yellow and she says that his stools are a strange, whitish colour. He is well otherwise. On examination you confirm deep jaundice, but in addition you notice that he is cyanosed and that he has a 3/6 ejection systolic murmur at the upper left sternal border – you suspect that he may have biliary atresia and tetralogy of Fallot. You also note that he looks a little unusual, but you can't quite put your finger on it.

On further investigation, it is found that John indeed has biliary atresia and tetralogy of Fallot. A geneticist suggests that he may have Alagille syndrome, and this is subsequently confirmed by the finding of a microdeletion on chromosome 20p. What now? Should he be offered repair of the tetralogy, or does the decision depend on the outcome of his Kasai operation? Who makes the choice? He will require a liver transplantation in due course. Is it fair to put John and his family through this ordeal? Does the decision depend on a favourable cardiac prognosis or liver prognosis?

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Congenital heart disease and comorbidities

The birth incidence of congenital heart disease (CHD) is just less than 1%.[1] Of these children, approximately 50 - 60% will require surgery. Between 25% and 30%[2] of children with CHD will have some form of additional congenital lesion, a comorbidity or structural extracardiac anomaly (ECA) that may or may not be immediately apparent. However, a comorbidity may have an important, even crucial, bearing on the course and outcome of the management of a child with a congenital heart lesion. In recent times the surgical options for complex congenital cardiac surgery have increased significantly and therefore the presence and severity of comorbidities have become increasingly important in the management of CHD. This includes both the complexity of the surgery in the first place and the decision to offer surgery at all. It is known that the surgical mortality of CHD surgery of children with ECAs may be as high as 60%.[3] Does one offer John a repair of his tetralogy?

This article highlights the frequent association between CHD and comorbidities, offers a structured approach to management, discusses the implications of management of these complex patients and raises some ethical concerns.

At the outset it is important to note that a complete clinical examination and a CXR of a child with ECAs have been shown to be 100% sensitive for the exclusion of CHD. A referral to a cardiologist is only warranted if any signs are detected, or if the surgeon requires anatomical cardiac detail (e.g. aortic arch sidedness) for the correction of an ECA.[4]

Associations

For practical purposes extracardiac associations can be broadly grouped under 4 headings:

- known genetic syndromes
- structural malformations
- metabolic associations
- teratogens.

Known genetic syndromes

A large number of known genetic syndromes have a cardiac defect as part of their typical dysmorphic spectrum. These are generally classified under chromosomal disorders (both aneuploidy and deletion syndromes) and single gene mutations.

Down syndrome is the commonest recognisable syndrome, making up 9% of the clinical load of a tertiary referral centre.[5] Fifty per cent of children with Down syndrome will have a significant cardiac lesion.[2] The 22q11.[2] deletion syndrome (also known as DiGeorge syndrome) is the commonest microdeletion syndrome in humans, and is associated with various intracardiac and outflow lesions. Noonan syndrome is typical of a single gene mutation syndrome that may or may not present with serious cardiac defects.[2] In none of these syndromes are firm genotype-phenotype correlations possible.

See Table I for some cardiogenetic syndromes and their commonly associated comorbidities.

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Structural malformations

There are several well-known structural malformations that are associated with diverse CHD. The most common are gastro-intestinal (GIT) malformations, congenital diaphragmatic hernias, abdominal wall defects, genito-urinary abnormalities and limb and musculoskeletal malformations. Some of these are occasionally grouped together into recognised malformations, such as CHARGE syndrome or the VACTERL association, but many may be individually associated with CHD. An important consideration is that if one element of a malformation association is encountered, then the patient should be investigated for the presence of the other known defects. Once more, specific malformations are not associated with specific congenital heart lesions.

Table I. Cardiogenetic syndromes and their commonly associated extracardiac abnormalities

Syndrome	Genetic aetiology	CHD	ECAs
Down	Trisomy 21	AVSD, TOF, VSD	Duodenal atresia, hypothyroidism, atlantoaxial instability, strabismus, GORD
Edward	Trisomy 18	Various	Multiple
Patau	Trisomy 13	Various	Multiple
Turner	45, X karyotype	Coarctation of Ao, bicuspid aortic valve, PS	Growth, infertility
22q11.2 (Di George)	Microdeletion at 22q11.2	Conotruncal defects, various	Hypocalcaemia, immune deficiency, GORD, psychiatric, developmental delay
Williams	Microdeletion at 7q11.23	Supravalvar AS, branch PS	Behavioural, renal artery stenosis, hypercalcaemia
Noonan	PTPN11 gene mutation	PS, HOCUM	Undescended testes, habitus, bleeding diathesis
Marfan	Fibrillin gene mutation	Mitral and aortic dilatation	Lens dislocation, growth, hypermobility
Kabuki	MLL2 mutations	Various	Skeletal, developmental delay, growth delay, deafness, renal
Holt-Oram	TBX5 mutation	ASD, HOCUM, various	Forearm
Alagille	Chromosome 20p deletion	TOF	Biliary atresia, vertebral
Goldenhar	Unknown	VSD, TOF, various	Costovertebral, orofacial, renal
Duchenne	Dystrophin gene mutation	DCMO	Muscular weakness, respiratory failure
Barth	Tafazzin gene mutation	DCMO	Neuromuscular, neutropenia, growth delay, organic aciduria
Mitochondrial	Mitochondrial gene mutations	DCMO	Seizures
Pompes disease	Glycogen storage GAA gene mutations	Cardiomegaly, cardiomyopathy	Hepatomegaly, macroglossia, weakness, respiratory distress
Hurler	Lysosomal storage	Cardiomegaly	Mental retardation, dwarfism, hepatosplenomegaly
Long QT	Multiple channelopathies	Sudden death, syncope, torsades de pointes	Deafness

AVSD = atrioventricular septal defect; TOF = tetralogy of Fallot; VSD = ventricular septal defect; GORD = gastro-oesophageal reflux disease; PS = pulmonary stenosis; AS = aortic stenosis; HOCUM = hypertrophic cardiomyopathy; ASD = atrial septal defect; DCMO = dilated cardiomyopathy.

Some common structural malformations associated with CHD are given in Table II.

Metabolic associations

Uncommonly, certain inherited metabolic disorders may be associated with heart disease, either congenitally, or as a longer-term consequence of the syndrome. Examples include storage disorders, muscular dystrophies, Barth syndrome and certain mitochondrial disorders. Usually the patient will present with ventricular dysfunction.

Teratogens

Many environmental factors may cause congenital defects, and some are associated with heart disease. The commonest teratogens resulting in congenital heart disease are rubella, vitamin A (e.g. teenagers on acne treatment) and smoking.[6] In South Africa, fetal alcohol syndrome is an enormous social burden and is associated with an increased risk of CHD,[7] particularly ventricular septal defects. Anticonvulsant intake during pregnancy is also known to be teratogenic.[8]

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Some maternal diseases, such as diabetes,[9] obesity[10] and phenylketonuria,[11] have been linked to an increased risk for CHD. It is worth remembering that mothers on warfarin after valve replacements due to congenital or acquired valvar disease are at high risk of having children who suffer from teratogenic sequelae, especially nasal hypoplasia and joint damage.

Table III lists some common teratogens associated with CHD and ECAs. Table IV presents a structural approach to CHD and comorbidities.

Discussion

Best medical care dictates that we have a holistic approach to our patients and their families. Yet, when comorbidities are detected it may seem that we are opening a Pandora's box. Recent progress of paediatric cardiac care has highlighted that extracardiac abnormalities are becoming increasingly important factors in the determination of the outcome of these patients. Most CHD is isolated, but as many as 30% of patients with CHD will have extracardiac anomalies.[2] The technical outcome of surgical repair of CHD may

Table II. Structural malformations associated with CHD: some pointers

Structural malformations	Note
CHARGE	Overlap with 22q11.2 deletion syndrome with significant immunodeficiency parallels
VACTERL	Complex patient care Arch sidedness is important
Anorectal malformation	Complex patient care High ARMs are more commonly associated with CHD
Tracheo-oesophageal fistula	Aortic arch sidedness is important for correction
Omphalocoele	High association with CHD (45%)
Gastroschisis	Low association with CHD (15%)
Musculoskeletal abnormalities	Commonest association with CHD
Renal abnormalities	May render cardiac surgery problematic
Congenital diaphragmatic hernia	Pulmonary hypoplasia may dictate prognosis regardless of CHD severity

Table III. Common teratogens associated with CHD and extracardiac anomalies

Teratogen	CHD	ECAs
Rubella	PS, PDA, branch PS	Deafness, cataracts, microcephaly
Maternal diabetes	Diverse, cardiomegaly	Macrosomia, sacral agenesis
Fetal alcohol	Ventricular septal defects	Developmental delay, skeletal
Maternal obesity	Various	Macrosomia
Smoking	Various	Small for gestational age
Phenylketonuria	Various	Mental retardation, microcephaly, IUGR
Warfarin	-	Nasal, skeletal

Table IV. A 5-point structured approach to CHD and comorbidities

- All neonates deserve a thorough cardiac examination before discharge from the nursery. If possible, use a pulse oximeter, to exclude differential cyanosis by placing the probe on the foot or big toe. The majority of missed critical congenital heart lesions are left-sided lesions such as coarctation and interrupted aortic arch.
- This examination should be repeated at 4 - 6 weeks of age, since during this time major haemodynamic changes have occurred that may have unmasked significant CHDs (e.g. acyanotic heart defects with left to right shunts).
- At every examination, a careful check should be made for any extracardiac congenital anomalies (ECAs). The presence of any ECA warrants an examination that specifically excludes a congenital cardiac lesion. This includes an ECG and CXR.
- The detection of any congenital heart lesion warrants a careful check for any dysmorphic features or extracardiac lesions.
- All children with genetic syndromes or malformations known to be associated with CHD (e.g. Down syndrome) should be referred for specialist cardiac review, even if clinical examination is unremarkable.

be successful, but the quality of life of the patient may remain affected or be limited by the comorbidity of the ECAs.

Missed diagnosis: the impact

Using Californian death registry data, Chang *et al.*[1] have shown that a significant number (up to 30 per year) die because of a missed critical cardiac diagnosis. Conversely, Abu-Harb *et al.*[12] have shown, in a study from the UK, that a normal neonatal examination does not exclude life-threatening CHD. The reasons that critical CHD may be missed include tremendous transitional changes in neonatal cardiac haemodynamics (e.g. the closing PDA), as well as a trend to early discharge from the nursery. Wren *et al.*[13] found that 55% of children with CHD were discharged from UK hospitals without a diagnosis. Although there are conflicting reports, this trend seems to have been decreasing in recent years, but missed critical CHD continues to be a significant problem. Therefore the finding of an ECA, however trivial, may be an invaluable pointer towards critical CHD.

How is management affected?

Experience in children with Down syndrome has shown that despite the previous reluctance to offer cardiac surgery to this group, correction of the CHD renders their comorbidities more manageable. In addition, this effect of improved quality of life is reflected in a reduced burden of care to society.[5]

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Surgical correction generally results in a better quality of life for patients and their families.[2] Awareness of the exact nature of the ECA may have a fundamental impact on the cardiology management strategy of the patient in the pre-, peri- and postoperative periods. What may be a routine perioperative experience for non-syndromic patients may become a protracted period of morbidity for children with severe ECAs undergoing CHD surgery. Conversely, co-occurring CHD may add significant anaesthetic risk to what may usually be a low-risk repair of an ECA requiring surgical repair.

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Prognosis of CHD with comorbidities

The reduction of perioperative mortality of CHD surgery in recent years has been remarkable, but the association with ECA continues to lead to higher morbidity and mortality figures[3] and worse

neurodevelopmental outcome.[14] Decreased survival does not necessarily depend on the specific ECA, but holds true for this heterogeneous group as a whole, in the absence of Down syndrome.[15] This should be borne in mind when children with ECAs are offered CHD surgery.

Resource allocation: what is fair?

In the light of resource constraints and the known higher morbidity and mortality associated with CHD surgery for children with comorbidities, one should reflect on the rational allocation of scarce resources to these children. This is a necessary but difficult aspect of the care and management of this group of patients. Robinson and Newburger state: 'A persistent theme in the ethics of pediatric cardiac surgery over the past few decades has been the use of complex life-saving cardiac surgery in infants and children for whom the cardiac defect is but one star – and perhaps not the brightest star – in their constellations of disease.'[16]

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As in our clinical scenario, the CHD and comorbidity may be of equal severity and importance, both requiring a large expenditure of resources to correct (or palliate). Correction of one will not suffice: for a reasonable outcome, both problems deserve correction as far as possible, and some would argue that the one disqualifies the other. In a country where many common (and simple) heart lesions and ECAs fail to be corrected, is it fair to allocate an inordinate amount of resources to the John Smiths?

One cannot generalise with these difficult decisions, and each patient should be considered on individual merit. How is this done?

Three rules of thumb

Categorical decisions that assist us to offer or decline surgery for children with CHD and comorbidities are often sought, but are rarely appropriate or applicable. Robinson and Newburger (2003; p151)[16] suggest the following three broad 'rules of thumb' to guide decision-making in this regard:

- If the proposed intervention is clearly of medical benefit to the child as a whole then it should proceed, even against the wishes of the parents.
- If the proposed intervention is clearly not beneficial to the child as a whole, then it is ethically permissible to withhold or withdraw it, even against the wishes of the parents.
- If the balance of benefits and burdens of the intervention for the child are uncertain, then in most cases deference to the wishes of the parents is the best choice.

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These rules are primarily based on the individualisation of each patient and his or her unique circumstances. The presence of a recognised syndrome *per se* should not dictate a preconceived approach.

The functionality argument

Bove[17] argues that survival from CHD surgery is a valid measure of success, but is not necessarily the only measure that should be used to judge the value of the surgery in the first place. It should be considered whether the surgery would bring value to the functionality of the patient and facilitate his or her integration into family and society. The important question is whether it will improve quality of life.

Conclusion

In conclusion, we have highlighted the importance of comorbidities in children with CHD, and the possible implications of missing a critical CHD. While holistic medical care is crucial, the Pandora's box that we may open often overwhelms us. But remember that Hope was at the bottom of Pandora's box, and that the return of a more functional child to the family may be the best we can hope for.

Pandora watched as the creature drifted painlessly into her flesh and took up residence in her heart. She knew she had been given the gift that, even though it could not erase the pain she had brought to the world, could make that pain easier. She smiled a soft smile for knowing there is hope, and hope is sometimes enough.

Pandora's Box, retold by Robert Hoffman[18]

References available at www.cmej.org.za

IN A NUTSHELL

- As many as 30% of children with CHD will have co-occurring extracardiac abnormalities.
- The aetiologies of extracardiac associations may be classified into known genetic syndromes, structural (surgical) malformations, the sequelae of inborn metabolic defects and teratogenic effects.
- As the success of surgery for isolated CHD has improved, ECAs have become increasingly important in determining the outcome of CHD surgery.
- The finding of an ECA may be an invaluable pointer to critical CHD, which is often otherwise missed.
- The finding of CHD should elicit a structured investigation for comorbidities, while all children with ECAs should be screened for CHD, including a CXR.
- Correction of CHD in these syndromic children renders their comorbidities more manageable.
- The association of ECAs with CHD is known to lead to higher peri-surgical morbidity and mortality.
- The decreased survival does not necessarily depend on the specific ECA.
- The co-occurrence of CHD and comorbidities often raises difficult ethical dilemmas.
- Surgery for CHD with comorbidities should be considered in those cases where the CHD may improve the *functionality* of the child and its family, within their social context.