GENETIC SYNDROMES AND ASSOCIATED CARDIOVASCULAR ANOMALIES IN ADULTS: A SINGAPORE PERSPECTIVE.

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ABSTRACT

Children with genetic syndromes are increasingly surviving to adulthood in Singapore. This is due to early detection and significantly improved multi-dimensional care. Congenital heart disease is one of the characteristic abnormalities in patients. However, the cardiac anomalies of some of these patients may only manifest later in early adulthood. A significant number of such patients are not on regular medical follow-ups to monitor for future complications. This article describes based on the common syndromic conditions that are present in Singapore. Advanced genetic tests like chromosomal microarray analysis can help diagnose these syndromes that are not obvious clinically, thus instituting appropriate management and treatment for such patients. Creating awareness of such syndromes and its cardiac complications will translate to them being referred to the cardiologists to prevent further morbidity and mortality. Timely counselling regarding fertility, prenatal testing and complications due to pregnancy are also discussed in this article.

Keywords:
Common genetic conditions; Congenital heart disease; Cardiac complications; Chromosomal microarray analysis; Prenatal testing;

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INTRODUCTION

In Singapore, an increasing number of children with genetic syndromes and its associated cardiovascular heart disease are surviving into adulthood. This is because of earlier detection of these conditions during postnatal or early childhood; along with significantly improved surgical, medical, anaesthetic and intensive care over the last few decades. About close to 85% of the patients survive to adulthood as compared to only 15% a few decades ago. [1] In these syndromes the incidence of congenital cardiac anomalies at birth is 8.12/1000 live births based on the study done in Singapore from 1994 to 2000, which is the most up to date local data published thus far. [2] The top most phenotypically recognizable congenital syndromes with cardiac comorbidities at birth are Down's, Patau's, Edwards', and Turner's syndrome. However, Patau's and Edwards' syndrome do not survive to adulthood.[2] Some of the congenital syndromes have subtle features and may not manifest itself obviously and may be missed till they reach their teens or even adulthood. Moreover, cardiovascular abnormalities usually present later in late teens or adulthood for a number of syndromes due to connective tissue defects such as in Osteogenesis Imperfecta and Marfan's syndrome.

The largest paediatric tertiary hospital in Singapore, KK Women's & Children's Hospital, in 2015 introduced the first accredited chromosomal microarray analysis, a DNA based method of genetic investigation to help detect these syndromes with subtle manifestations. [3] Their work showed that the most common genetic syndrome were Angelman/ Prader-Willi, Velocardiofacial and 1p36 microdeletion syndrome. The latter two have cardiac defects that can survive to adulthood. By increasing awareness of these genetic syndromes among the family physicians more of such patients could be referred early to the genetic services for confirmation of syndromes possibly aided by such diagnostic tests, and subsequently managed. This article will discuss the common genetic syndromes based on international and local data in order to build awareness among primary care physicians in Singapore. Based on consensus among the authors, ten common syndromes in Singapore that have significant cardiovascular comorbidities and which survive into adulthood are discussed.

CONGENITAL SYNDROMES WITH CARDIOVASCULAR ABNORMALITIES

1) Down's syndrome

Inheritance: Most cases are not inherited and occur randomly during the formation of reproductive cells in a parent. Some inherit an unbalanced translocation involving chromosome 21 may have extra genetic material from chromosome 21, which causes Down's syndrome. [4]

Clinical features

They include the patient having: [5-6]

MUSCULOSKELETAL FEATURES

i. Single palmar (Simian) crease
ii. Fifth finger clinodactyly
iii. Short stubby digits
iv. Abnormal dermatoglyphics
v. Wide sandal gap between first and second toes
vi. Small stature

Facial features

i. Round face, epicanthic folds
ii. Brachycephaly, low set hairline, flattened occiput.

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iii. Brushfield spots in the iris
iv. Protruding tongue and open mouth
v. Small set dysplastic ears
vi. Short neck with excessive skin at nape.

CNS (Central Nervous System) features

i. Generalised hypotonia.

Type of heart problem that is most common or distinctive

Approximately one-half of individuals with Down's syndrome (DS) have congenital heart disease.[7-9] In the largest population-based study, cardiovascular abnormalities were identified in 342 of 821 (42%) infants born with DS. [9]

23% had more than one anomaly. The secondary lesion was most commonly an atrial septal defect (ASD) or patent ductus arteriosus (PDA). The primary lesions identified were:

i. Complete atrioventricular septal defect (CAVSD) – 37%
ii. Ventricular septal defect (VSD) – 31%
iii. ASD – 15%
iv. Partial atrioventricular septal defect (PAVSD) – 6%
v. Tetralogy of Fallot (TOF) – 5%
vi. PDA – 4 %
vii. Miscellaneous –2%

In adult Downs', congenital heart cardiac heart defects were found in 24.8% of patients. Among those patients with abnormalities the predominant lesions were VSD 31.4%, AVSD 17.4%, ASD 17.4% and PDA 6.3%.

Also, 77% of the screened patients without known cardiac lesions had mild to moderate regurgitation in one or more heart valves. The majority being aortic regurgitation (AR). In that study, the overall prevalence of congenital heart disease in adult Down's syndrome patients living in residential centres was at 33%. [10]

2) Turner's syndrome

Inheritance: It is not inherited, it usually occurs after the egg has been fertilized and appears to be a random event caused by the complete or partial loss of one of the two X chromosomes in girls. [11]

Clinical features

The typical features are: [12]

Musculoskeletal features

i. Short stature
ii. Shield chest with widely spaced nipples
iii. Cubitus valgus
iv. Madelung deformity of the forearm and wrist (prominent ulnar head and apparent volar subluxation of the wrist)

Facial Features

i. Short webbed neck
ii. Neonates may have congenital lymphedema of the hands and feet, webbed neck, nail dysplasia, narrow and high-arched palate, and short fourth metacarpals and/or metatarsals.

Type of heart problem that is most common or distinctive

About 30% of Turner's have heart problems:

i. Left sided obstructive lesions predominate especially
ii. Bicuspid aortic valve (30-50%),
iii. Coarctation of the aorta (30%).
iv. Aortic root dilatation is uncommon (5%) but potentially devastating if aortic rupture occurs.[13]

3) Marfan's syndrome (MFS)

Inheritance : Autosomal dominant [14]

Clinical features given based on the Revised Ghent Criteria. [15,16,17]

Musculoskeletal Features	Scoring
Wrist AND thumb sign	3 points
Wrist OR thumb sign	1 point
Pectus carinatum deformity	2 points
Pectus excavatum OR chest asymmetry	1 point
Hindfoot deformity	2 points
Plain pes planus	1 point
Dural ectasia	2 points
Protrusio actabuli	2 points
Reduced upper segment/lower segment ratio AND increased	1 point
Arm span/height AND no severe scoliosis.	1 point
Scoliosis thoracolumbar kyphosis	1 point
Reduced elbow extension (< 1700 with full extension)	1 point

Facial features at least 3 of the 5 following features:

a) Dolichocephaly
b) Enophthalmos
c) Downslanting palpebral fissures
d) Malar hypoplasia
e) Retrognathia

Other features

Skin striae	1 point
Pneumothorax	2 points

Type of heart problem that is most common or distinctive

Mitral valve prolapse	1 point
Aortic root dilatation	

In the absence of family history

Aortic diameter at the Sinus of Valsalva (Ao) Z score ≥2 and ectopia lentis =MFS

Aortic diameter at the Sinus of Valsalva (Ao) Z score ≥2 and causal FBN1 (Fibrillin 1 gene) mutation=MFS

Aortic diameter at the Sinus of Valsalva (Ao) Z score ≥2 and systemic points greater than 7= MFS.

Ectopia lentis with FBN1 with known Ao enlargement = MFS

In the presence of family history

Ectopia lentis and family history of MFS= MFS

Systemic points greater than 7 and family history of MFS =MFS

Ao (Z ≥2 above 20 years, ≥3 below 20 years) + family history of MFS=MFS

4) Di George/Velocardiofacial syndrome

Inheritance: Most cases of 22q11.2 deletion syndrome are not inherited. The deletion occurs most often as a random event during the formation of reproductive cells (eggs or sperm) or in early foetal development. However, the inheritance of 22q11.2 deletion syndrome is considered autosomal dominant because a deletion in one copy of chromosome 22 in each cell is sufficient to cause the condition. [18]

Clinical features

The classic triad of features of Di George/ Velocardiofacial syndrome (DGS) on presentation is [19]

i. Conotruncal cardiac anomalies i.e. cardiac outflow anomalies that includes defects such as Tetralogy of Fallot, pulmonary atresia with VSD, truncus arteriosus, transposition of the great arteries etc.)
ii. Hypoplastic thymus
iii. Hypocalcaemia.

The phenotype typical features are: [19-25]

Musculoskeletal features

i. Short stature

Facial Features

ii. Cleft lip or palate
iii. Small jaw,
iv. Small upper lip or mouth,
v. Eyes slanted upward or downward,
vi. Low -set and/or abnormal folding of ears

A broad spectrum characterizes the presence and severity of individual features, and the severity of each feature appears to be independent of other features. Older children with DGS may be detected through clinics for congenital heart defects or craniofacial clinics, may be referred to developmental specialists for poor school performance, or may be diagnosed due to frequent infections or autoimmune conditions.

TYPE OF HEART PROBLEM THAT IS MOST COMMON OR DISTINCTIVE

The most common cardiac defects account for two-thirds of the cardiac anomalies seen in patients with DGS and include the following: [19, 21,23,26,27]

i) Interrupted aortic arch
ii) Truncus arteriosus
iii) Tetralogy of Fallot
iv) Atrial or ventricular septal defects (ASDs or VSDs)

5) Alagille syndrome

Inheritance: This condition is inherited in an autosomal dominant pattern. A minority is due to the spontaneous mutation on chromosome 20 that occur as random events during the formation of reproductive cells (eggs or sperm) or in early foetal development. [28]

Clinical features

Alagille syndrome is characterized by the lack of interlobular bile ducts and the following associated features: [49-52]

Facial Features

i. Posterior embryotoxon (prominent Schwalbe line) of the eye
ii. Broad nasal bridge,
iii. Triangular facies,
iv. Deep-set eyes

Other features

i. Chronic cholestasis
ii. Butterfly vertebrae

Type of heart problem that is most common or distinctive

Congenital heart disease is the second most common manifestation of Alagille syndrome affecting greater than 90% of patients. [32] The lesions noted were

i) Pulmonary outflow tract involvement with peripheral pulmonary stenosis being the hallmark in 70%.
ii) Tetralogy of Fallot
iii) Ventricular septal defects
iv) Atrial septal defects
v) Aortic stenosis

6) CORNELIA DE LANGE (CDLS)

Inheritance: Most cases result from new gene mutations and

occur in people with no history of the condition in their family. For the minority depending which genes are affected, it can manifest as autosomal dominant or X-linked dominant. [33]

Clinical features

The typical features of this syndrome are: [34]

Musculoskeletal features

i. Upper limb reduction defects that range from subtle phalangeal abnormalities to oligodactyly (missing digits).

Facial features

i. Craniofacial features include synophrys (a single eyebrow created when the two eyebrows meet in the middle above the bridge of the nose)
ii. Highly arched eyebrows
iii. Long eyelashes
iv. Short nose with anteverted nares
v. Small widely spaced teeth
vi. Microcephaly
vii. Hirsutism

CNS features

i. IQ ranges from below 30 to 102 (mean: 53)
ii. Many individuals demonstrate autistic and self-destructive tendencies

Frequent findings include cardiac septal defects, gastrointestinal dysfunction, hearing loss, myopia, and cryptorchidism or hypoplastic genitalia. Individuals with a milder phenotype have less severe growth, cognitive, and limb involvement, but often have facial features consistent with CdLS. [34]

Type of heart problem that is most common or distinctive

Approximately 25% of individuals with CdLS have congenital heart disease. [35-37] The most common abnormalities include (in descending order):

i) Ventricular septal defects
ii) Atrial septal defects
iii) Pulmonary stenosis
iv) Tetralogy of Fallot
v) Hypoplastic left heart syndrome
vi) Bicuspid aortic valve

7) Noonan's syndrome

Inheritance: Autosomal dominant. [38]

Clinical features:

The features typically present are: [39]

Musculoskeletal features

i. Chiara malformation
ii. Lymphedema

Facial features

i. High forehead
ii. Hypertelorism,
iii. Downslanting palpebral fissures
iv. High arched eyebrows, epicanthic folds
v. Full upper lip
vi. Depressed nasal bridge
vii. Low-set ears.
viii. Strikingly blue irides
ix. Ptosis
x. Degree of neck webbing may be observed.
xi. Triangular shaped face.

CNS features

i. Intellectual function, from average to significantly impaired, with most patients having mild developmental delay.

Other features

i. Male infertility even with those with no cryptorchidism

Type of heart problem that is most common or distinctive [40]

More than 80% of patients with NS have cardiac involvement.

i. Most common are pulmonary valve stenosis.
ii. Atrial septal defects are also frequent.
iii. 20% of patients overall have hypertrophic cardiomyopathy

8) Fragile X Syndrome

Inheritance: X-linked dominant [41]

Clinical features

The physical features of Fragile X in males vary depending upon age. [42-47]

The classic physical manifestations are more evident in adolescents:

Facial features

i. Long and narrow face with prominent forehead and chin (prognathism).
ii. Large ears.

CNS features

i. Intellectual disability

Others

i. Testicular enlargement (volume >25 mL after puberty) with normal testicular function.

Type of heart problem that is most common or distinctive

In a recent paper, the author reviewed the literature and found that the predominant lesions among patients with Fragile X were [48]

i. Aortic root dilatation in 25%
ii. Mitral valve anomalies in 3-12% of the patients

9) Osteogenesis Imperfecta (OI)

Inheritance: Most are autosomal dominant and minority are autosomal recessive. [49]

Clinical features

Clinical manifestations of osteogenesis imperfect include: [50-53]

Musculoskeletal features

i. Excess or atypical fractures (brittle bones); fractures most commonly associated with OI were transverse humerus, olecranon, and diaphyseal humerus fractures.
ii. Short stature
iii. Scoliosis
iv. Increased laxity of the ligaments and skin
v. Wormian bones (small, irregular bones along the cranial sutures)

Facial features

i. Blue sclerae
ii. Hearing loss (usually detected in later childhood to early adulthood
iii. Opalescent teeth that wear quickly (dentinogenesis imperfecta)

CNS features

i. Basilar skull deformities, which may cause nerve compression or other neurologic symptoms

Other features

i. Easy bruisability

Type of heart problem that is most common or distinctive

All aortic diameters were significantly larger in the OI group than in the control group, they also have in: [54]
i) Aortic regurgitation (AR)
ii) Mitral regurgitation. (MR)

10) 1p 36 microdeletion syndrome

Inheritance: Most cases of 1p36 deletion syndrome are not inherited. They result from a chromosomal deletion that occurs as a random event during the formation of reproductive cells (eggs or sperm) or in early foetal development. Affected people typically have no history of the disorder in their family.
About 20% of people with 1p36 deletion syndrome inherit the chromosome with a deleted segment from an unaffected parent. In these cases, the parent carries a chromosomal rearrangement called a balanced translocation. [55]

Clinical features:

Characteristic features are: [56-63]

Musculoskeletal features

i. Skeletal abnormalities

Facial features

ii. Microcephaly
iii. Brachycephaly,
iv. Large and persistently open anterior fontanelle
v. Deep-set eyes, straight eyebrows
vi. Posteriorly rotated and low-set ears
vii. Midface hypoplasia
viii. Flat nasal bridge
ix. Pointy chin
x. Orofacial clefting

CNS features

i. Moderate to severe intellectual disabilities
ii. Hearing loss
iii. Oropharyngeal dysphagia
iv. Ophthalmological abnormalities
v. Seizures

Other features

i. Renal abnormalities

Type of heart problem that is most common or distinctive [56]

i. PDA
ii. VSD
iii. Dilated cardiomyopathy

Table 1: Summary of Genetic syndromes, their phenotypic features and cardiac lesions present.

No	Syndrome	Typical Phenotypic features	Cardiac lesions
01	Down's syndrome	Round face, epicanthic folds, clinodactyly, wide sandal gap, small stature, brachycephalic, protruding tongue, low set hairline, small dysplastic ears	CAVSD, VSD, ASD, TOF, PDA, AR
02	Turner's syndrome	Short stature, shield chest, short and webbed neck cubitus vulgus, Madelung deformity.	Coarctation of the aorta, aortic root dilatation.
03	Marfan's syndrome	Wrist and/or thumb sign, pectus carinatum, retrognatia, malar hypoplasia, enopthalmos.	Dilated aortic root, MVP
04	Di George/Velocardiofacial syndrome	Small jaw, small upper lip or mouth, eyes slanted upwards or downwards, abnormal folding of the ears, short stature.	Interrupted aortic arch, truncus arteriosus, TOF, ASD, VSD
05	Alagille syndrome.	Dysmorphic facies, broad nasal bridge, triangular facies, deep set eyes.	Peripheral pulmonary stenosis, TOF, VSD, ASD, AS
06	Cornelia de Lange	Synophrys, high arched eye brows, long eyelashes, short nose with anteverted nares, widely spaced teeth, microcephaly.	VSD, ASD, PS, TOF, hypoplastic left heart syndrome
07	Noonan's syndrome	High forehead, hypertelorism, downslanting palpebral fissures, full upper lip, neck webbing.	PS, ASD, hypertrophic cardiomyopathy
08	Fragile X	Long and narrow face, prominent forehead and chin, large ears, testicular enlargement.	Dilated aortic root, MVP.
09	Osteogenesis Imperfecta	Short stature, scoliosis, basilar skull deformities, dentinogenesis imperfecta.	AR, MR
10	1p 36 microdeletion syndrome	Mid face hypoplasia, flat nasal bridge, pointy chin, low set ears, straight eyebrows.	PDA, VSD

AR (Aortic Regurgitation), ASD (Atrial Septal Defect), Complete Atrioventricular Septal Defect (CAVSD), MR (Mitral Regurgitation), MVP (Mitral Valve Prolapse), PDA (Patent Ductus Arteriosus), PS (Pulmonary Stenosis), TOF (Tetralogy of Fallot), VSD (Ventricular Septal Defect)

DISCUSSION

The spectrum of genetic syndromes with associated cardiac anomalies as discussed above is essential for family physicians to recognize and refer to geneticist and cardiologist for appropriate diagnosis and management.

Lin et al, published a seminal paper on adults with genetic syndromes and cardiovascular abnormalities. [64] The author advocated healthcare providers to address the immediate needs of young people with genetic syndromes and cardiovascular abnormality making the transition to adulthood. Multiple issues likely fertility, prenatal testing, complications due to pregnancy, and child developing genetic defects needs to be explored. The individual with a syndrome and their partner should meet with a geneticist or genetic counsellor, an experienced obstetrician/gynaecologist, and, as needed, an infertility specialist, e.g. woman with Turner syndrome, man with Klinefelter syndrome. Establishing a genetic diagnosis in the individual is as important as defining the cardiovascular abnormality. [64]

KK Women's and Children's Hospital (KKH) launched Southeast Asia's first accredited chromosomal microarray analysis (CMA) diagnostic test, to aid the diagnosis of genetic disorders in children. CMA, a DNA-based method of genetic investigation, helps to identify clinically significant chromosome anomalies that are too small to be detected by conventional chromosome analysis – also known as karyotyping. With an expected diagnostic yield of about 20%, compared with 3.7 to 9.5% for traditional karyotyping, CMA is expected to provide an underlying genetic diagnosis in a higher proportion of patients. This benefits patient as it ends the diagnostic odyssey, preventing further unnecessary investigations. It also includes information about possible complications, allowing appropriate monitoring and early management, and facilitates the provision of accurate information about recurrence risks in future pregnancies, and the reproductive choices available. [3]

Primary care physicians are specially trained for and skilled in comprehensive first contact and continuing care for persons with any undiagnosed sign, symptom, or health concern (the "undifferentiated" patient) not limited by problem origin (biological, behavioural, or social), organ system, or diagnosis. [65] Hence, as primary care physicians we must have a high index of suspicion to identify such patients to prevent downstream complications like Eisenmenger's, infective endocarditis, etc. The authors hope that this guide of the common syndromic conditions with congenital heart abnormalities will empower the primary care physicians to identify such situations and refer them appropriately for further management and treatment.

CONCLUSION

This article endeavour to create awareness of adults with common genetic syndromes and its cardiac complications. This awareness will hopefully translate to them being referred to our cardiologists' colleagues early in order to prevent further morbidity and mortality. Increased availability of data of such patients would translate into determining the actual prevalence of such syndromes or other syndromes seen in Singapore, with targeted measures to manage them well.

Conflict of interest :

Both Dr Farhad Fakhrudin Vasanwala and Dr Ong Chong Yau have no conflict to declare in terms of sponsorship, or remuneration for the article we are submitting.

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