Heart disease of Genetic Diseases

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Goals:

- Review common genetic disease
  - Phenotype
  - Genetic Lesion
- Discuss the associated cardiac lesion
  - Frequency
  - Severity
  - Repair/Palliation
• 19-36% of spontaneous abortion have chromosomal AND cardiac defects

• Congenital heart defects are the most congenital malformation
  • Depending on who you read it may be as high as 1:100

• Of those born with genetic syndrome 13-18% will have some form of congenital heart disease.

Hoffman, J. I. E. Pediatric cardiology 1995
The genetics of congenital heart disease...
Now onto the meat of the presentation
Trisomy 21

• First completely described by a British physician John Down in 1866. Genetic cause was found in 1959.

• Complete trisomy secondary to maternal non disjunction in 94% of patients, mosaicism in about 6%.
Heart disease breakdown

- ~50% are born with congenital heart disease of which ~40% are complete AV canal defects, ~60% when primum atrial septal defects, inlet VSDs and transitional AV canals are included.
- ~75% of patients with complete AV canal have Down syndrome.
- Other associated CHDs include: ASD, VSD, PDA, TOF, coarctation of aorta.
So how bad is it?
Well, it’s a spectrum

- AV Canals are probably the most varied presentation
  - Some can be safely ignored
  - Some can be tolerated well for the first several months
  - Some are quickly fatal because they may be shunt dependent
Trisomy 21

• Median age at death has increased from 25 to 49 years from 1983 to 1997.

• Similar post operative results as compared to genetically normal patients.
  • 4350 Down syndrome pts/45779 total pts
  • Mortality rates not different
  • Younger at the time of surgery for TOF and AVSD repair
  • Longer duration of stay post ASD/VSD/TOF repair
  • Higher incidence of heart block requiring pacemaker placement post VSD closure

Trisomy 18

- Described in 1960
- Prevalence 1:3000-1:8000 at birth. 3:1 F:M, ~90% died in their first year in life.
- ~90% are complete trisomy, 10% mosaic, <1% translocation
- ~95% have a cardiac lesion. Most common cardiac lesions are: perimembranous VSD, TOF, DORV, polyvalvar dysplasia, AVSD.
- Other comorbidities: Severe developmental delay, growth restriction, central apnea, renal dysplasia, severe reflux.

Trisomy 13

- Incidence 1:2000-1:5000 live births. M=F, 75% complete trisomy, 20% translocation, 5% mosaicism.
- ~40% die in first 1 month of life, ~85-90% die within the first year of life.
- ~50-80% have cardiac defects. TOF, DORV, VSD, ASD, PDA, AVSD, polyvalvar disease.
- Other comorbidities: developmental delay, FTT, holoprosencephaly, polydactyly, seizures, deafness, microcephaly, omphalocele, renal dysplasia.

Their heart are a little rough

- Not only is there a high incidence of complex heart disease in these patients
  - Very high incidence of pulmonary hypertension
  - Frequently are trach/vent dependent
  - Post operative course is *challenging*
Several groups have been quite aggressive in managing 13/18
- Japan reports that cardiothoracic surgery has been effective in increasing the lifespan of these patients
- Several TS13/18 centers of excellence have sprouted up across the country

Ethically the debate continues
Turner Syndrome

• Incidence is ~1:2000 live births. ~50% true monosomy, ~33% structurally abnormal X chromosome (milder phenotype), ~13% mosaic turner’s 45X/46XY.

• ~30% have CHD. BAV (~25%) may progress to aortic stenosis (~10%), PAPVC (~13%), aortic coarctation (~7-10%), MVP (~5%), HLHS (rare), LSVC, arch anomalies.

• CHD significantly associated with neck webbing.

Turner’s Syndrome

- Long term follow up for recoarctation, hypertension, aortic stenosis and regurgitation, and CAD.
- ~33% aortic dilation, ~1.4% aortic dissection. MRI preferred for evaluation in adults, every 5-10 years.
- Spontaneous puberty ~10%, pregnancies 2-5%.
  - Risk for major pregnancy complication ~10%
  - Risk for maternal death ~3.5%

Trisomy 22

- Complete trisomy 22 is very rare and most fetuses die in utero or shortly after birth.

- Mosaic trisomy 22 is associated with cardiac abnormalities (ASD, VSD, TOF), developmental delay, FTT.

- Emmanuel syndrome: unbalanced translocation 11/22

- Cat eye syndrome/Schmid-Fraccaro syndrome: partial trisomy or tetrasomy. Developmental delay, coloboma of iris (~50% cases), anal atresia, cardiac anomalies (TAPVR/PAPVR), renal anomalies, short stature, scoliosis.
22q11.2 Deletion Syndrome

• Occurs in about 1 in 6000 live births. 6-10% are familial.
• CHD occurs in ~75-80% pts, conotruncal abnormalities (TOF ~15%, IAA type B ~50%, truncus arteriosus ~ 35%), VSD ~ 10%, VSD + aortic arch abnormalities ~45%.
• Hypocalcemia, absent thymus, immunodeficiency, palate anomalies, feeding and speech issues, renal and skeletal abnormalities, cognitive deficiencies and behavioral issues.
Williams-Beuren Syndrome

• 1 per 20,000 live births, AD.
• 7q11.23 deletion in ~90%. ELN gene affected.
• ~55-80 % have CHD, supravalvar aortic stenosis (45-75%), supravalvar pulmonary stenosis (30-75%) / pulmonary arterial stenosis, diffuse arteriopathy, VSD/ASD (10%), MVP.
• Hypertension ~ 50%, hypercalcemia ~ 15%, feeding disorders and growth retardation, skeletal and renal abnormalities (renal artery stenosis), cognitive defects, social personality.

Jacobsen Syndrome

• 11q23 deletion.
• ~55% with CHD, VSD 1/3rd, left sided abnormalities/LVOTO 1/3rd.
• Thrombocytopenia/abnormal platelets, short stature, genitourinary problems, pyloric stenosis, and eye issues, varying intellectual disabilities.
Smith-Magenis Syndrome

- 17p11.2 deletion
- CHD in ~10%, assorted CHDs
- Brachycephaly, moderate intellectual disability, aggressive/self injurious behavior, sleep disturbances, eye/ear abnormalities
Alagille Syndrome

- Deletion of ch 20p12. AD mutation of JAG 1 (~94% patients) / NOTCH 2 genes.

- Presence of bile duct paucity on liver biopsy with 3 out of the 5 following features:
  - CHD ~90%
  - PPS (~60%), PS, TOF, ASD, VSD, coarctation
  - Arteriopathy
  - Cholestasis
  - Skeletal abnormalities
  - Ocular abnormalities, embryotoxon
  - Typical facial features
Holt-Oram Syndrome

- Cardiomelic syndrome
- AD, chromosome 12q24, *TBX 5* gene
- All have upper extremity skeletal abnormalities involving preaxial radial ray.
- CHD ~75%, ASD ~60%, VSD ~30%, AVSD, conotruncal anomalies, left sided lesions.
- AV block (1\textsuperscript{st}-3\textsuperscript{rd} degree) can also be seen.
Rasopathies

- Ras/mitogen-activated protein kinase (MAPK) pathway defects or Noonan Syndrome Spectrum.
- Role in cell proliferation, differentiation, survival and cell death.
- Noonan syndrome, cardiofasciocutaneous syndrome, Costello syndrome, LEOPARD syndrome.
- Distinctive facial appearance, cardiovascular abnormalities, musculocutaneous abnormalities, intellectual disability.
- CHD, HCM, arrhythmias.
Noonan Syndrome

- Genes: \textit{PTPN11} (most common, \(~50\%\)), \textit{RAF1, SOS1, KRAS, NRAS, BRAF and SHOC2}.
- Cardiovascular abnormality \(~80\%\) (60\% CHD, 20\% HCM). PS (25-35\%), ASD, VSD, TOF, pulmonary artery stenosis, coarctation, AVSD, polyvalvulopathy
- Other comorbidities: intellectual disability, abnormal lymphatic tissues, bleeding diathesis, cryptorchidism.
Other Rasopathies

- **LEOPARD syndrome**
  - PTPN11 gene mutation
  - Multiple Lentigines, Electrocardiographic conduction abnormalities, Ocular hypertelorism, Pulmonary valve stenosis, HCM, Abnormal genitalia, growth Retardation, SN Deafness

- **Costello syndrome**
  - Ulnar hand deviation, hyperpigmentation, loose skin, deep palmer and planter creases, Chiari 1 malformation, developmental delay, rhabdomyosarcoma ~10%
  - HCM more common in Costello and LEOPARD syndrome
  - Multifocal atrial tachycardia

- **Cardiofasciocutaneous syndrome**
  - coarser facial features, dry skin, eczema, hyperkeratosis, severe intellectual disability
CHARGE Syndrome

• 1:10,000-15,000. Mutation of CHD7 gene on chromosome 8q12.1, ~65% patients.
• Coloboma, Heart defects, choanal Atresia, growth Retardation/brain anomalies, Genitourinary problems, external Ear anomalies.
• CHD ~90%, conotruncal and arch anomalies.
• New associations: cranial nerve palsy (7th), oral clefts and swallowing difficulties, developmental/behavioral disorders (autism).
Kabuki syndrome

• *MLL2* gene mutation, encodes methyl transferase.
• Characteristic facial appearance.
• CHD ~45-55%, ASD, VSD, left sided lesions (HLHS, Shone’s).
• Renal and digital abnormalities, immunological and feeding problems (cleft lip and palate), intellectual disability.
Cornelia de Lange syndrome

Rubinstein-Taybi syndrome
Other Autosomal Dominant Syndromes

- **Cornelia de Lange syndrome**
  - *NIPBL, SMC1A* gene
  - CHD ~25%, VSD, ASD, PS, HCM
  - Upper limb deficiencies, GI anomalies

- **Rubinstein-Taybi syndrome**
  - *CREBBP, EP300* genes
  - CHD ~40%, PDA, ASD, VSD, coarctation, HLHS
  - Broad thumbs and great toes

- **Char Syndrome**
  - *TFAP2B* gene
  - CHD ~20-70%, PDA, muscular VSD
  - Anomalies of 5th finger, supernumerary nipple
Ellis-van Crevald Syndrome

Smitz-Lemli-Opitz Syndrome
Autosomal Recessive Syndrome

• Ellis-van Crevald Syndrome
  • EVC gene on ch 4, AR
  • CHD ~ 70%, common atrium and ASD most common (~40%), MV/TV abnormalities, AVSD.
  • Short limbs, polydactyly, hypoplastic nails, dental anomalies

• Smitz-Lemli-Opitz Syndrome
  • DHCR7 gene
  • CHD ~ 45%, ASD, VSD, AVSD, TAPVR
  • Syndactyly, cleft palate, lung anomalies, genital anomalies, neuropsychiatric and neurodevelopmental issues (autism)
Pulmonary Outflow Obstruction

- Pulmonary valve stenosis
  - Noonan’s syndrome
  - Alagille syndrome
  - Costello syndrome
  - LEOPARD syndrome
- PA branch stenosis
  - Alagille syndrome
  - William-Beuren syndrome
  - Noonan Syndrome
- Pulmonary atresia
  - Ring 9 chromosome abnormality
Aortic Outflow Obstruction

- BAV
  - Turners, trisomy 13, 18
- Aortic valve stenosis
  - Jacobsen’s syndrome
  - Trisomies (13, 18)
- Supravalvar aortic stenosis
  - Williams-Beuren syndrome
- Coarctation of the aorta
  - Turner’s syndrome
Thank you!