NDV OUTCOMES AND FOLLOW-UP IN CHILDREN WITH COMPLEX CONGENITAL HEART DISEASE
ROADMAP

- Congenital Heart Disease
- Terms and Lingo
- Prevalence and Patterns
- Specific Outcome Studies & Risk Factors
- AHA Guidelines
- CHDD Cardiac NDV Clinic
CONGENITAL HEART DEFECTS

- Most common type of birth defect in the US
- Leading cause of infant mortality associated with birth defects
- Prevalence of 9/1000 live births
- 3/1000 requiring repair
- New surgical techniques, advances in cardiopulmonary bypass, intensive care, catheterization, non-invasive imaging and medical therapies significantly lowered mortality rates
- 85% children with CHD survive into adulthood
  - 95% simple
  - 90% moderate
  - 80% great complexity
  - 70% hypoplastic left heart
TERMS AND LINGO
CONGENITAL HEART DISEASE

Isolated
- Pulm stenosis
- Aortic stenosis
- VSD
- ASD
- PDA

Complex
- Tetralogy of Fallot
- Transposition of the great A
- Truncus arteriosus
- AV septal defect

Single Ventricle
- Hypoplastic left heart
- Tricuspid atresia
- Critical pulmonary atresia

Acyanotic
Temporary cyanosis
Prolonged cyanosis

Disclosure: slide idea copyright Dr. Matt Files
Hypoplastic left heart syndrome
Fatal until 1980’s
Most morbidity in first 6 months
Approximately 1000 infants in the US every year born
STAGED PALLIATION

- Staged surgical approach for single ventricle physiology
- Norwood procedure in first week of life
  - Time between first and second stages – 10-15% mortality
- Glenn or Hemi-Fontan – 4-6 months of age
- Fontan (Total caval pulmonary connection) – 3-5 years
CARDIAC SURGERY - BYPASS
- Time when heart is arrested, allowing for intracardiac repair
- **Deep hypothermic circulatory arrest**
  - Operations that require a bloodless field
  - Cooled to 12-18°C
  - All blood into reservoir
  - No BP or brain activity
  - Max time 40-60 mins

- **Low flow cerebral perfusion**
  - More moderate hypothermia
  - Very low flow of blood
  - More common

**CARDIAC SURGERY**
PREVALENCE AND PATTERNS
Most common complication for survivors of surgery for CHD
Currently known risk factors explain only about 30% of observed variation in NDV outcome
- Modifiable risk factors?
Prevalence and severity of DD increases with complexity of CHD and association with genetic syndromes.
## GENETIC SYNDROMES

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Common Genetic Cause*</th>
<th>% With CHD</th>
<th>Common Lesions*</th>
<th>Developmental Disorder or Disability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alagille</td>
<td>JAG1 gene mutation or deletion</td>
<td>85</td>
<td>PPS, TOF</td>
<td>IQ varies between normal and moderate intellectual disability</td>
</tr>
<tr>
<td>CHARGE</td>
<td>CHD7 gene mutation or deletion</td>
<td>&gt;50</td>
<td>TOF, IAA, TA, PDA, VSD, ASD</td>
<td>Intellectual disability in almost all cases</td>
</tr>
<tr>
<td>Down</td>
<td>Trisomy 21</td>
<td>40</td>
<td>AVSD, VSD, TOF, PDA</td>
<td>Median IQ &lt;50</td>
</tr>
<tr>
<td>Deletion 22q11</td>
<td>22q11.2 microdeletion</td>
<td>60</td>
<td>IAA, TOF, TA</td>
<td>Mean IQ 70–80; ADHD</td>
</tr>
<tr>
<td>Jacobsen</td>
<td>11q23 deletion</td>
<td>65</td>
<td>HLHS</td>
<td>Intellectual disability in 97% of cases</td>
</tr>
<tr>
<td>Noonan</td>
<td>PTPN11 gene mutation; SOS1, RAF1, KRAS, or NRAS gene mutations (less common)</td>
<td>&gt;50</td>
<td>PVS, ASD, HCM</td>
<td>Mean IQ 84</td>
</tr>
<tr>
<td>Turner</td>
<td>Monosomy of chromosome X</td>
<td>30</td>
<td>BAV, CoA</td>
<td>Mean IQ 90</td>
</tr>
<tr>
<td>VACTERL</td>
<td>Unknown</td>
<td>75</td>
<td>VSD, ASD, PDA, TGA</td>
<td>Majority with normal IQ but majority with DD caused by multiple congenital anomalies; malformations</td>
</tr>
<tr>
<td>Williams</td>
<td>Microdeletion 7q11.23</td>
<td>60</td>
<td>SVAS, PPS</td>
<td>Mean IQ 56; visual-spatial impairments; hypotonia/hypertonia</td>
</tr>
</tbody>
</table>
How is the prevalence and severity of developmental delay in congenital heart disease typically described?

A. Low prevalence, low severity
B. High prevalence, low severity
C. High prevalence, high severity
D. Low prevalence, high severity
NON-SYNDROMIC PATTERN OF IMPAIRMENT

- High prevalence
- Low severity
- Mild cognitive impairment
- Mild impairments in fine and gross motor skills (usually early)
- Impaired social interaction
- Impaired core communication skills
  - Pragmatic language
- Inattention
- Impulsive behavior
- Impaired executive functioning
SPECIFIC OUTCOME STUDIES & RISK FACTORS

- Review of studies/data from individual institutions
- N = 1770 pts from 22 institutions born 1996-2009

**Inclusion**
- Cardiac surgery with CPB in infancy (no transplants)
- Enrollment in RCT or observational cohort
- NDV eval 6-30 months using BSID 2
- Data available on patient and operative management

**Investigators/institutions invited to participate**
NEURODEVELOPMENTAL OUTCOMES AFTER CARDIAC SURGERY IN INFANCY

Class I
2 Ventricles
No aortic arch obstruction
Transposition
TOF

Class II
2 Ventricles
+ Aortic arch obstruction

Class III
Single Ventricle
No aortic arch obstruction

Class IV
Single ventricle
+ Aortic arch obstruction
HLHS
NEURODEVELOPMENTAL OUTCOMES AFTER CARDIAC SURGERY IN INFANCY

- Assessments at 14.5 ± 3.7 months
- Psychomotor Developmental Index: 77.6
- Mental Developmental Index: 88.2
- PDI
  - 63.5% > 1 SD below the population mean
  - 36.8% > 2 SD below the population mean
- MDI
  - 36.1% > 1 SD below the population mean
  - 15.3% > 2 SD below the population mean
- No improvement over time until multivariable analyses adjusting for patient and preoperative factors
  - ? Patient and environment factors more important determinants than operative management strategies
Patient risk factors for lower PDI
- Lower birth weight
- White race
- Presence of genetic anomaly

Patient risk factors for lower MDI
- Male gender
- Lower birth weight
- Lower maternal education
- Presence of genetic anomaly

- N = 99 pts with CHD
  - 34 with single ventricle
  - 65 with 2 ventricles
  - 19% with identified genetic syndrome

- Evaluated with Bayley 3, 3-6 times in first 3 years of life
RISK AND PREVALENCE OF DEVELOPMENTAL DELAY IN YOUNG CHILDREN WITH CONGENITAL HEART DISEASE

- 1V equivalent outcomes to 2V
- 75% with DD in ≥1 area at ≥ 1 assessment
- Motor deficits most common in early assessments
- Cognitive and language deficits more prevalent with time
Risk factors:
- Inability to achieve full oral feeding
- Medical comorbidities
- Genetic d/o
- Poor growth
- Longer duration of CPB (> 200 mins)(range 145-308 mins)
- Shorter time since last hospitalization

Not associated with poor outcomes
- Race
- Ethnicity
- Gender
- +/- prenatal diagnosis
- Age at first operation

Data from the 1997-2011 National Health Interview Survey

Controls = 180,000 total children

Cases = 440 children aged 0-17 with CHD (parent reported, random child from household).

Outcomes: subjective measures of health, missed days, limits in activities, need for equipment, prescription medication, healthcare utilization, comorbidities (CP, asthma, etc)

NDV outcomes: ASD, ADHD, ID dx
Quality of life for children growing up with congenital heart disease is most significantly impacted by:

A. Gross motor ability

B. Executive function

C. Presence of anxiety/depression

D. All of the above
Children with CHD:

- 3 times more likely to miss school
- 8 times more likely to need special equipment
- 14 times more likely to have some impairment in physical activities
- 5 times more ASD
- 2 times more ADHD

Limitations – no data on type of CHD (some may have been arrhythmias), severity of defect, or +/- genetic syndrome, prematurity, etc.
Patient Factors
- Genetic syndromes
- Genetics
- Birth factors – prematurity, BW, etc
- Brain
  - Smaller total brain volumes into adolescence
    - Depending on lesion – 8-33% with microcephaly
  - Abnormal brain metabolism
  - Delayed cortical development and folding
  - Brain maturation delayed in HLHS and TGA
  - WM injury evident in 1/5 before surgery

Type/Severity of CHD
- Presence of seizures

Operative Factors – duration of CPB

Environment
- Sociodemographic factors
- Early Intervention
AMERICAN HEART ASSOCIATION CHD ALGORITHM FOR DEVELOPMENTAL DELAY SURVEILLANCE AND TREATMENT
Table 3. Categories of Pediatric CHD Patients at High Risk for Developmental Disorders or Disabilities

1. Neonates or infants requiring open heart surgery (cyanotic and acyanotic types), for example, HLHS, IAA, PA/IVS, TA, TAPVC, TGA, TOF, tricuspid atresia.

2. Children with other cyanotic heart lesions not requiring open heart surgery during the neonatal or infant period, for example, TOF with PA and MAPCA(s), TOF with shunt without use of CPB, Ebstein anomaly.

3. Any combination of CHD and the following comorbidities:
   3.1. Prematurity (<37 wk)
   3.2. Developmental delay recognized in infancy
   3.3. Suspected genetic abnormality or syndrome associated with DD
   3.4. History of mechanical support (ECMO or VAD use)
   3.5. Heart transplantation
   3.6. Cardiopulmonary resuscitation at any point
   3.7. Prolonged hospitalization (postoperative LOS >2-wk in the hospital)
   3.8. Perioperative seizures related to CHD surgery
   3.9. Significant abnormalities on neuroimaging or microcephaly*

4. Other conditions determined at the discretion of the medical home providers
Behavioral and Psychosocial
- Increased risk of internalizing and externalizing difficulties
- 15-25% by parent report
- HLHS: 8 fold increase in depression/anxiety in school age
- Heightened surveillance, screening, and evaluation

Autism Spectrum Disorder
- Preliminary studies show increased risk
- 22q11 deletion: 20-40%
- Heightened surveillance
Formal Developmental and Medical Evaluation

- Individualized approach with multi-disciplinary team
- Genetic evaluation (2007 AHA scientific statement):
  - Often discussed with prenatal diagnoses - CVS, amnio
  - Conotruncal anomalies (TOF, VSD, TA, aortic arch anomaly) – FISH for 22q
  - Suspicion for aneuploidy – chromosomes
  - Others: contact friendly geneticist or microarray
  - AHA statement: genetic consultation whenever CHD + DD, hypotonia, FTT, microcephaly, dysmorphic features

Brain Imaging

- Many centers do HUS prior to surgery
- Seizures → MRI
- Unlike preemies MRI WM differences can go away? predictive value?
- Case by case basis
CARIAC NEURODEVELOPMENTAL CLINIC AT CHDD
CARDIAC NEURODEVELOPMENTAL CLINIC AT CHDD

- Multi-disciplinary team consisting of developmental peds, psychology, audiology, PT, nutrition, social work, nurse care manager, cardiology
- Children with complex congenital heart disease requiring open heart surgery in the first year of life or long term cyanotic heart condition
- Seen at 12, 24 and 36 months and yearly thereafter if needed
WHAT DO WE STILL NEED TO KNOW

- Models of developmental follow-up
  - How long to follow?
    - AHA Guidelines: 12-24 months, 3-5 years, 11-12 years
    - Intermittent school age and adolescent visits for psychosocial/mental health/behavioral screening?
  - How much communication with schools? Education liason?
- Risk factors – what can we modify?
- Long-term follow up (Oldest single ventricle kids nearing 30’s)
- Need to better understand trajectories of individual lesions
REFERENCES


