Neuro-Consequences of Congenital Heart Disease

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Care of the Newborn Brain Symposium
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No disclosures
Objectives

» Describe the neurodevelopmental (ND) & neurobehavioral (NB) problems in patients with congenital heart disease (CHD)

» Review specific ND/NB problems in patients with CHD
  ~ infancy, childhood, adolescence

» Review risk factors for ND/NB problems in patients with CHD
Neurodevelopmental (ND) & Neurobehavorial (NB) Disabilities in CHD
Neurodevelopmental (ND) & Neurobehavioral (NB) Disabilities in CHD

- Over 50% of survivors of cardiac surgery during infancy are identified with learning disabilities and behavioral issues once they reach school age.

- These learning disabilities & neurobehavioral problems ultimately limit academic achievements, employability, lifelong earnings and quality of life.
Neurodevelopmental (ND) & Neurobehavioral (NB) Disabilities in CHD

» Motor/Speech Problems
  ~ Fine and gross motor delays
  ~ Speech delays

» Academic difficulties
  ~ Mild cognitive impairment
  ~ Impairments in visual motor integration
  ~ Impairment in executive function

• Neurobehavioral issues
  • Impaired social interactions
  • Inattention
  • Impulsive behavior

Wernovsky et al. Cardiol Young 2006
Marino et al. Circulation 2012
Quality of Life in CHD

Marino et al. Progress in Pediatric Cardiology 2010
Neurodevelopmental Disabilities in CHD

Wernovsky et al. Cardiol Young, 2006
IQ in CHD with and without genetic disorders

Latal et al. Clini Perinat 2016

LOMA LINDA UNIVERSITY
CHILDREN’S HOSPITAL

Goff 2017
### Genetic Syndromes-CHD & ND

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>% CHD</th>
<th>Common Lesions</th>
<th>Developmental Disability (DD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22q11.2 deletion</td>
<td>60</td>
<td>IAA, TOF, Truncus</td>
<td>Mean IQ 70-80 ADHD</td>
</tr>
<tr>
<td>CHARGE syndrome</td>
<td>&gt;50%</td>
<td>TOF, IAA, TA, VSD, PDA</td>
<td>Majority with Intellectual disability</td>
</tr>
<tr>
<td>VACTERL</td>
<td>75%</td>
<td>VSD, ASD, PDA</td>
<td>Normal IQ, DD</td>
</tr>
<tr>
<td>Turner’s Syndrome</td>
<td>30%</td>
<td>Coarctation, BAV</td>
<td>Mean IQ 90</td>
</tr>
<tr>
<td>Noonan’s Syndrome</td>
<td>&gt;50%</td>
<td>PS, HCM</td>
<td>Mean IQ 84</td>
</tr>
</tbody>
</table>

Wernovsky et al. Cardiol Young 2006
CHD Cohorts at High Risk for ND/NB

Any combination of CHD with the following comorbidities

~ Prematurity < 37 weeks
~ Developmental delay recognized in infancy
~ Suspected genetic syndrome/chromosomal abnormality
~ History of ECMO use
~ Heart Transplant
~ CPR at any point
~ Prolonged hospitalization (postoperative LOS > 2 weeks)
~ Perioperative seizures related to CHD surgery
~ Significant abnormalities on neuroimaging or microcephaly

Wernovsky et al. Cardiol Young, 2006
Post Heart Transplant Intellectual Function Impairment

Baum et al. J. Pediatr., 2004
Age Related ND Impairments

Motor delay - developmental coordination disorder
30–60%

Language disorders
20–30%

Behavioral problems
20–40%

Learning difficulties
30–50%

Latal et al. Clini Perinat 2016
Age Related ND Impairments

Infant/Toddler
- Motor and cognitive delay
- Feeding problems
- Abnormal tone

School Age
- Lower IQ
- ↓ Performance
  - Executive function
  - Language
  - Fine & Visual-motor skills

Adolescent
- ↑ Psychosocial maladjustment
- ↑ Educational needs
18 months BSDIII Scores in CHD

18-mo BSID-III Scores by CHD Diagnosis

Williams I et al. Ultrasound Obstet Gynecol 2012
Neurodevelopmental Outcomes at 4 y.o.

*(Total cohort: n=378)*

- Cognition
- Language
- Executive Function
- Memory
- Visual-Motor
- Fine Motor

Goff D et al. JTCVS 2012
Gestational Age and Neurodevelopmental Outcomes after Cardiac Surgery in Infancy

Gestational Age and Neurodevelopmental Outcomes

(Late preterm-Early term subgroup: n=351)

* p<0.05

- Cognition
- Language
- Executive Function
- Memory
- Social Skills
- Visual-Motor
- Fine-motor

GA < 40 weeks
GA ≥ 40 weeks

Goff D et al. JTCVS 2012
School Age Children with CHD

CHD Lesions (n=109)

- Single Ventricle: 40%
- d-TGA: 35%
- TOF: 10%
- VSD/Arch: 5%
- Other: 10%

School Support (n=109)

- None: 51%
- Inside Class: 21%
- Outside Class: 13%
- Special Ed: 15%

Boston Circulatory Arrest Trial

» Prospective Trial 1988-1992
» d-TGA with intact ventricular septum or VSD
» Surgical repair by 3 months of age
  ~ Randomized to Total Circulatory Arrest vs. Low flow CPB
» 165/171 alive at 8 y.o.
  ~ 155 agreed to return for developmental evaluation

Newburger J et al. NEJM 1993
Bellinger DC et al. NEJM 1995
Rey-Osterrieth Test
Visual Spatial Assessment

Model

Bellinger DC et al. Dev Behav Ped 2003
Rey-Osterrieth Test
8 y.o. Normal Neurodevelopment

Bellinger DC et al. *Dev Behav Ped* 2003
Rey-Osterrieth Test
8 y.o. with d-TGA s/p infant cardiac surgery

Drawing by an 8 year old child who had undergone infant cardiac surgery with cardiopulmonary bypass

Bellinger DC et al. Dev Behav Ped 2003
Visual Spatial Abnormalities

8 y.o. d-TGA s/p infant cardiac surgery

Bellinger DC et al. *Dev Behav Ped* 2003
# Psychosocial Dysfunction

## Adolescents with d-TGA

<table>
<thead>
<tr>
<th></th>
<th>Report Type</th>
<th>d=TGA (n=139)</th>
<th>Referent (n=61)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global Psychosocial Functioning</strong></td>
<td>Clinician</td>
<td>80.6 ± 11.2</td>
<td>87.2 ± 7.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Psychiatric Symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Overall Symptoms</td>
<td>Clinician</td>
<td>2.5 ± 5.2</td>
<td>1.1 ± 2.3</td>
<td>0.01</td>
</tr>
<tr>
<td>• Depressive Symptoms</td>
<td>Self</td>
<td>43.5 ± 8.2</td>
<td>41 ± 5.8</td>
<td>0.01</td>
</tr>
<tr>
<td>• Anxiety Symptoms</td>
<td>Self</td>
<td>4.2 ± 5.5</td>
<td>1.9 ± 2.3</td>
<td>0.001</td>
</tr>
<tr>
<td>• Disruptive Behavior</td>
<td>Parent</td>
<td>53.6 ± 13</td>
<td>46.3 ± 6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Self</td>
<td>48 ± 10.5</td>
<td>44.8 ± 10.9</td>
<td>.03</td>
</tr>
</tbody>
</table>

Young Adults with ACHD

Canada & US
28% - 35% meet diagnostic criteria for psychiatric diagnosis

Prevalence of mood disorders is 3 times that observed in the general population

0 – 31% of ACHD patients with psychiatric disorders receive mental health treatment

Adapted from Dr. Kovacs lecture, Cincinnati ND Conference, 2013
### 25-year old male with TOF

- Repeated first grade: underwent psychological evaluation at that time, but neither he nor his parents were informed of results.
- Second evaluation in Grade 7 or 8 “to prepare for high school”: does not recall learning results.
- High school English grade: 40%.
- After high school, enrolled in college but was withdrawn after failing several classes.
- Diagnosed with learning disability after submitting writing sample.

Adapted from Dr. Kovacs lecture, Cincinnati ND conference 2013.
Young Adults with ACHD

25-year old male with TOF

- Began taking classes at a different college
- Sometimes received academic considerations
- Failed his English class several times
- Underwent intelligence & achievement testing
  - PIQ: 30th percentile, VIQ: 6th percentile
  - Reading abilities: Grade 4-6
- His goal: 4 year advertising program
- Presenting problem: stress re. academic performance

Therefore, neurodevelopmental problems can impact adult education, employment, and quality of life

Adapted from Dr. Kovacs lecture, Cincinnati ND conference 2013
Risk Factors for ND in CHD
Risk Factors for PVL in CHD

- Impaired brain growth
- Delayed brain maturation
- Deep Hypothermic Circulatory Arrest (DHCA)
  - Low flow CPB
  - Alpha/pH stat

- Prenatal
  - “Brain Sparing” Effect

- Pre-op
  - ↓Cerebral blood flow

- Intra-op Post-op
  - Impaired cerebral autoregulation
PVL in Complex CHD

Support time as significant predictors of PVL. When the analysis was restricted to the 82 neonates, DBP and SBP remained significant predictors of PVL in the multivariable analysis with age at surgery considered as a continuous variable. PO2min and longer total support time were no longer significant.

Discussion

This study demonstrates that PVL is a frequent finding on MRI of the brain following cardiac surgery in neonates. The occurrence of PVL is much less common in older infants. Prolonged exposure to CPB (with or without DHCA) is a risk factor for PVL, possibly secondary to the systemic inflammatory response to CPB. Hypotension and hypoxemia in the early postoperative period, especially diastolic hypotension, significantly increase the risk of PVL, possibly secondary to cerebral ischemia. In infants without CHD, PVL is associated with developmental dysfunction including impaired motor function, learning disabilities, and ADHD. The significance of PVL identified on an early postoperative MRI as a predictor of a long-term neurodevelopmental outcome must be determined.

PVL was described as a specific entity in 1962 by the neuropathologic studies of Banker and Larroche. PVL is defined by the presence of focal necrosis of all cellular elements in the deep white matter surrounding the walls of the lateral ventricles and a more diffuse injury to oligodendroglial precursors.

PVL was recognized initially as a pathologic condition relatively specific to the preterm neonate; however, appreciation of its clinical significance was overshadowed by its common coexistence with more dramatic-appearing lesions such as germinal matrix, intraventricular, and parenchymal hemorrhages. Cranial ultrasonography has demonstrated that PVL may be detected in 7% to 26% of preterm infants. PVL in preterm infants is highly associated with subsequent cerebral palsy, mental retardation, learning disabilities, visual-motor deficits, and ADHD. PVL may be encountered in the term infant following significant asphyxia, hypoglycemia, meningitis, CHD, and other conditions.

The late consequences of PVL in term infants without CHD are comparable to those in prematurity and resemble the long-term neurodevelopmental "signature" of some children following surgical repair of CHD.

One of the key developmental processes in premature and very young infants is progression of myelination, in which precursors of myelin are created, mature, and eventually envelop axons in the cerebral hemispheres, cerebellum, brain stem, and spinal cord. There is an age-dependent window of vulnerability to injury of developing white matter. PVL is one of the hallmarks of brain injury in premature and some term infants but is much less common thereafter. The target for diffuse white matter injury in PVL is the early differentiating oligodendrocyte, histologically distinguished from its mature counterpart by the absence of myelin basic protein staining.
Pre-operative PVL in d-TGA is similar to preterm newborn

Brain Maturation in CHD

Licht D et al. JTCVS 2009

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Brain Volume/Curvature is Delayed in HLHS

T1 weighted images

White matter Curvature-(gyri & sulci)

- Concave (Blue-green)
- Convex (Red-yellow)

McQuillen P et al. Prog Ped Card 2010
Fetal Brain Development in CHD

Complex CHD (n=55)

» 3rd trimester (>28 weeks)
» Fetal MRI
» CHD vs Normal fetuses
  ~ Median GA 30 weeks
  ~ 19 HLHS & 13 d-TGA
  ~ Progressive decrease in GA adjusted brain growth
    • More pronounced in HLHS

Fetal MRI

Limperopoulos C et al. Circulation 2010
Lower TMS is a Risk for Preop PVL in d-TGA & HLHS

Preoperative PVL

Low total brain maturity score (TMS) associated with PVL ($p=0.002$)

Andropoulos D et al. JTCVS 2009
# PVL: Neurodevelopmental Outcomes

One year of age

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cognitive Score</th>
<th>Language Score</th>
<th>Motor Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p Value</td>
<td>Coefficient, 95% CI</td>
<td>p Value</td>
</tr>
<tr>
<td>Preoperative rSO₂</td>
<td>0.005</td>
<td>1.14 (0.40–1.87)</td>
<td>NA</td>
</tr>
<tr>
<td>Intraoperative rSO₂</td>
<td>NA</td>
<td>NA</td>
<td>0.008</td>
</tr>
<tr>
<td>Preoperative MRI brain injury</td>
<td>NA</td>
<td>NA</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU length of stay</td>
<td>0.014</td>
<td>−2.46 (−4.36 to −0.57)</td>
<td>0.027</td>
</tr>
<tr>
<td>Total CPB time first 12 months</td>
<td>0.016</td>
<td>−0.07 (−0.13 to −0.02)</td>
<td>NA</td>
</tr>
<tr>
<td>Fentanyl first 12 months</td>
<td>0.007</td>
<td>0.06 (0.02–0.11)</td>
<td>NA</td>
</tr>
<tr>
<td>Midazolam first 12 months</td>
<td>NA</td>
<td>NA</td>
<td>0.013</td>
</tr>
<tr>
<td>Chromosome anomaly</td>
<td>NA</td>
<td>NA</td>
<td>0.002</td>
</tr>
<tr>
<td>Maternal Intelligence Quotient</td>
<td>NA</td>
<td>NA</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Conclusions

- Neurodevelopmental & Neurobehavioral Disabilities affect >50% of children with CHD

- Different impact on Quality of Life at different ages

**Infant/Toddler**
- Feeding problems

**School Age**
- Decrease Performance

**Adolescent**
- Increase Psychosocial maladjustment
Conclusions

» Risk factors for Neurodevelopmental & Neurobehavioral Disabilities in children with CHD are multifactorial

» Increase awareness and screening for risk factors will contribute to improving QOL throughout childhood/adolescence and into adulthood for CHD patients
Quality of Life (QOL) in CHD

Marino et al. Progress in Pediatric Cardiology 2010
THANK YOU