

## **Cardiac Neurodevelopment**

Caitlin K. Rollins, M.D., S.M. Assistant Professor of Neurology Department of Neurology

Michael J. Bresnan Child Neurology Course September 2020



Boston Children's Hospital Until every child is well



#### **Disclosures**

None





Copyright © 2020 Boston Children's Hospital

### **Learning Objectives**

- Describe the neurodevelopmental phenotype of children ulletwith congenital heart disease (CHD)
- Understand the factors contributing to ulletneurodevelopmental impairment in children with CHD
- Be aware of follow-up recommendations for children with CHD



Boston Children's Hospital Until every child is well



HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

### Congenital heart disease (CHD) is the most common birth defect

- CHD affects 0.5-2% of all live births ullet
- As recently as the 1980s, many infants with congenital heart disease died
- Most children born with even severe CHD now expected to survive well into adulthood
- Focus shifted to optimizing quality of life for survivors •



**Boston Children's Hospital** l every child is well



HARVARD MEDICAL SCHOOL TEACHING HOSPITA

## Survival is now expected for most children with congenital heart disease (CHD)



#### Khairy et al., 2010





HARVARD MEDICAL SCHOOL **TEACHING HOSPITAL** 

# Neurodevelopmental disability (NDD) is the most common morbidity survivors face



#### **Overview**



Neurodevelopmental phenotype



**Causal factors** 



#### **Opportunities**





HARVARD MEDICAL SCHOOL TEACHING HOSPITAL



Phenotype





HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

#### Many children with CHD experience neurodevelopmental impairment in multiple domains 100

- Attention •
- **Executive function**
- Visuospatial skills
- Social cognition
- Anxiety



Sample courtesy Newburger/Bellinger



Boston Children's Hospital Until every child is well



Data from DeMaso et al., 2017





# Neuroimaging shows both injury and developmental disturbance

- Overt brain injury
- Quantitative abnormalities
  - Reduced brain volumes
  - Difference in white matter microstructure and connectivity
- Dysmature brain patterns

Findings persist from infancy through adolescence





HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

# White matter injury (WMI) is the dominant imaging abnormality



- 15-40% neonates before surgery
- ~40% new postoperative injury
- Overt evidence often
  resolves over time
- Stroke and hemorrhage also occur but less common





# White matter microstructural abnormalities in TGA may contribute to cognitive differences



## Neuroimaging abnormalities precede surgery with dysmature brain patterns at birth

- Prior to surgery, full-term neonates with CHD have ~10% lower fractional anisotropy of cerebral white matter than healthy full-term neonates (*Miller et al., 2007*)
- The NAA: Choline ratio is ~10% lower than that of healthy control neonates (*Miller et al., 2007*)
- In full-term neonates with CHD, the semi-quantitative total maturation score, an indicator of brain maturity, corresponds to what should be seen one month earlier in gestation (*Licht et al., 2009*)



Boston Children's Hospital every child is well



HARVARD MEDICAL SCHOOL **FEACHING HOSPITAL** 



Phenotype



#### Causal factors

Perioperative •





HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Copyright © 2020 Boston Children's Hospital

#### Bypass factors that may relate to brain injury

**Development Index** 

105

100

95

90

85

80

75

70

Linear trend:

Two-year means:

- Total support time
- Cooling duration
- Cooling degree
- **Circulatory** arrest
- Hematocrit
- pH management
- Arterial filtration
- **Regional cerebral perfusion**



ICCON Investigators, 2016 Gaynor, 2015







96-97 98-99 00-01 02-03 04-05 06-07 08-09

Year of Birth

PDI

PDI

---- MDI

Copyright © 2020 Boston Children's Hospital

# Known risk factors explain only ~30% of the variance in neurodevelopmental outcome



Copyright © 2020 Boston Children's Hospital



Phenotype



•

#### Causal factors

- Perioperative
- Innate genetics





HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Copyright © 2020 Boston Children's Hospital

# Genetics play important role in CHD and influence brain development

- Whole exome sequencing of 1213 CHD parent-offspring ullettrios
- Excess of protein-damaging de novo mutations: ٠
  - 20% of children with CHD, NDD, and congenital anomalies
  - 2% isolated CHD
- Substantial overlap between mutations in CHD and those previously identified in NDD

Homsy et al. 2015



**Boston Children's Hospital** every child is well



HARVARD MEDICAL SCHOOL TEACHING HOSPITAL



Phenotype



#### **Causal factors**

- Perioperative
- **Innate genetics**
- Fetal cerebral hemodynamics





HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Copyright © 2020 Boston Children's Hospital

# CHD disrupts normal fetal circulation, whereby oxygen-rich blood preferentially goes to brain



(Centers for Disease Control and Prevention, National Center on Birth Defects and Developmental Disabilities)



HARVARD MEDICAL SCHOOL

### Total brain volume in CHD fetuses is reduced by 15-20% at 36 weeks gestation



Limperopoulos et al., 2010





Caitlin D Rollins MD SM

#### Cardiac Neurodevelopment

## Reduced prenatal cerebral oxygen delivery and consumption in mixed cohort of CHD







Sun et al., 2015



# Fetal brain MRI research ongoing at Boston Children's Hospital









# Based on early data, clinical trials of neuroprotective intervention began

MATernal hyperoxygenation in Congenital Heart Disease (MATCH)



Children's Hospital of Philadelphia

CHOP Announces Fetal Neuroprotection Program

improve neurodevelopmental outcomes in newborns with CHD who subsequently undergo cardiac surgery. The first such study will evaluate whether the hormone progesterone, administered prenatally to the mother, has a neuroprotective effect on brain

> HARVARD MEDICAL SCHOOL TEACHING HOSPITAL



Copyright © 2020 Boston Children's Hospital

### Novel potential postnatal toxins that may influence outcome



- Pain
- Anesthetics
- **Environmental noise** •
- **Plasticizers** •

#### Slide adapted from Jane Newburger





HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Copyright © 2020 Boston Children's Hospital



Phenotype



**Causal factors** 



#### **Opportunities**





HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Copyright © 2020 Boston Children's Hospital

# In 2012, the AHA released a scientific statement recommending routine evaluation and management for high risk patients

#### **AHA Scientific Statement**

#### **Neurodevelopmental Outcomes in Children With Congenital Heart Disease: Evaluation and Management**

#### A Scientific Statement From the American Heart Association

This statement has been approved by the American Academy of Pediatrics.





HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

#### AHA statement specifies high-risk patients

- Neonates or infants requiring open heart surgery
- Other cyanotic heart lesions
- Comorbidities
  - Developmental delay in infancy
  - Prematurity < 37 weeks</p>
  - Suspected genetic syndrome associated with developmental disability
  - Mechanical support, heart transplant, or CPR at any point
  - Postoperative length of stay longer than 2 weeks
  - Perioperative seizures, neuroimaging abnormalities, or microcephaly
- Other conditions at discretion of medical home provider





# AHA: Neurodevelopmental assessment differs based on risk stratification

#### Low risk

- Developmental screening per AAP guidelines
  - Surveillance at all visits
  - Screening at specific ages
- Medical and developmental evaluation if concerning results

## High risk

- Early intervention
- Formal developmental and medical evaluation
- Periodic re-evaluation
  - 12-24 months
  - 3-5 years
  - 11-12 years

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL



Boston Children's Hospital Until every child is well<sup>-</sup>



### **Updated recommendations available online:** cardiacneuro.org







HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

### While there remains much work to do, many children are thriving!





HARVARD MEDICAL SCHOOL TEACHING HOSPITAL