Psychomotor Development of Foetuses and Children with Congenital Heart Defects – Review with Special Focus on the so-called Congenital Brain Disease and Recommendations for a Systematic

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After infant open-heart surgery, children are at significantly elevated risk of developmental difficulties at school entry that enhances risk for learning challenges and decreased social participation in school age and adolescence.

“Functional disabilities”
comorbidity of complex CHD

The neurodevelopmental and psychosocial signature: What's that?

Neurodevelopment

- Gross motor function
- Fine motor function
- Academic achievement
- Executive functions
- Neurologic status
- Memory
- Brain imaging
- Visual-spatial skills
- Formal intelligence
- Social competence
- Attention
- Speech & language
- Memory
Prevalence of CHD and severe developmental dysfunction

Adapted from:
Severity of CHD and degree of developmental dysfunction

- HLHS
  - 0%
  - 25%
  - 50%
  - 75%
  - 100%

- TGA
  - 0%
  - 25%
  - 50%
  - 75%
  - 100%

- TOF
  - 0%
  - 25%
  - 50%
  - 75%
  - 100%

- VSD
  - 0%
  - 25%
  - 50%
  - 75%
  - 100%

Degree of dysfunction:
- Mild CHD - rare / mild dysfunction
- Severe CHD – frequent / severe dysfunction

Percentage of school age children with dysfunction dependent on severity of CHD

Adapted from:
Risk factors for developmental impairment

Multifactorial

Patient-specific
- Genetics
  - Parental IQ
- Sociodemographic status
- Prenatal (Intrauterine) brain development
- Perinatal course

Procedure-specific
- Preoperative course
- Perioperative parameters
- Cardiopulmonary bypass
- Postoperative course
Risk factor
Prenatal brain development

- Brain of full term neonates with cardiac defect – structural similarity to that of immature, preterm neonates
- Delayed brain maturation *in utero*
- Interactions between abnormal foetal circulation and brain development
- Alterations in cerebral structure and metabolism
- Microcephaly
- Delayed neurodevelopment at age 1 and 2 years

*foetal Doppler ultrasound studies of brain vessels:*

*foetal and neonatal brain magnetic resonance imaging (MRI) studies:*
Limperopoulos C et al., Circulation 2010; Miller SP et al., N Engl J Med 2007; Park IS et al., Pediatr Cardiol 2006
RISK FACTOR
Prenatal brain development

- Full oxygenation and antegrade brain perfusion in normal foetal circulation

(Herberg U and Hövels-Gürich HH, Z Geburtsh Neonatol 2012)
Effects of chronic foetal hypoxaemia in CHD

- Autoregulation with dilatation of foetal brain vessels = "brain sparing effect"
  - Doppler pulsatility index of the a. cerebri media < 5th percentile
- **Aim**: augmentation of oxygen supply to the brain
- **But**: delayed maturation of the brain
- Enhanced risk for psychomotor delay even in full-term small for gestational age foetuses without cardiac defect
**Risk factor**
**Prenatal brain development**

- Chronic foetal hypoxaemia and retrograde brain perfusion in hypoplastic left heart syndrome
  - Brain sparing effect

(Christian U and Hövels-Gürich HH, Z Geburtsh Neonatol 2012)
Risk factor
Prenatal brain development

- Chronic severe foetal hypoxaemia and antegrade brain perfusion via right ventricle in transposition of the great arteries
  - Brain sparing effect

(Herberg U and Hövels-Gürich HH, Z Geburtsh Neonatol 2012)
Smaller brain volume

Impaired neuroaxonal development and metabolism

- In third trimester foetuses
- dependent on haemodynamic factors in complex cardiac defects as HLHS and TGA
  - ventricular output through the aortic valve

(Limperopoulos C et al., Boston, Circulation 2010:
foetal echocardiography + foetal brain-MRI
55 foetuses, 25.-37.week of gestation with HLHS, TGA, PA-IVS, etc. vs 50 normal foetuses)
Delayed structural brain maturation in full-term newborns with HLHS and TGA
- Semiquantitative maturation score on MRI
- Maturation delay of 1 month
- Head circumference minus 1SD

Enhanced susceptibility to periventricular white matter injury (leukomalacia) in the pre-, intra-, postoperative periods

A. Block arrows: deep interhemispheric sulcation
B. Residual germinal matrix
C. Migrating glial cells
D. Underdeveloped opercular spaces

(Licht DJ et al., Philadelphia, J Thorac Cardiovasc Surg 2009)
„Congenital brain disease“

- Marker for delayed brain maturation in full-term neonates with CHD before surgery
  - Underdeveloped opercular spaces (20%)
  - Delayed myelinization and microcephaly (10-30%)

» MRI studies in neonates with CHD (McQuillen PS, Prog Pediatr Cardiol 2010; Licht DJ, J Thorac Cardiovasc Surg 2004; Mahle WT, Circulation 2002)

(From: Wernovsky G, Cardiol Young 2006)
Microcephaly

Microcephaly at birth 10-30%
- 129 full-term neonates with HLHS, 12% of whom with microcephaly
- correlation with narrow diameter of the ascending aorta

(Philadelphia: Shillingford AJ et al., Cardiol Young 2007; n=129 neonates with HLHS)
Periventricular leukomalacia

- Focal white matter injury
  - Hypoxic ischaemic lesions in immature oligodendroglia cells
  - Association with developmental delay and ADHS syndrome
- Common in immature preterm neonates
- Increased incidence in term newborns with CHD

(Miller SP, McQuillen PS, Arch Dis Child Fetal Neonat Ed 2007)
Periventricular leukomalacia

- Preoperative and postoperative incidence
  - Preoperative incidence in term newborns with CHD **20-30%**
  - Postoperative incidence increased to **> 40 - 50%**

Galli KK et al., J Thorac Cardiovasc Surg 2004
Postoperative „New white matter injury“ associated with

- Type of CHD (need for aortic arch reconstruction)
- Brain immaturity (MRI)
- Impaired neurodevelopment at 2 years of age

(Beca J et al., Circulation 2013)

Resolution of focal white matter injury possible within 3-6 months

(Mahle WT et al., Philadelphia, Circulation 2002)

Functional significance in long-term follow-up not clear

HLHS
Preop.:
No PVL
subdural bleeding

Early postop.:
frontal PVL
subdural tentorial bleeding

5 months postop.:
Complete PVL resolution

Periventricular leukomalacia
Postoperative reduced brain volume

- Global reduction of gray matter volume, especially in the frontal brain (MRI):
  - HLHS after Norwood step 1 and after Norwood step 2 surgery vs. control patients
  - Association to preoperative hypoxia

(Watanabe K et al., Osaka. J Thorac Cardiovasc Surg. 2009)
Abnormal brain development in the newborn: MR metabolic aspects

- Dysfunction of preoperative brain metabolism in term newborns with CHD
  - Magnetic resonance spectroscopy (MRS) and diffusion tensor imaging (DTI)
    » Elevated ratio of lactate to choline
    » Reduced ratio of aspartate to choline
    » Altered white matter diffusivity and anisotropy
  - Indicator of delayed brain maturation
  - MRI conventional
    » White matter injury in 32%

( Miller SP et al., N Engl J Med 2007, San Francisco:
41 term-neonates with TGA and univentricular heart, resp., vs. 16 control neonates)
Risk factor
Preoperative MRI brain lesions

Structural lesions:
- a. Extended interhemisphere cleft
- b. Reduced brain volume
- c. Open operculum insulae
- d. Periventricular leukomalacia
- e. Focal embolic event
- f. Hemosiderin focus
Psychomotor and Brain Development – CHD - Review

Time axis of brain development and risk factors for psychomotor development

Stages of brain development:

Fetus  Birth  Newborn  Infant  Preschool age  School age

Axonal sprouting  Synaptic development  Myelinization

Somatic imprinting

Prenatal:
• Genetics
• Dysfuntion of foetal circulation
• Dysfuntion of cerebral vessel autoregulation
• Delay of cerebral maturation

Preoperative:
• Cyanosis
• Haemodynamic instability
• Microcephaly

Perioperative:
• Cardiopulmonary Bypass modalities
• Circulatory arrest
• Dysfunction of cerebral perfusion
• Hypothermia
• Haemodynamic instability

Later factors:
• Persistent hypoxaemia
• Reoperation
• Reduced physical fitness
• Socioeconomical status
• Genetics

Psychomotor and Brain Development – CHD - Review

Hedwig Hövels-Gürich

<table>
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<tr>
<th>Newborn</th>
<th>Infant</th>
<th>Preschool age</th>
<th>School age</th>
<th>Adolescent</th>
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<td><strong>Preoperatively</strong></td>
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<td>Cerebral maturation delay</td>
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<td>Periventricular leukomalacia</td>
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<td>Infarction</td>
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<td>Bleeding</td>
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<th>Birth</th>
<th>Early-postoperatively</th>
<th>Late-postoperatively</th>
<th>Adult age</th>
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<tr>
<td>Dysregulation of tone</td>
<td>Augmentation of periventricular leukomalacia (newborns)</td>
<td>White matter injury</td>
<td>Problems with …</td>
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<td>Feeding problems</td>
<td>Focal brain lesions (embolization, infarction, bleeding)</td>
<td>Global brain atrophy</td>
<td>Socialization,</td>
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<td>Hypotonia</td>
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<td>Focal brain atrophy</td>
<td>Finding jobs,</td>
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<td>reduction of quality of life</td>
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Synopsis
MRI and brain lesion in neonates with CHD

STUDIES: Coherence brain MRI and psychomotor development

Heart - brain: common morphogenesis

Dysfunction of foetal cerebral blood flow

Pre-/perioperative noxa (e.g. CPB):
- Acquired focal lesions
- Periventricular leukomalacia (MRI)

Increased vulnerability of the brain

Delayed brain maturation (MRI)

STUDIES: Time pattern, degree, causes of delayed brain maturation

Delayed brain maturation (MRI)

(adapated from: McQuillen PS und Miller SP; Ann N Y Acad Sci 2010)
Summary

- **Normal psychomotor development**
  in the majority of children and adolescents with CHD, especially in those without brain abnormality at birth

- **Dysfunction**
  often subtile; reduced participation adequate to age; impact on further conception of life and adulthood

- **Reasons**
  multifactorial: strong influence of patient-specific factors as nature of CHD, genetic factors, „congenital heart disease“
Future directions

♥ **International collaborative long-term studies**
- Serial brain magnetic resonance imaging and correlation to developmental assessment at the same time

♥ **Neuromonitoring**
- Near-Infrared-Spectroscopy, transcranial Doppler ultrasound, EEG monitoring

♥ **Neuroprotection**
- Optimizing modifiable risk factors of the pre-, peri- and postoperative management:
  Prenatal diagnosis, bypass modalities, intensive care medicine
Early Neurodevelopmental Outcomes after Cardiac Surgery in Infancy: A Multi-center Retrospective Analysis of 1,718 Patients

Gaynor JW et al. (18 centers world-wide): AHA presentation, San Francisco, November 2012

- Year of birth 1996-2009
- Surgery with CPB at age ≤ 9 months
- Bayley Scales of Infant Development-II at age 6-30 (m=14±4) months
  - PDI: 78±19, significantly reduced
    - Tendency to improvement with time
    - Independent risk factors: complex CHD class, age at surgery >30 days, low birth weight
  - MDI: 88±17, significantly reduced
    - Rare improvement with time
    - Independent risk factors: complex CHD class, age at surgery >30 days, low birth weight, male, low maternal education

Genetic and management factors in analysis

4 classes of CHD:
1. 2 Ventricles, no Coarctation 50%
2. 2 Ventricles, Coarctation 6%
3. 1 Ventricle, no Coarctation 6%
4. 1 Ventricle, Coarctation 38%
Future directions

Clinical consequences / demands

- Extensive neuropsychological developmental assessment for all children after CPB surgery in neonatal and infant age
  - as standard performance of health insurances
  - in analogy to standard aftercare in preterm neonates in Germany

- Comprehensive prevention and support – especially in periods of crisis as puberty and transition to adulthood
Additional neuropsychological follow-up examinations

Age 5 years
Neurological, psychomotor, cognitive, speech and language, psychosocial development

Age 2 years
Cognitive, academic, speech and language, motor development

Problems Impairment

Cardiac surgery with cardio-pulmonary bypass at neonatal or infant age

Centers for social-pediatric affairs
Centers for early development
Centers for child / adolescent psychiatry
Institutions for public health
...and other institutions...
Further diagnostics and therapy

Demands of the German association for paediatric cardiology

Review of the literature (364 publications 1966-2011) and recommendations to optimize neurodevelopmental outcome in the pediatric congenital heart disease (CHD) population.

“Children with CHD are at increased risk of developmental disorder or disabilities or developmental delay.

Periodic developmental surveillance, screening, evaluation, and reevaluation throughout childhood may enhance identification of significant deficits, allowing for appropriate therapies and education to enhance later academic, behavioral, psychosocial, and adaptive functioning.”
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<th>Alter</th>
<th>Testverfahren</th>
<th>Quelle</th>
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<tr>
<td>2 Jahre</td>
<td><strong>Formalisierte kinderneurologische Untersuchung</strong></td>
<td>G. Reuner, J. Rosenkranz, J., Pietz, R. Horn; Pearson, Frankfurt/M., 2007</td>
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<td><strong>Psychomotorische und geistige Entwicklung:</strong> Bayley-II-Entwicklungsskalen; deutsche Fassung; kognitive und motorische Skala, zusätzlich Verhaltensbeobachtung</td>
<td>H. Grimm u. H. Doil; 2. Auflage, Hogrefe, Göttingen, 2000 u. 2006</td>
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<td><strong>Sprachliche Entwicklung:</strong> ELFRA-2, Elternfragebogen zur Wortschatzentwicklung</td>
<td>W. von Suchodoletz u. S. Sachse, kjp.med.uni-muenchen.de, 2010</td>
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<td><em>oder</em> SBE-2-KT, Fragebogen-Sprachbeurteilung durch Eltern</td>
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<td><strong>Psychosoziale Daten:</strong> Auszüge aus der KiGGS-Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland, Elternfragebogen mit Kind im Alter bis zu 2 Jahren</td>
<td>Robert-Koch-Institut Berlin, Springer; Bundesgesundheitsblatt 50 (5/6), 2007</td>
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Gemäß Positionspapier der „Arbeitsgemeinschaft psychosoziale Belange und Rehabilitation von Kindern, Jugendlichen und jungen Erwachsenen mit angeborenen Herzfehlern“ der Deutschen Gesellschaft für Pädiatrische Kardiologie 2010

### Empfehlungen für standardisierte neuropsychologische Nachuntersuchungen bei Kindern nach Herzlungenmaschinen-Operation im Neugeborenen- und Säuglingsalter

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<td>5 Jahre</td>
<td><strong>Intelligenz und erworbene Fertigkeiten u. Sprache:</strong>&lt;br&gt;K-ABC, Kaufman-Assessment Battery for Children, deutsche Version&lt;br&gt;oder&lt;br&gt;HAWIVA-III, Hannover-Wechsler-Intelligenztest für das Vorschulalter&lt;br&gt;<strong>Motorik:</strong>&lt;br&gt; Movement Assessment Battery for Children-2, deutschsprachige Adaptation&lt;br&gt;oder&lt;br&gt; KTK, Körperkoordinationstest für Kinder&lt;br&gt;<strong>Lebensqualität:</strong>&lt;br&gt; Kiddy-Kindl®, Kinderversion und Elternversion, Fragebogen zur Erfassung der gesundheitsbezogenen Lebensqualität&lt;br&gt;oder&lt;br&gt; PCQLI-D, Pediatric Cardiac Quality of Life Inventory, Fragebogen für Eltern herzkranker Kinder, USA (in Deutschland multizentrisch validiert)</td>
<td>P. Melchers u. U. Preuß; PITS, Leiden /NL, 2009&lt;br&gt;G. Ricken, A. Fröltz, K.-D. Schuck, U. Preuß; Huber, Bern, 2010&lt;br&gt;F. Petermann (Hrsg.); Pearson, Frankfurt/M., 2010&lt;br&gt;E. Kiphard u. F. Schilling; Beltz, 2007&lt;br&gt;Ravens-Sieberer U et al., <a href="http://www.kindl.org">www.kindl.org</a>, 2000&lt;br&gt;Marino BS et al., Qual of Life Res 2008&lt;br&gt;Goldbeck L et al., Kinder- und Jugendpsychiatrie Ulm</td>
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