Insight into the structural and neurobiological developmental features leading to an altered fetal brain development

Prenatal consequences of congenital heart disease on brain development

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Summary

In fetuses with complex congenital heart disease (CHD), impaired brain growth and brain development starts in utero. A complex interplay between heart, brain, body and placenta takes place in the second and third trimesters of pregnancy. Altered fetal cardiovascular hemodynamics due to differnt types of CHD lead to altered cerebral, body and placental perfusion, all factors contributing to maturational delay of body and brain development. Impaired cerebral perfusion, oxygenation and nutritive energy supply affects brain growth and leads to a brain developmental delay of 3–4 weeks until birth. Comparable to the altered brain development in preterm infants, similar pathogenic mechanisms lead to an encephalopathy of CHD on a micro- and macrostructural level. After birth palliative or corrective cardiac surgery is needed, which further contributes to the brain maturational delay with consequences on the neurodevelopmental outcome.

Introduction

Congenital heart disease (CHD) is the most frequent inborn disease in humans. Every year, around 800 neonates are born with different types of CHD in Switzerland. Their severity ranges from trivial anomalies with no need for further treatment to the most complex type of CHD necessitating immediate treatment after birth. Thanks to the tremendous advances in the treatment of CHD in recent decades, which include early and accurate diagnosis during fetal life, corrective or palliative cardiac surgery in the neonatal period, perioperative intensive care and long-term cardiac follow-up, up to 95% of children with CHD may survive to adulthood. Although the overall mortality in patients born with CHD continues to decline, relevant long-term comorbidities remain a challenge today. These comorbidities include the risk of an impaired neurodevelopmental outcome, particularly in those infants treated early after birth with a high degree of medical invasiveness. Impaired outcome may become apparent in different domains of the child's development, including cognitive, motor, language and social domains [1]. The extent of impairment is associated with the severity of the CHD and syndromic comorbidities such as trisomy 21 [2]. Great efforts have been made to improve patients' outcome by implementing neuroprotective strategies. Neuroprotective strategies focus on the influence of modifiable risk factors for brain injury. This becomes possible after birth by refining neonatal cardiopulmonary bypass techniques, for example. But it still remains far more limited before birth, where altered fetal cardiovascular hemodynamics lead to altered fetal brain development at a time when medical or surgical interventions are limited [3]. This article will give insight into the structural and neurobiological developmental features leading to an altered fetal brain development determined by cerebral magnetic resonance imaging (MRI).

Altered brain development – encephalopathy of CHD

One of the ways CHD can lead to altered brain development in the fetus may be through altered fetal cardiovascular hemodynamics due to the CHD (fig. 1). Changes in brain development start early and are described in fetal MRI studies in the second trimester of pregnancy, before birth and before any routine medical treatment may begin. Different types of CHD interfere with the fetal cerebral perfusion, oxygenation and brain metabolism. For example, the two most frequent types of cyanotic CHD, the Tetralogy of Fallot and D-Transposition of the Great Arteries are associated with lower cerebral arterial oxygenation during fetal life. Normal fetal circulation provides preferential blood flow streaming of well-oxygenated placental blood redirected by the Eustachian valve via the foramen ovale into the left atrium, left ventricle to the ascend-

Published online first – please cite as: Cardiovasc Med. 2022;25:w10150. doi: 10.4414/cvm.2022.w10150 EMH Media

ing aorta and finally to the brain, which ensures adequate cerebral oxygenation of the most metabolically active fetal organ.

In D-transposition of the Great Arteries, the main pulmonary artery arises from the left (instead from the right) ventricle, thus well-oxygenated placental blood flow runs to the pulmonary artery and the descending aorta across the patent arterial duct, bypassing the brain.

In Tetralogy of Fallot, due to pulmonary valve stenosis an intra-cardiac right-to-left shunt across the ventricular septal defect results in preferential blood flow of low-oxygenated, non-placental blood to the brain [3].

This may be even more accentuated in the most complex type of CHD, Hypoplastic Left Heart Syndrome, where the cerebral perfusion is also limited due to retrograde aortic arch perfusion during fetal life [4]. Therefore, both chronic hypoxia and ischemia are the primary factors contributing to impaired brain development before birth. At birth, this may result in impaired brain development of a term CHD newborn, which is 4 weeks less mature than expected [5]. For this entity, the term encephalopathy of CHD has been proposed to define these changes including anatomical, cellular, and metabolic features [6].

Neuropathological findings

Post-mortem neuropathological studies provided insight into the fetal changes of CHD in the postnatal period. The most frequent findings are (1) cerebral white matter injuries comparable to periventricular leukomalacia (up to 75%), followed by (2) affects on the gray matter (cerebral cortex, basal ganglia, cerebellum and brain stem) with neuronal loss and gliosis (50%), and less commonly, cerebral infarcts, multifocal parenchymal bleeding and watershed injury (25%) [7, 8].

Chronic hypoxia-ischemia in CHD fetuses during the third trimester of pregnancy leads to brain abnormalities comparable to those of preterm infants in a similarly vulnerable brain development period [9]. These disturbances affect sensitive cellular structures at a dedicated time span within the early-to-mid third trimester of pregnancy, as shown in animal models [10]. The most sensitive cellular structures include the pre-myelinating oligodendrocytes arising from the sub-ventricular zone and serving to myelinate neuronal axons during fetal brain development, coinciding with the time starting point of impaired brain growth and brain development in CHD fetuses.

Regarding cerebral alterations combined with CHD, fetal cerebral ultrasound is a widely used diagnostic tool, but it has its limitations.

Prenatal cerebral imaging

Due to the high diagnostic impact of fetal echocardiography, CHD can be diagnosed during the second trimester of pregnancy [11]. Regarding cerebral alterations combined with CHD, fetal cerebral ultrasound is a widely used diagnostic tool, but it has its limitations. Therefore, for complex malformations or an inconclusive ultrasound diagnosis, fetal cerebral MRI has become increasingly valuable, especially for fetal central nervous system (CNS) anomalies [12]. Furthermore, fetal cerebral MRI has established itself as a safe scientific tool for analysing fetal brain growth and development. Modern MRI techniques with fast, single-shot sequences and advanced image processing methods used for motion correction and image reconstruction enable the acquisition of high resolution 3D images for qualitative and quantitative analysis [13].

On an anatomical level, alterations in brain development and growth are observed in CHD patients during fetal life. Fetal MRI in patients with complex types of CHD, such as D-Transposition of the Great Arteries or Hypoplastic Left Heart Syndrome, showed in case-control studies a reduced brain growth for intracranial and total brain volume compared with healthy control babies between the 25th and 37th weeks of gestation [14]. This often leads to a higher incidence of microcephalic newborns with complex types of CHD, which becomes evident at birth. Furthermore, alteration of the fetal brain development manifested itself by a po-

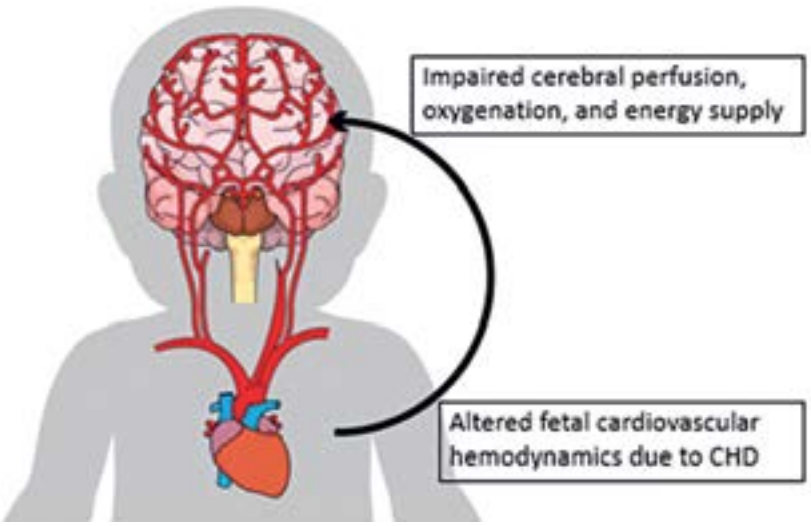

Figure 1: Fetal hemodynamic consequences of congenital heart disease (CHD).

Published online first – please cite as: Cardiovasc Med. 2022;25:w10150. doi: 10.4414/cvm.2022.w10150 EMH Media

tentially delayed gyrification of both cerebral hemispheres and reduced surface area in a similar case control study for fetuses with Hypoplastic Left Heart Syndrome [15]. Altered brain sulcal patterns in CHD fetuses between the 21st and 30th weeks of gestation compared with healthy fetuses were found. The alteration of early emerging sulci described suggests that disturbances in brain development already occur during the second trimester [16], which is part of the physiological local tissue growth pattern in normal fetal human brain gyrification [17].

Despite a reduced cardiac index (up to 30%) in patients with a single ventricle, such as Hypoplastic Left Heart Syndrome, normal cerebral perfusion may be obtained by the so-called brain sparing vascular effect.

Insight into metabolic brain development is provided by fetal cerebral MRI spectroscopy, allowing measurement of neurometabolites such as lactate, glutamate, N-acetyl aspartate, choline and creatinine. The ratio of N-acetyl aspartate to choline serves as biomarker for fetal brain development, which is reduced in patients with a complex type of CHD [5, 14].

With regard to cerebral oxygenation and cerebral perfusion, fetal aortic oxygen saturation (SaO_2) and umbilical vein oxygen saturation are reduced in patients with different complex types of CHD up to 10% respectively to 6% in the late third trimester (36th week of gestation) before birth [4]. Despite a reduced cardiac index (up to 30%) in patients with a single ventricle, such as Hypoplastic Left Heart Syndrome, normal cerebral perfusion may be obtained by the so-called brain sparing vascular effect. This brain sparing physiology may not always be adequate for sufficient cerebral blood flow in all types of CHD. Brain sparing physiology may be obtained by a cerebral vasodilation in CHD patients to ensure cerebral blood flow [3]. In Hypoplastic Left Heart Syndrome, cerebral perfusion is maintained as much as possible by inducing brain sparing physiology with cerebral vasodilation through reduced cerebral vascular resistance. As a complicating factor in Hypoplastic Left Heart Syndrome or even in less severe forms of left ventricular outflow tract obstruction, intrinsic functional and structural underdevelopment of the cerebral capillary bed limits this brain sparing effect. In Tetralogy of Fallot, contrary to the expected cerebral vasodilation, increased aortic output triggers a brain sparing effect by cerebral vasoconstriction that outweighs the estimated vasodilatory response, which is particularly pronounced in the extreme forms of Tetralogy of Fallot with pulmonary atresia and ventricular septal defect. In Transposition of the Great Arteries, the magnitude of the brain sparing effect of cerebral vasodilation may be related to the presence of a ventricular septal defect with a right-to-left shunt during diastole, which increases the amount of well-oxygenated placental blood reaching the brain [3]. In conclusion, fetal adaptive cerebral vasodilation (brain sparing effect) seems to be limited to ensure normal brain growth, which may be reduced in CHD patients. Reduced cardiac index associated with a reduced cerebral oxygen delivery (DO_2) (up to 15%) and by a lower cerebral oxygen consumption (VO_2) (up to 32%) is leading to smaller total brain volumes (up to 13%) in the late third trimester before birth [4]. After birth, the cerebral vascular autoregulation is impaired undergoing neonatal cardiopulmonary bypass after surgery [18].

Beyond the described relationship between the fetal brain and heart, a third vital organ may interact – the placenta. This organ receives 40% of fetal cardiac output and is the largest fetal organ [19]. Alterations of placental function in patients with a complex type of CHD have been described and may also impact on fetal brain development. There is growing evidence that functional and structural placental abnormalities described in CHD patients include disrupted microvasculature and vascular immaturity and impaired oxygen extraction [20]. This may lead to decreased cerebral oxygen delivery beyond the auto-regulatory cerebral vascular capacity, resulting in overall small-to-normal sized fetuses regarding fetal body growth as well as impaired brain growth and brain development [4].

Postnatal cerebral imaging

After birth, within the first months of life, the impaired brain development and brain growth continues in ways similar to those in the last trimester of fetal life. Longitudinal analysis of prenatal (third trimester) to postnatal (4 months) brain growth trajectories in patients with a complex type of CHD show continuous brain growth. However, although total brain volume, (sub-)cortical grey matter volume, white matter volume and cerebellar volume increase, they continue to be reduced compared with healthy controls [21].

CHD infants have lower total and regional brain volumes before and after neonatal cardiac surgery than healthy controls, but the distribution of the lower regional brain volumes are without a specific regional predilection.

Published online first – please cite as: Cardiovasc Med. 2022;25:w10150. doi: 10.4414/cvm.2022.w10150 EMH Media

Special attention has to be given to the circumstance that the majority of these newborns with complex type of CHD need immediate cardiac surgery after birth, often using cardiopulmonary bypass under moderate hypothermia. During moderate hypothermia and other techniques to protect CNS structures during surgery, the vulnerability of the brain due to a developmental delay of 4 weeks remains a matter of concern [5].

CHD infants have lower total and regional brain volumes before and after neonatal cardiac surgery than healthy controls, but the distribution of the lower regional brain volumes are without a specific regional predilection [22]. Despite cardiac surgery and perioperative intensive care, brain growth goes on continuously, but is reduced affecting the total as well as the regional brain volumes at a comparable range between 10% and 20% at birth [23]. There is growing evidence that this variation in brain volumes continuous after birth during early childhood [24], school-age [25] until adulthood [26].

Different structural brain lesions after birth include small, punctuated white matter injury, periventricular leukomalacia, small cerebral stroke, and cerebral (micro-) bleeding in up to 50% of patients with complex type of CHD. Different influencing factors for postnatal (pre-, intra- and postoperative) structural brain lesions have been determined as modifiable or non-modifiable factors [27], such as reduced brain development, cyanosis, reduced Apgar score at 5 minutes, pathological aEEG before surgery, and later time point of surgery [28].

Neurodevelopmental outcome

Depending on the severity of CHD and other (genetic) comorbidities, neurodevelopmental outcome may be impaired in CHD patients compared with healthy controls [1, 2]. Although impaired neurodevelopmental outcome is frequently described, the degree remains rather mild. During infancy and early childhood, all domains of neurodevelopment such as motor, language and cognitive function can be involved with a mild delay of developmental milestones [1]. During preschool age, delay in speech competence and social behavioural aspects may become more evident. Memory deficits, mild learning disabilities and impaired executive function follow during school age [29] until adolescence, and may persist until adulthood with lower educational and occupational levels as compared with healthy controls [26], influencing quality of life [30].

Due to the multifactorial influences on neurodevelopmental outcome in CHD patients, the relative contribution of prenatal, surgical, perioperative intensive care and psychosocial factors during neurodevelopment (i.e., socioeconomic status) remains difficult to determine. Therefore, studies showing a direct correlation between prenatal findings and early postnatal findings before and after cardiac surgery are limited. In serial fetal and postnatal pre- and postoperative cerebral MRI, smaller cerebellar size compared with healthy controls was associated with deficits in language function [31]. Perioperative neonatal regional brain growth trajectories provides evidence on auditory and language development at 1 year of age [32]. Whereas little is known about the correlation between early fetal cerebral alterations and mid-term outcome, more data show an impact of perioperative brain injuries on mid-term neurodevelopmental outcome. there is evidence that pre- [33] and postoperative [34, 35] brain injury is associated with motor [33, 34], language [33, 34] and cognitive [34, 35] outcome at one [33, 34] or two [35] years of age using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III), a standardised neurodevelopmental Test tool.

The neurodevelopmental outcome until adulthood is arguably linked with the cardiac outcome, but it is also highly dependent on socioeconomic and psychosocial factors.

As the child develops with age, more sophisticated evaluated long term neurodevelopmental outcome become possible. This includes a battery of diagnostic tools with focus on executive function, which resembles a kind of "metacognition" with aspects of planning daily life activities including flexibility performance and social interacting with pears [36].

The neurodevelopmental outcome until adulthood is arguably linked with the cardiac outcome, but it is also highly dependent on socioeconomic and psychosocial factors including a number of supportive treatment options (physiotherapy, speech therapy, occupational therapy), as well as environmental enrichment with support for "optimal" parenting including maternal affective involvement, parent-child synchrony, and positive and responsive parenting.

Practical guidelines for the systematic diagnostic evaluation and management have been developed in the past [37]. Therefore, a national neurodevelopmental Outcome Registry for CHIldren with complex congenital heart Disease (ORCHID) in Switzerland has been implemented as part of the Swiss Neonatal Network and Follow-Up Group (SwissNeoNet) [38].

Published online first – please cite as: Cardiovasc Med. 2022;25:w10150. doi: 10.4414/cvm.2022.w10150 EMH Media

Key points

- CHD patients may develop impaired brain development even before birth.
- A reason for impaired brain development is the altered fetal cardiovascular hemodynamics due to complex CHD affecting oxygen delivery and brain nutrition by impaired cerebral perfusion.
- Prenatal to postnatal brain growth trajectories might be different from healthy controls. The brain volume reduction affects global as well as regional brain segments.
- Structural brain lesions are frequently found after birth including small white matter lesions, cerebral bleeding and small cerebral strokes.
- New structural brain lesions may be detected after neonatal cardiopulmonary bypass surgery in a time window when the brain vulnerability is increased due to impaired brain development.
- Reasons for impaired neurodeveopmental outcome in children with complex type of CHD are multifactorial and include cumulative effects with repetitive hypoxemic and ischemic conditions at different time points (fetal, postnatal, intraoperative and postoperative) leading to impaired micro- and macrostructural brain development.

Long-term outcome

The overall long-term cardiac outcome up to adulthood depends on the type of CHD and its patient-specific severity and clinical course, which requires chronic medical care with the need for further surgical or catheter-based re-interventions after biventricular repair or staged palliation in single ventricle CHD patients [39].

Long-term neurodevelopmental outcome shows a relatively high rate of impairment in a number of domains (in some up to 50%), while the severity of impairment is rather determined at low degree, described as high prevalence, but low severity [1]. Patients born with a complex type of CHD may show some type of delay until adolescence and adulthood. This includes (age-dependent) motor, behavioural, social and intellectual, including higher-order cognitive difficulties (executive functions, memory and learning disabilities) [1]. A survey in the United Kingdom showed that adult CHD patients found employment in a variety of professions [40]. For CHD patients, early educational advice and appropriate occupational health guidance might contribute to a successful career and further maximise their quality of life [41].

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Outlook

Advanced neuropathological studies analysing the fetal brain development are needed to confirm comparable changes in the white matter and nuclear structures in the CHD fetus, so far predominantly shown for preterm infants.

Longitudinal studies focusing on the long-term follow up on neurodevelopmental outcome will provide valuable information on how the observed changes *in utero* may relate with the long-term outcome in CHD patients.

The heart–brain–placenta interplay represents a key topic for further research including hemodynamic alterations, (micro-) structural influences and the modification by genetic/epigenetic factors.

Acknowledgment
Celine Steger is supported as PhD Student by the Swiss National Science Foundation 320030_184932 "Altered cerebral growth and development in infants with single ventricle congenital heart disease". The paper was presented at the SSC/SSCS joint annual meeting on 10 June 2021.

Disclosure statement
No financial support and no other potential conflict of interest relevant to this article was reported.

References
The full list of references is included in the online version of the article at https://cardiovascmed.ch/article/doi/CVM.2022.w10150.