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Neurodevelopmental outcome in children with congenital heart disease

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SUMMARY

Children with congenital heart disease (CHD) have multiple factors contributing toward their risk of later neurodevelopmental difficulties. With earlier diagnosis and improved survival rates, the management of CHD now includes the recognition of neurodevelopmental risks and optimisation of neurodevelopmental outcomes is emphasised. Neuroimaging studies have shown early differences in brain development for children with CHD, who then are vulnerable to additional brain injury in the perinatal period. For some children, complications and co-morbidities may further increase the risk of brain injury. Synthesis of multiple factors is necessary to estimate neurodevelopmental prognosis for an individual child. Long-term neurodevelopmental follow-up of children with CHD is warranted for early identification of and intervention for difficulties.

1. Introduction

As survival of babies with congenital heart disease (CHD) has improved, more attention is focused on long-term neurodevelopmental outcomes. It is increasingly recognised that children with CHD are more likely to have neurodevelopmental difficulties than their peers, though the underlying pathophysiology is not always well understood. Quantification of the risk of such problems and predicting their type and severity remains difficult for individual children. Current research attempts to understand whether the brain develops differently as a primary issue or secondary to circulatory consequences of the cardiac abnormality and also how neurodevelopmental difficulties are specific to different types of cardiac problems. Research on fetal brain development is in its early stages; more is known about the brain at term age and the effects of postnatal experiences in children with CHD.

This review describes current knowledge of neurodevelopmental outcomes in children with CHD. We also discuss the range of brain abnormalities found on neuroimaging, and the neurological complications associated with CHD.

2. Early brain abnormalities associated with congenital heart disease

Improvements in magnetic resonance imaging (MRI) have accelerated understanding of structural differences in the brains of children with CHD. These differences fall into two categories: abnormalities of brain development, and acquired brain injury. Investigation into the nature of these brain abnormalities seeks to identify structural precursors to later functional impairments.

2.1. Structural differences in the fetal and neonatal brain

Limperopoulos et al. examined brain MRI scans from a series of 50 fetuses with CHD.[1] The majority had hypoplastic left heart syndrome (HLHS) or transposition of the great arteries (TGA). These fetuses had smaller brain volumes and altered brain metabolism compared with controls and these findings were related to the proportion of blood flow through the aortic valve and the absence of forward flow in the transverse aortic arch. Later studies also demonstrated delayed cortical development in fetuses with HLHS that preceded the appearance of volumetric abnormalities.[2] This finding suggests that altered blood flow and/or substrate delivery in fetal life impacts cerebral growth and development in at least a subset of infants.[52,53]

Pathology studies confirm a high incidence of structural brain abnormalities in infants with CHD.[3,4] A study of postmortem brain specimens from 41 neonates with HLHS identified major or minor central nervous system abnormalities in 29%, including

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holoprosencephaly and agenesis of the corpus callosum. The most frequent finding was microcephaly, seen in 13 of 36 infants (36%). As the mean age of death of these infants was 31 days, this microcephaly was, in most cases, likely related to poor fetal brain growth. Cortical mantle malformations were seen in 8 of 39 patients (21%), ranging in severity and location. From these data it appears that, prior to any acquired complications, early brain development is abnormal in many infants with CHD.

2.2. Acquired brain lesions in CHD

Beyond these structural differences, infants with CHD are also at high risk for acquired brain injury in infancy (see Fig. 1). MRI studies have found brain injury both before and after surgical intervention; injury is often clinically silent in the neonatal period, in part related to the need for sedation and pharmacological paralysis.[54] White matter rather than basal ganglia injury frequently occurs in CHD. Interpretation of the literature is complicated by inconsistency in classification of brain lesions: many studies use the term 'stroke' to include ischaemic and haemorrhagic arterial stroke as well as a more watershed pattern of injury. The term 'periventricular leukomalacia' is used broadly to describe a range of white matter injury, including a global increase in signal on T2-weighted magnetic resonance images in the white matter and focal punctate lesions; overt cystic change is seldom described in this group of infants.

Pre- and postoperative factors can influence rates and patterns of injury seen on MRI. An early preoperative MRI study of 24 neonates with CHD described periventricular leukomalacia in four (16%), and stroke in two (8%)[5]; elevated brain lactate was also seen on proton magnetic resonance spectroscopy (MRS) in 53% of patients, indicating inadequate oxygen delivery to meet aerobic demands. On postoperative MRI 5–12 days after surgery, 67% of patients had new or worsened lesions. These results have since been confirmed, and expanded to include descriptions of delayed postnatal brain maturation.[6–9] (Table 1, see also Fig. 2). Oxygen saturation, acidosis, and time to surgery appear to influence the pattern of brain injury.[10,11] Postoperative white matter injury has been associated with low mean blood pressure during the first postoperative day.[12] However, the surgery itself may not necessarily worsen existing injury: a study of infants with clinically silent preoperative MRI abnormalities found that these were not exacerbated by cardiac surgery.[13] Similar findings were reported in a series of 26 babies with TGA.[10] MRI studies have elucidated some factors increasing risk for brain injury, though further work is required.

Proton MRS allows non-invasive measures of relative levels of specific molecules in the brain, among which are lactate (reflecting metabolism) and *N*-acetyl aspartate (NAA, a neuronal marker). Diffusion tensor imaging (DTI) algorithms analyse MR data to recognise movement of water within tissue, allowing the delineation of white matter tracts and intracerebral connectivity. As summarized in Table 1, work using both techniques suggests that infants with CHD have altered brain metabolism and connectivity, often in the absence of overt lesions. Of particular promise has been work showing that patterns of white matter development and injury in babies with CHD share metabolic and microstructural features in common with patterns seen in preterm newborns.[14] This suggests a potential shared pathway in the evolution of injury between these populations. Evolving MR approaches to assessing cerebral blood flow have given insight into how brain injury may evolve in infants with CHD.[15] These MRI techniques have the potential to allow in-vivo examination of the biochemical and cellular disruptions that exist in babies with CHD, offering an avenue to investigate possible interventions.

3. Long-term neurodevelopmental outcomes in subtypes of congenital heart disease

While MR techniques offer insight into the likely pathophysiology of brain development and injury in children with CHD, larger cohort studies shape our current understanding of the clinical neurodevelopment of these children. Three recent reviews summarise neurodevelopmental outcomes in infants with CHD.[16–18] Despite heterogeneity in methodology between studies, results show a consistent pattern of developmental impairment in children with CHD, characterised by motor and cognitive delay in the first 2–3 years and then lower intelligence quotient (IQ), decreased performance in executive function, language, and fine motor and visual–motor skills at school age with increased rates of psychosocial maladjustment and educational needs.[16,17,19–21] On the other hand, these patients show low rates of major disabilities such as cerebral palsy, severe intellectual disability, significant visual impairment or sensorineural hearing loss.[22] Neurodevelopmental dysfunction rates vary by disease complexity; children with HLHS and related abnormalities have the highest risk of problems (Table 2).[19,21] Because many neurodevelopmental deficits seemingly become apparent only at school age, long-term follow-up of

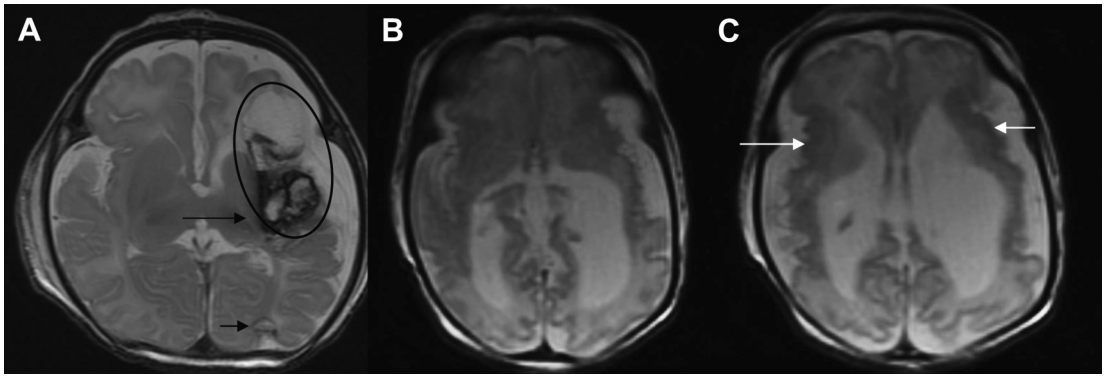

Fig. 1. (A) Axial T2-weighted image from a 6-week-old infant showing haemorrhagic stroke (circle) within the territory of the left middle cerebral artery. The lesion is already atrophic indicating that it is at least 3–4 weeks old. The posterior limb of the left internal capsule is not normal (arrow) and the basal ganglia are smaller than on the right making it highly likely that the child will develop contralateral hemiplegia. There is another smaller lesion posteriorly (short arrow) and one (not shown) on the medial border of the anterior lobe. (B, C) Axial T2-weighted images at the level of the lower basal ganglia (B) and mid-ventricular level (C) from a growth-estricted infant with hypoplastic left heart syndrome. There is marked irregular lateral ventriculomegaly. The white matter is severely reduced in volume and of abnormally high signal more posteriorly. The cortex is clearly abnormal with the appearance of polymicrogyria (arrows) bilaterally in the periSylvian regions. (Images reproduced by courtesy of S.O. Algra MD; UMC Utrecht).