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ORIGINAL RESEARCH

Assessment of Neurodevelopmental Outcomes in Children With Congenital Heart Disease Using Magnetic Resonance Imaging (MRI): Focus on Brain Volume as a Predictor of Neurodevelopmental Abnormalities

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Objective: This study aims to evaluate the neurodevelopmental outcomes in children with congenital heart disease (CHD) using magnetic resonance imaging (MRI), and to assess the role of brain volume metrics as predictors of neurodevelopmental abnormalities.

Methods: In this retrospective cohort study, 160 children with CHD treated at Children's Hospital of Nanjing Medical University from January 2020 to December 2023 were analyzed. Patients were classified into normal (DQ ≥ 70, n=106) and abnormal neurodevelopment (DQ < 70, n=54) groups based on Developmental Quotient (DQ) scores. MRI scans were used to measure total brain volume, cortical gray matter, deep gray matter, white matter, and cerebrospinal fluid volumes. Neurodevelopmental assessments focused on adaptive behavior, motor skills, language, and personal-social behavior. ROC analysis was performed to determine the predictive value of brain volume metrics for neurodevelopmental abnormalities.

Results: Total brain volume in the normal group (341.82 ± 10.43 mL) was significantly higher than in the abnormal group (323.92 ± 10.24 mL) ($P < 0.05$). Cortical gray matter volume in the normal group (131.47 ± 4.02 mL) was also significantly greater than in the abnormal group (121.63 ± 6.91 mL) ($P < 0.05$). No significant differences were observed in white matter, deep gray matter, or cerebrospinal fluid volumes. Children in the abnormal group scored significantly lower in all developmental domains ($P < 0.05$). ROC analysis showed that total brain volume (AUC = 0.968) and cortical gray matter volume (AUC = 0.936) were strong predictors of neurodevelopmental abnormalities ($P < 0.001$).

Conclusion: Total brain volume and cortical gray matter volume, as measured by MRI, are effective predictors of neurodevelopmental abnormalities in children with CHD and can serve as valuable tools for early neurodevelopmental assessment.

Keywords: magnetic resonance imaging, MRI, congenital heart disease, children, neurodevelopmental outcomes

Introduction

Congenital heart disease (CHD) is one of the most common congenital anomalies, affecting approximately 1% of live births. Advances in surgical techniques, catheter interventions, and perioperative care have significantly improved survival rates for children with CHD.[1] However, despite these surgical improvements, many CHD patients continue to face neurodevelopmental disorders (NDD), including cognitive decline, delayed motor development, language impairments, social difficulties, attention deficits, and autism spectrum disorders.[2] Research indicates that the incidence of NDD is about 10% among children with mild CHD and can rise to 50% among those with severe CHD. These neurodevelopmental issues not only severely impact the quality of life for affected children but also place a substantial burden on families and society.[3,4]

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The mechanisms underlying neurodevelopmental disorders in CHD may be related to factors such as preoperative chronic hypoxia, brain ischemia-reperfusion injury associated with surgery, and postoperative complications.[5] Currently, the gold standard for the diagnosis of CHD is cardiac catheterization, which is an invasive procedure with high requirements for both equipment and technique. As a result, its clinical application is somewhat limited. Ultrasound has always been the preferred method for assessing the fetal cardiovascular system and brain development. However, its imaging quality can be compromised when influenced by factors such as advanced gestational age, maternal obesity, oligohydramnios, fetal rib calcification, cranial ossification, and fetal position. In recent years, with continuous advancements in imaging technology, MRI has gained increasing recognition as a tool for evaluating brain structure and function in CHD patients due to its non-invasive nature, high resolution, and ability to provide detailed soft-tissue imaging.[6,7]

Recent developments in MRI technology, such as high-resolution imaging, diffusion tensor imaging (DTI), and magnetic resonance spectroscopy (MRS), have allowed for more precise assessments of brain microstructure and function in children with CHD. These advancements have provided novel insights into how brain development is altered in the presence of congenital heart defects. For example, studies have shown that structural changes in brain volumes, including reduced cortical gray matter and white matter, and increased ventricular volumes, are commonly observed in CHD patients. While some of these abnormalities have been identified through MRI in previous studies, there remains a gap in the understanding of how specific brain volume changes correlate with clinical neurodevelopmental outcomes.[8,9]

Despite the growing body of research, MRI is still underutilized in routine clinical practice to assess neurodevelopmental outcomes in CHD patients. More importantly, few studies have investigated how MRI-derived metrics, such as brain volume, might serve as predictors of neurodevelopmental disorders in these children. This study aims to evaluate the brain structure of CHD children using MRI, analyze the relationship between brain volume and neurodevelopmental disorders, and explore the predictive value of MRI in detecting these abnormalities. Our findings may contribute to filling this gap and enhance the early detection and management of neurodevelopmental disorders in CHD patients.

Methods

Study Design

This study is a retrospective cohort analysis involving children with congenital heart disease (CHD) who underwent surgical treatment and MRI scans at Children's Hospital of Nanjing Medical University between January 2020 and December 2023. Based on the Full-Scale Intelligence Quotient (FSIQ) scores from the Wechsler Preschool and Primary Scale of Intelligence, fourth edition (WPPSI-IV),[10] patients were divided into two groups: a normal neurodevelopment group (DQ $\geq$ 70, n=106) and an abnormal neurodevelopment group (DQ < 70, n=54). The study was approved by the Ethics Committee of Children's Hospital of Nanjing Medical University and complies with the Declaration of Helsinki. Informed consent was obtained from the guardians of all participants.

Inclusion Criteria

The study included CHD patients aged 6 months to 5 years who met the following criteria:

1. All the children were confirmed to have congenital heart disease through surgery.
2. Complete pre- and post-operative MRI scans and neurodevelopmental assessment data available.

Exclusion Criteria

Patients were excluded if they met any of the following criteria:

1. Presence of severe genetic or metabolic disorders.
2. Central nervous system structural abnormalities, such as congenital brain malformations.
3. Death or severe complications due to non-cardiac-related conditions post-surgery.
4. Incomplete follow-up data.

A total of 11 patients were excluded due to the reasons outlined above, which represents 6.88% of the total enrolled cohort.

MRI Scanning Method

For children with poor compliance, chloral hydrate solution (Nanjing Children's Hospital, [Approval Number] Su Yao Pharmaceutical H04000508) was administered orally 20 minutes prior to the scan, at a dosage of 1ml/kg body weight. All subjects underwent MRI scans using the same 3.0T (Tesla) superconducting MRI scanner (General Electric Company, USA) and a 16-channel head phased-array coil for head imaging. Initial scans were performed using T2-weighted imaging (T2WI) and T2-FLAIR sequences to exclude any intracranial lesions.

Three-dimensional T1- weighted high-resolution structural images (3DT1WI) were obtained using the following parameters: echo time (TE) = 3.5 ms, repetition time (TR) = 7.9 ms, field of view (FOV) = 200 × 200 × 200 mm, slice thickness 1 mm, and acquisition time = 4 min 24 s. imaging was performed using a multi-delay multi-echo (MDME) sequence with the following parameters: TR = 10,205.0 ms, TE = 11.3 ms and 90.3 ms, FA = 12°, ETL = 16, FOV = 256 mm × 256 mm, slice thickness = 2 mm, no inter-slice gap, 75 slices, matrix = 128×128. The scanning direction was axial, and the acquisition time was 5.5 minutes.

Image Processing and Analysis

Cortical morphology was evaluated by SBM analysis based on Statistical Parametric Mapping (SPM12) and the Computational Anatomy Toolbox (CAT12) on the MATLAB 8.2 platform (R2013b). The software automatically segmented the brain into white matter, gray matter, cerebrospinal fluid (CSF), and other tissue volumes (ie, tissues that are not classified as gray matter, white matter, or CSF). Brain parenchymal volume was defined as the sum of the white matter, gray matter, and other tissue volumes. Cranial volume was defined as the sum of the brain parenchymal volume and the cerebrospinal fluid (CSF) volume.

Neurodevelopmental Assessment

Neurodevelopmental assessment was conducted using the Wechsler Preschool and Primary Scale of Intelligence, fourth edition (WPPSI-IV), Gesell Developmental Scale by trained personnel. This scale evaluates the overall development of children aged 2 years and 6 months to 6 years and 11 months, covering five areas: adaptive behavior (AB), fine motor skills (FM), gross motor skills (GM), language (L), and personal-social behavior (PSB). The Developmental Quotient (DQ) is calculated as the average score across these five areas, with a DQ ≥ 86 considered normal, 70–85 as borderline, and DQ < 70 indicating possible developmental delay. All assessments were performed by the same rehabilitation physician following the standard procedures of the Gesell Developmental Scale. The assessments were conducted in a quiet, independent, well-lit room with a temperature controlled between 20–30°C. Children were dressed in 1–2 layers of clothing, and family members were allowed to be present during the assessment to encourage optimal performance.

Statistical Analysis

Data analysis was performed using SPSS version 24.0. Descriptive statistics are expressed as means ± standard deviations, with group comparisons conducted using *t*-tests for normally distributed continuous variables or Mann–Whitney *U*-tests for non-normally distributed continuous variables Categorical data were analyzed using chi-square tests. Pearson correlation was used for correlation analysis, and ROC curve analysis was employed to evaluate the predictive value of brain volume for diagnosing neurodevelopmental abnormalities in CHD patients. Statistical significance was set at $P < 0.05$.

It is important to note that ROC analysis is a univariate analysis, meaning it evaluates the diagnostic accuracy of a single variable (eg, total brain volume or cortical gray matter volume) without controlling for other potential confounding factors such as age, sex, or comorbidities. Although ROC analysis provides valuable insights into the predictive ability of these imaging markers, future studies may benefit from employing multivariate analysis techniques (eg, logistic regression) to control for confounders and enhance the robustness of the findings.

Results

Comparison of Basic Characteristics Between Groups

The study included 160 children with congenital heart disease (CHD). Based on developmental quotient (DQ) scores, 54 children were classified into the neurodevelopmental disorder group, while the remaining 106 were classified into the neurodevelopmentally normal group. There were no statistically significant differences between the two groups in terms of gender, birth weight, gestational age, multiple births, preoperative arterial oxygen saturation, use of ventilatory support, prematurity, or presence of cyanotic congenital heart disease ($P > 0.05$). See Table 1.

Comparison of Brain Volumes Between Groups

The total brain volume in the neurodevelopmentally normal group was 341.82 ± 10.43 mL, significantly higher than 323.92 ± 10.24 mL in the neurodevelopmental disorder group ($P < 0.05$). Among brain structures, only the cortical gray matter volume differed significantly, with the normal group showing a volume of 131.47 ± 4.02 mL compared to 121.63 ± 6.91 mL in the disorder group ($P < 0.05$). No significant differences were observed in the volumes of white matter, deep gray matter, or cerebrospinal fluid ($P > 0.05$). See Table 2.

Comparison of Neurodevelopmental Scores Between Groups

Children in the neurodevelopmental disorder group had significantly lower scores in adaptive behavior, fine motor skills, gross motor skills, language, personal-social behavior, and DQ compared to the neurodevelopmentally normal group ($P < 0.05$). See Table 3 and Figure 1.

Table 1 Comparison of Basic Characteristics Between Groups

Characteristic	Neurodevelopmental Disorder Group (n=54)	Neurodevelopmentally Normal Group (n=106)	t/χ^2	p
Gender	0.16	0.988		
Male	30	59		
Female	24	47		
Birth Weight (kg)	3.16 ± 0.62	3.22 ± 0.64	0.567	0.572
Gestational Age (weeks)	37.29 ± 2.43	37.18 ± 2.54	0.263	0.793
Multiple Births (n)	14	27		
Preoperative Arterial Oxygen Saturation (%)	87.73 ± 6.80	87.79 ± 6.49	0.544	0.956
Ventilatory Support	15	30	1.116	0.958
Prematurity	5	9	0.291	0.864
Cyanotic Congenital Heart Disease	31	55	0.861	0.769

Table 2 Comparison of Brain Volumes Between Groups

MRI Metric	Neurodevelopmental Disorder Group (n=54)	Neurodevelopmentally Normal Group (n=106)	t	p
Total Brain Volume (mL)	323.92 ± 10.24	341.82 ± 10.43	10.328	0.001
Cerebrospinal Fluid (mL)	34.80 ± 1.45	34.20 ± 1.12	2.893	0.441
Cortical Gray Matter (mL)	121.63 ± 6.91	131.47 ± 9.02	7.491	0.001
Deep Gray Matter (mL)	28.90 ± 1.63	28.73 ± 1.78	0.587	0.558
White Matter (mL)	175.79 ± 4.49	177.21 ± 6.80	1.387	0.167

Table 3 Comparison of Neurodevelopmental Scores Between Groups

Gesell Developmental Scale Metric	Neurodevelopmental Disorder Group (n=54)	Neurodevelopmentally Normal Group (n=106)	t	p
Adaptive Behavior (AB)	63.64 ± 7.21	106.25 ± 12.27	23.513	0.001
Fine Motor Skills (FM)	68.83 ± 7.29	102.31 ± 11.35	19.689	0.001
Gross Motor Skills (GM)	57.83 ± 7.18	98.04 ± 10.26	25.748	0.001
Language (L)	62.25 ± 6.61	116.41 ± 11.90	31.062	0.001
Personal-Social Behavior (PSB)	60.27 ± 6.35	108.26 ± 10.34	31.211	0.001
Developmental Quotient (DQ)	62.46 ± 7.77	106.18 ± 11.71	24.778	0.001

ROC Curve Analysis of Total Brain Volume and Cortical Gray Matter for Predicting Neurodevelopmental Abnormalities

ROC curve analysis demonstrated that both total brain volume and cortical gray matter volume were significant predictors of neurodevelopmental abnormalities ($P < 0.05$). See Table 4.

Discussion

Neurodevelopmental disorders are common and significant long-term complications in children with congenital heart disease (CHD).[11] Although modern surgical techniques have greatly improved survival rates, these patients often experience post-operative neurodevelopmental issues such as cognitive decline and motor development delays. These problems significantly impact their quality of life and impose a burden on families and society.[12] Research suggests that neurodevelopmental disorders in CHD children may be closely related to preoperative chronic hypoxia, brain ischemia-reperfusion injury caused by surgery, and postoperative complications.[13] Particularly in infants, whose brain white matter is still developing, acute changes in brain perfusion and oxygen transport can cause damage. This damage may result in neuronal maturation problems or necrosis, leading to neurodevelopmental abnormalities.[14] Therefore, timely identification and intervention of these issues are crucial challenges in the treatment of CHD.

Despite the widespread concern about neurodevelopmental disorders, abnormalities in newborns are often overlooked due to subtle symptoms.[15] Neuroimaging techniques such as ultrasound, CT, and MRI are crucial for the early detection of brain damage. While ultrasound and CT can detect some brain abnormalities, MRI has clear advantages due to its high

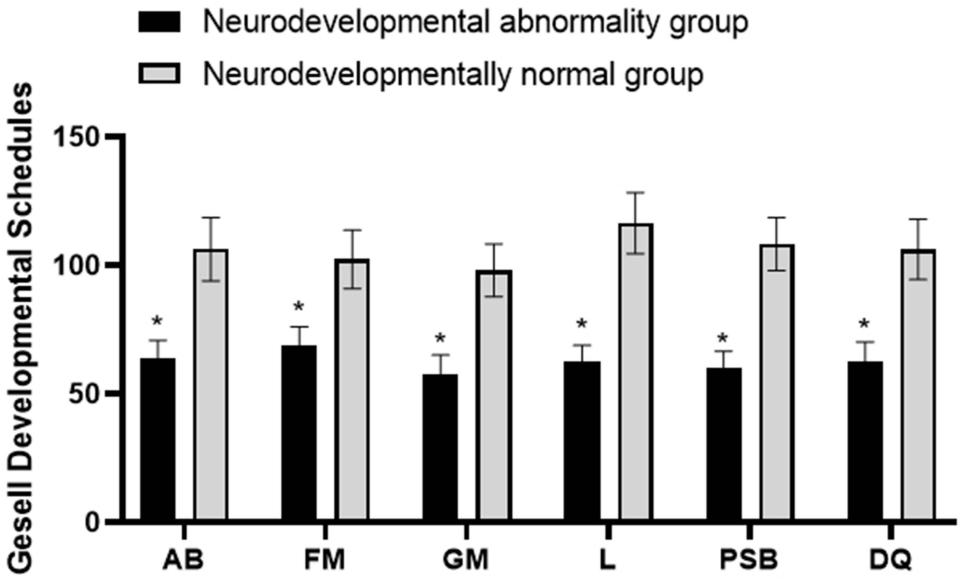

Figure 1 Comparison of DQ Scores Between Groups. * indicates significance with neurodevelopmentally normal group, $P < 0.05$.

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Table 4 ROC Curve Analysis of Total Brain Volume and Cortical Gray Matter for Predicting Neurodevelopmental Abnormalities

Variable	AUC	95% Confidence Interval	Sensitivity (%)	Specificity (%)	P
Total Brain Volume	0.968	0.825–0.982	95.1	75.3	<0.001
Cortical Gray Matter	0.936	0.811–0.995	89.4	71.1	<0.001

resolution and lack of radiation, making it superior for visualizing damage to white and gray matter. MRI can reveal subtle changes in brain structure and provide important information for early intervention.[16,17]

Currently, there are two main macroscopic morphological development indicators based on routine brain MRI images: 1) TMS scoring, which quantifies cortical gyration, myelination, residual germinal matrix, and migration bands; and 2) Volumetric MRI, which uses post-processing software to directly calculate volumes in different brain regions. Although early TMS scores are closely related to long-term neurodevelopmental outcomes,[18] their clinical application requires specialized knowledge in neuroimaging. In contrast, volumetric MRI is more widely accepted in neonatal clinical practice due to its clear and precise nature, which enhances its utility in research. This study utilized volumetric MRI as an early developmental assessment tool. The results indicated that total brain volume in the neurodevelopmentally normal group was significantly higher than that in the neurodevelopmental disorder group ($P < 0.05$). Additionally, in the analysis of internal brain structures, only cortical volume showed significant differences. These findings align with previous studies, such as those by Esposito et al,[19] who demonstrated reduced brain volumes (total brain, gray matter, white matter, and cerebellar volumes) in children with CHD. A recent longitudinal study[20] also found that CHD children exhibit a slower rate of brain volume growth compared to normal children, suggesting an altered brain growth trajectory. This may result from various prenatal and postnatal factors. The development of complex brain structures such as cortical sulci, cortical folding, surface area, and volume is dynamic, serving as important markers of brain maturity and health. Research has shown that CHD children often have reduced cortical volume and delayed cortical folding, with these abnormalities linked to inadequate brain oxygen supply. Such changes may originate during the fetal period and persist into adolescence. Notably, structural brain damage in CHD children may have long-lasting impacts on neurodevelopment. Valdeolmillos et al[21] reported a structural-functional relationship between hippocampal volume and executive function in CHD children. Multiple studies[22–24] have confirmed that brain structural damage and impaired brain development in CHD children can lead to long-term motor, cognitive, and behavioral deficits, underscoring the need for early intervention and long-term follow-up. Additionally, other studies[25,26] have highlighted dendritic branching damage as a key cause of cortical immaturity in CHD children. Impaired microstructural brain development underlies macroscopic structural changes such as reduced brain volume and cortical folding. Studies using DTI and NODDI have revealed significant reductions in the apparent axonal density of white matter tracts in CHD children post-surgery, particularly in long association fibers related to higher cognitive functions such as language, learning, memory, attention, and visuospatial processing.[27,28] Future research could explore the neurocognitive consequences of white matter microstructural changes in CHD children to deepen the understanding of the mechanisms underlying long-term neurodevelopmental disorders in this population.

The Gesell Developmental Scale results further support these findings. This scale is used to evaluate central nervous system function and identify treatable developmental abnormalities, particularly valuable in diagnosing autism and developmental delays. It tracks behavior changes in high-risk children across multiple areas, including adaptive behavior, language ability, gross and fine motor skills. Adaptive behavior is a key area of the Gesell Scale, reflecting a child's understanding of organization, association, and problem-solving abilities, serving as an important indicator of cortical function and often used in IQ assessments.[29,30] Our results show that the neurodevelopmental disorder group had significantly lower scores in adaptive behavior, fine motor skills, gross motor skills, language, and personal-social behavior compared to the neurodevelopmentally normal group ($P < 0.05$). This indicates that neurodevelopmental disorders impact these crucial developmental areas. The findings of this study indicate that total brain volume and cortical gray matter volume are strong predictors of neurodevelopmental abnormalities in children with congenital heart

disease (CHD), as evidenced by high AUC values (0.968 and 0.936, respectively), suggesting excellent diagnostic performance. However, it is important to acknowledge that these high AUC values may raise concerns about their validity and external applicability. Potential reasons for this include selection bias, as the study only included children who underwent surgery and MRI scans, which may have led to an overrepresentation of those with significant neurodevelopmental issues, limiting the generalizability of the findings. Additionally, the high sensitivity of the MRI volume measurements used could contribute to the high AUC values, highlighting the need for careful interpretation. The strong correlation between neurodevelopmental abnormalities and structural brain changes, particularly in cortical gray matter, further supports the use of these MRI parameters as sensitive tools for early neurodevelopmental evaluation in CHD children. To validate these results, larger, multi-center studies with more diverse CHD populations are needed, along with multi-variable analyses to control for potential confounders such as surgical age and CHD severity. Longitudinal studies will be essential for clarifying the long-term development of neurodevelopmental abnormalities and their relationship to MRI changes.

Although this study provides valuable insights into neurodevelopmental assessment for CHD children, there are some limitations. First, the sample size of 160 may affect the generalizability of the results. Future studies should consider larger sample sizes to improve reliability and applicability. Second, being a single-center study, there may be selection bias. Multi-center studies are needed to enhance the broad applicability of the findings. Additionally, this cross-sectional design only reveals correlations between neurodevelopmental abnormalities and MRI metrics without exploring causal relationships. Longitudinal studies could help understand the long-term development of neurodevelopmental abnormalities and their relationship with MRI changes. While MRI offers high resolution in brain structure assessment, it may not detect some subtle brain injuries. Combining MRI with other neuroimaging methods, such as functional MRI or magnetic resonance spectroscopy, may provide a more comprehensive assessment. Lastly, the Gesell Developmental Scale relies on the clinical evaluator's subjective judgment, which may introduce assessment bias. Future research should incorporate objective biomarkers and quantitative measures to enhance assessment accuracy.

Conclusion

In conclusion, this study demonstrates that total brain volume and cortical gray matter volume, as measured by MRI, are strong predictors of neurodevelopmental abnormalities in children with congenital heart disease (CHD). Regular MRI assessments can effectively identify CHD children at high risk for neurodevelopmental impairments, allowing for early intervention to improve their long-term developmental outcomes. Our findings suggest that MRI metrics, particularly brain volume parameters, can be used as reliable biomarkers for early neurodevelopmental screening in this population. Future studies should further investigate the underlying mechanisms linking these MRI metrics to neurodevelopmental outcomes and explore the potential for integrating MRI findings into clinical decision-making to optimize personalized care and interventions for CHD children.

Disclosure

The authors report no conflicts of interest in this work.

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