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Associations between preoperative cerebral white matter microstructural changes and neurodevelopmental deficits in CHD infants: a diffusion tensor imaging study

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Abstract

Background Neurodevelopmental deficits(NDs) frequently occur in patients with cyanotic congenital heart disease (CCHD) because of the hemodynamic abnormalities. We aimed to evaluate white matter(WM) microstructural changes in infants with CHD and analyze the relationship between WM microstructural changes and NDs.

Methods A total of 40 infants, 20 with CCHD and 20 with ACHD (matched on age and sex), who underwent preoperative DTI scanning were prospectively enrolled in the study. Multiple linear regression analysis were used to investigate the associations between brain microstructural changes and both clinical variables and neurodevelopmental outcomes, assessed with Gesell Developmental Schedules-Third Edition (GDS-III).

Results Infants with CCHD showed lower fractional anisotropy (FA) values in the bilateral cingulum hippocampus (CGH), right anterior thalamic radiation (ATR), and forceps minor (fminor) and exhibited poorer performance in adaptive, motor, language, and personal-social behaviors (all $P<0.05$). For CHD infants, the FA values of fminor were positively correlated with adaptive, fine motor, and language behaviors ($P=0.026$, 0.040, and 0.038, respectively). The microstructures of right ATR were positively correlated with adaptive and fine motor behaviors ($P=0.047$ and 0.035, respectively), and FA values of right CGH were positively correlated with language behavior ($P=0.007$). Hypoxia-related indicators and the internal diameters of the heart and large vessels were associated with neurodevelopmental and brain microstructural changes.

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Conclusions This study suggests that cerebral white matter microstructural changes may serve as imaging markers of neurodevelopmental deficits, with oxygen supply playing a crucial role in white matter microstructural development.

Keywords Diffusion tensor imaging, Neurodevelopmental deficit, White matter microstructural changes

Introduction

Congenital heart disease (CHD), defined as structural malformations of the heart and great vessels caused by abnormalities in embryonic development, affects approximately 0.4–1.0% of live births [1–3]. CHD can be categorized as cyanotic congenital heart disease (CCHD) and acyanotic congenital heart disease (ACHD) according to cyanosis or not. Nowadays, over 90% of individuals with CHD survive into adulthood with advancements in medical care [4, 5]. CHD related neurodevelopmental deficits (NDs) have become increasingly significant alongside increased survival rates, nearly 50% of survivors with CCHD showing neurodevelopmental disorders [6]. NDs of CHD are observed across the lifespan, beginning as early as infancy [6, 7]. Impairments in neurodevelopmental outcomes, including motor skills, language skills, cognition, and neurological function, are predominantly noticed postoperatively [8], with few studies focusing on preoperative neurodevelopmental outcomes.

To optimize neurodevelopmental outcomes for this large and growing high-risk population, factors that increase neurodevelopmental risk are highlighted in a scientific statement from the American Heart Association [9]. Among them, preoperative macrostructural brain injuries (i.e., white matter injury) have been associated with lower Bayley Scales of Infant Development (BSID) scores, although no clear pattern has been identified between the type of injury and BSID domains [8, 10]. Consequently, diffusion tensor imaging (DTI) studies have been conducted to further investigate changes in brain white matter tracts and their correlation with neurodevelopmental outcomes.

DTI is a quantitative MRI technique that characterizes the ellipsoidal shape of the water diffusion profile in the brain to assess white matter integrity and connectivity, contributing to a deeper understanding of brain injury at the microstructural level. Fractional anisotropy (FA), derived from the tensor model, is the most common and critical metrics used in DTI research. FA value reflects the directionality of water molecule diffusion [11] and it increases as a newborn's brain matures, correlating with increasing structural complexity [12] and decreases with white matter injury [13].

Brain maturation, including the refinement of brain networks and myelination, continues through childhood, providing a significant window for recovery [7]. Identifying early functional correlates of observed neuroimaging abnormalities would reveal whether microstructural abnormalities have functional consequences. Since the fetal stage and the first two years are critical periods for brain development [11], only one study has investigated preoperative white matter microstructural conditions in CHD infants and their relationship with neurodevelopmental outcomes [14]. Currently, several studies have demonstrated differences of cerebral microstructures between children with CHD and healthy children or infants with hypoxic-ischemic encephalopathy [15, 16]. Since the differences of cerebral microstructures between CCHD and ACHD were investigated postoperatively [17], there is still a lack of research on whether there are differences between them preoperatively. To enhance the understanding of the impact of CHD itself on brain alterations, this study aimed to investigate the differences of microstructures between CCHD and ACHD infants (with the most common subtype of CHD) and link the cerebral white matter microstructural changes to neurodevelopment. Additionally, we explored risk factors influencing white matter microstructures and neurodevelopmental outcomes.

Methods

Design and participants

A prospective cohort of 617 infants with Tetralogy of Fallot (TOF, $n=50$) or septal defect (atrial septal defect or ventricular septal defect, $n=567$) under 2 years of age was recruited at Children's Hospital of Nanjing Medical University from May 2021 to October 2023. Inclusion criteria were: (1) age under 2 years and (2) diagnosis of TOF, ASD, or VSD before surgery. Exclusion criteria were: (1) coexistence of other congenital cardiac or extracardiac abnormalities, (2) suspected or confirmed chromosomal abnormality, (3) suspected or confirmed congenital infection [18], (4) medical history of brain disorder, (5) born before 37 weeks gestation, (6) any previous surgery, (7) MRI contraindications, (8) failure to complete neurodevelopmental function tests, and (9) missing clinical information.

According to the inclusion and exclusion criteria, 20 infants with TOF and 46 infants with pure septal defect were considered. Finally, the study includes 20 infants with TOF (defined as CCHD group) and 20 infants with pure septal defect (defined as ACHD group), matched on age and sex (see Supplementary Fig. 1).

The study was approved by the Institutional Ethics Committee of Children's Hospital of Nanjing Medical University (chart: 201907212-1). Informed written

parental consent was obtained before imaging and neurodevelopmental function tests. All methods and experiments were performed in accordance with relevant guidelines and regulations.

Data collection

For each participant, we collected the demographic information: length, weight, gender, age, cardiac diagnosis, history of pre-term birth or low birth weight, surgical history, number of previous surgical procedures, and oxygen saturation. Clinical information included blood routine examination (including: red blood cell (RBC); hemoglobin (HB) and hematocrit (Hct)), hepatorenal function, anatomical parameters of the heart in the diastolic phase, and inner diameter of the aorta and pulmonary artery.

Anthropometric data were normalized for age and gender based on z-scores for weight for age (WAZ), length for age (HAZ), and weight for length (WLZ) to assess the nutritional status of the participants [19]. The WHO global database on child growth and malnutrition recommends a cut-off z-score < – 2 to classify low WAZ (underweight), low HAZ (stunting), and low WLZ (wasting) as malnutrition.

Neurodevelopmental assessment

Neurodevelopmental assessment of the infants was conducted by a physician with specialized training (Lin), who was unaware of the participant's condition, using the third version of the Gesell Developmental Schedules (GDS-III) [20]. The test included five domains for the evaluation of the developmental quotient (DQ): adaptability (i.e., cognitive), gross motor, fine motor, language (i.e., communication), and personal-social domains [21]. The mean score with standard deviation (SD) for the overall DQ was 100 ± 15. Infant was considered to have neurodevelopmental deficits if their DQ < 75 [22]. The testing process was supervised by another trained physician (Ma), who was also unaware of the participant's condition.

MRI data acquisition

All participants underwent brain MRI scanning on a 3.0 Tesla MRI system (Ingenia 3.0, Philips Healthcare, Best, the Netherlands) using a 16-channel head coil in the radiology department of Children's Hospital of Nanjing Medical University. Scans were performed upon admission. Participants were asked to remain awake for at least 8 h prior to scanning. MRI scanning was conducted at night during natural sleep or with chloral hydrate sedation (1 ml/kg) with parental consent. Earplugs and foam were used to reduce noise and minimize head motion, respectively.

DTI images were obtained using the following parameters: time of repetition = 4618 ms, time of echo = 96 ms, field of view = 200 × 200 × 140 mm, slice thickness = 2 mm, 32 isotropic directions, b-value = 1000 s/mm², and acquisition time = 6 min 32 s. Fluid-attenuated inversion recovery (FLAIR) images were acquired to exclude brain lesions using the following parameters: time of repetition = 8500 ms, time of echo = 130 ms, field of view = 200 × 200 × 119 mm, slice thickness = 5 mm, and acquisition time = 2 min 8 s. All images were reviewed by two experienced pediatric neuroradiologists who were unaware of the participants' medical histories. Consensus was reached through discussion in cases of differing opinions.

MRI data processing and analyses

DTI data processing and analysis were performed using software tools from the FMRIB Software Library (FSL). Initially, DTI data were preprocessed, including image format conversion using the dcm2niix tool, head motion eddy correction and gradient direction correction using the FDT tool from FSL, brain mask extraction using the BET tool from FSL, and diffusion tensor calculation to output FA using the DTIFIT tool from FSL.

Next, each participant's masked FA image was aligned to identify the most representative one, which served as the study-specific template. The aligned FA maps were then averaged to create a mean FA map. Finally, the region of interest for each white matter (WM) tract in the JHU WM tractography atlas was extracted using the FSLmaths tool from FSL, and mean DTI metric values within those regions were generated using the FSLmeants tool from FSL. Only clusters with more than 30 voxels were considered.

Statistical analysis

SPSS V26.0 software (IBM, New York) was used to analyze the differences between CCHD and ACHD groups. Continuous variables are presented as the mean ± SD or median and range and were analyzed using unpaired two-sample t-tests or Mann-Whitney U tests. Categorical variables are expressed as numbers and percentages and were analyzed using the chi-square test. Differences in white matter (WM) microstructures between the two groups were compared using unpaired two-sample t-tests, adjusting for age at MRI and sex, and corrected for multiple comparisons using family-wise error (FWE) at the cluster level. Pearson correlation analysis and multiple linear regression analysis were used to investigate the associations between cerebral white matter microstructural changes and both clinical variables and neurodevelopmental outcomes. P value < 0.05 was considered statistically significant.

Results

The clinical characteristics and neurodevelopmental outcomes of the participants is presented in Table 1. There were no differences in age, weight and sex distribution between the groups. CCHD infants exhibited significantly lower oxygen saturation ($P<0.001$), with increased RBC ($P<0.001$), HB ($P=0.009$), and Hct ($P=0.001$), and larger narrowest internal diameters of the ascending aorta (AAo) and aortic arch (ARCH) (all $P<0.001$). The left heart structure and pulmonary artery were less developed in the CCHD group compared to the ACHD group. Specifically, the internal diameters of the left atrium (LA), left ventricle (LV), main pulmonary artery (MPA), right pulmonary artery (RPA), and left pulmonary artery (LPA) in CCHD infants were smaller or thinner compared to those in ACHD infants (LA, $P=0.007$; others, $P<0.001$).

Preoperatively, 52.5% (21/40) of infants with CHD exhibited neurodevelopmental deficits, with motor function being the most prevalent (gross motor: 30%; fine motor: 32.5%). CCHD infants performed worse than ACHD infants preoperatively in adaptability ($P=0.013$), gross motor ($P=0.010$), fine motor ($P=0.014$), language ($P=0.038$), and personal-social ($P=0.035$) domains.

Compared to the ACHD group, the CCHD group demonstrated multiple areas of reduced FA values in the bilateral cerebral hemispheres preoperatively, with the most significant clusters of difference observed in the bilateral cingulum hippocampus (CGH), right anterior

Table 1 Demographic, clinical characteristics and neurodevelopmental outcomes of participants

	Total($n=40$)	CCHD($n=20$)	ACHD($n=20$)	*P* value
Demographic characteristics				
Male sex,%	22(55%)	11(55%)	11(55%)	1.000
Age, m	10.1 ± 4.5	10.1 ± 4.3	10.1 ± 4.9	0.979
SpO2,%	98.0(80.0,100.0)	94.0(80.0,100.0)	100.0(95.0,100.0)	< 0.001*
BW, kg	3.2(1.9,4.0)	3.1(1.9,4.0)	3.2(2.0,4.0)	0.533
Weight at admission, kg	8.5 ± 1.9	8.6 ± 1.6	8.4 ± 2.3	0.719
BMI/age, z-score	-0.07 ± 1.36	0.22 ± 1.26	-0.36 ± 1.43	0.180
WLZ, z-score	-0.03 ± 1.33	0.27 ± 1.19	-0.33 ± 1.42	0.157
WAZ, z-score	-0.23 ± 1.20	-0.11 ± 1.17	-0.34 ± 1.25	0.559
LAZ, z-score	-0.28 ± 1.69	-0.46 ± 1.68	-0.10 ± 1.73	0.508
Clinical characteristics				
RBC,10^12/L	4.8 ± 0.7	5.2 ± 0.7	4.4 ± 0.5	< 0.001*
HB, g/L	121.0(90.0,178.0)	137.5(90.0,178.0)	116.5(96.0,125.0)	0.009*
Hct,%	37.1(28.6,53.8)	42.4(32.3,53.8)	36.8(28.6,38.1)	0.001*
ALB, g/L	43.3 ± 2.6	42.6 ± 2.4	44.0 ± 2.7	0.112
GLU, mmol/L	4.2(3.2,7.8)	4.1(3.2,4.8)	4.2(3.3,7.8)	0.301
Anatomical parameters of the heart (Maximum diameter during the cardiac cycle)				
RA, mm	22.0(18.0,32.0)	21.5(18.0,30.0)	22.5(18.0,32.0)	0.131
RV, mm	14.0(10.0,23.0)	13.0(10.0,17.0)	14.5(10.0,23.0)	0.523
LA, mm	17.0(10.0,27.0)	16.0(10.0,19.0)	17.0(14.0,27.0)	0.007*
LV, mm	23.5(16.0,36.0)	21.5(16.0,27.0)	28.5(20.0,36.0)	< 0.001*
Narrowest inner diameter of the aorta and pulmonary artery				
AAo, mm	13.1 ± 2.6	14.6 ± 2.5	11.6 ± 1.7	< 0.001*
ARCH, mm	9.2 ± 1.5	10.0 ± 1.4	8.3 ± 1.1	< 0.001*
DAo(diaphragm level), mm	7.1 ± 0.8	7.2 ± 0.7	6.9 ± 0.9	0.200
MPA, mm	13.7 ± 4.4	10.5 ± 3.7	16.9 ± 1.9	< 0.001*
RPA, mm	8.6 ± 2.2	7.2 ± 1.8	10.0 ± 1.5	< 0.001*
LPA, mm	8.0 ± 1.8	6.8 ± 1.5	9.2 ± 1.3	< 0.001*
Preoperative neurodevelopmental outcomes				
Adaption behavior	86.569 ± 15.064	80.748 ± 14.133	92.391 ± 13.955	0.013*
Gross motor behavior	83.495 ± 16.660	76.863 ± 12.599	90.126 ± 17.844	0.010*
Fine motor behavior	82.511 ± 16.965	76.079 ± 16.345	88.943 ± 15.380	0.014*
Language behavior	87.795 ± 14.783	82.985 ± 14.522	92.605 ± 13.747	0.038*
Personal-social behavior	91.958 ± 16.528	86.512 ± 16.552	97.404 ± 14.977	0.035*

Data are presented as percentage, mean ± SD or median(range)

SpO2 indicates pulse oxygen saturation; BW, birth weight; RBC, red blood cell; HB, hemoglobin; Hct, hematocrit; ALB, albumin; GLU, glucose; RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; AAo, ascending aorta; ARCH, aortic arch; DAo, descending aorta; MPA, main pulmonary artery; RPA, right pulmonary artery; LPA, left pulmonary artery

* $P<0.05$

Table 2 Fractional anisotropy values of white matter microstructure for CCHD group and ACHD group

	Total($n=40$)	CCHD($n=20$)	ACHD($n=20$)	t value	*P* value
CGH-L	0.3487 ± 0.0775	0.3039 ± 0.0617	0.3935 ± 0.0656	-4.447	< 0.001*
CGH-R	0.3714 ± 0.0756	0.3283 ± 0.0513	0.4145 ± 0.0721	-4.357	< 0.001*
ATR-R	0.4656 ± 0.0501	0.4413 ± 0.0370	0.4900 ± 0.0504	-3.483	0.001*
Fminor	0.3249 ± 0.0474	0.2994 ± 0.0354	0.3504 ± 0.0445	-4.009	< 0.001*

Data are presented as mean ± SD

ATR indicates anterior thalamic radiation; CGH, cingulum hippocampus; fminor, forceps minor; L, left and R, right

* $P < 0.05$

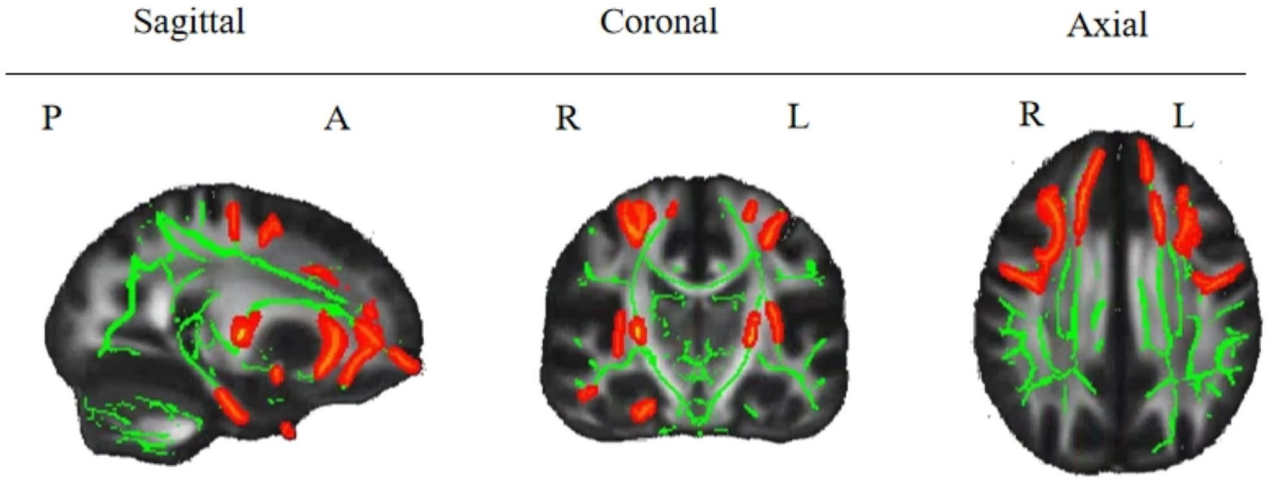

Fig. 1 Lower FA in cyanotic infants compared to acyanotic infants

Sagittal, coronal, and axial views of white matter microstructures show significantly lower FA in cyanotic infants compared to acyanotic infants. Red color indicates voxels where FA is significantly lower (TFCE corrected $P < 0.05$) in the cyanotic group compared to acyanotic group. L = Left, R = Right, P = Posterior, A = Anterior

thalamic radiation (ATR), and forceps minor (fminor) (Table 2; Figs. 1 and 2).

In infants with CHD, FA values of the fminor were positively correlated with adaptability, fine motor, and language behaviors. Additionally, FA values of the right ATR were positively correlated with adaptability and fine motor behaviors, while FA values of the right CGH were positively correlated with language behavior (Table 3).

Preoperative adaptability, gross motor, fine motor, and language behaviors were positively correlated with the diameters of the LA and LV in infants with CHD. Furthermore, adaptability was negatively correlated with the narrowest internal diameters of the AAo and ARCH, and gross motor behaviors were positively correlated with the narrowest internal diameters of the LPA and RPA. SpO2 was positively correlated with language behaviors, while HB and Hct were negatively correlated with them (Table 4 and Supplementary Table 1).

In the CCHD group, the internal diameters of the LA were positively correlated with fine motor behaviors compared to the ACHD group (β = 0.449, 95%CI = 0.016 to 1.339).

We observed that the preoperative microstructural maturity of the bilateral CGH, right ATR, and fminor in infants with CHD was clinically correlated with better-developed left cardiac structures and thicker pulmonary artery internal diameters, and negatively correlated with the narrowest internal diameter of the aorta. Additionally, higher SpO2 was found to correlate with higher FA values in the right CGH and ATR, while RBC and Hct were negatively correlated (Table 5 and Supplementary Table 2).

In CCHD group, the narrowest internal diameter of the preoperative RPA was positively correlated with right ATR (β = 0.446, 95% CI = 0.026 to 0.750).

Discussion

This study examined neurodevelopmental outcomes and white matter microstructural development before surgery in infants with CHD using GDS-III and DTI techniques with tract-based spatial statistics, providing detailed insights into differential microstructural brain development. Associations between altered cerebral microstructural properties and worse neurodevelopmental outcomes were identified in the CHD group. The degree of cerebral oxygen saturation plays a crucial role in both neurodevelopmental function and brain white matter microstructural development preoperatively.

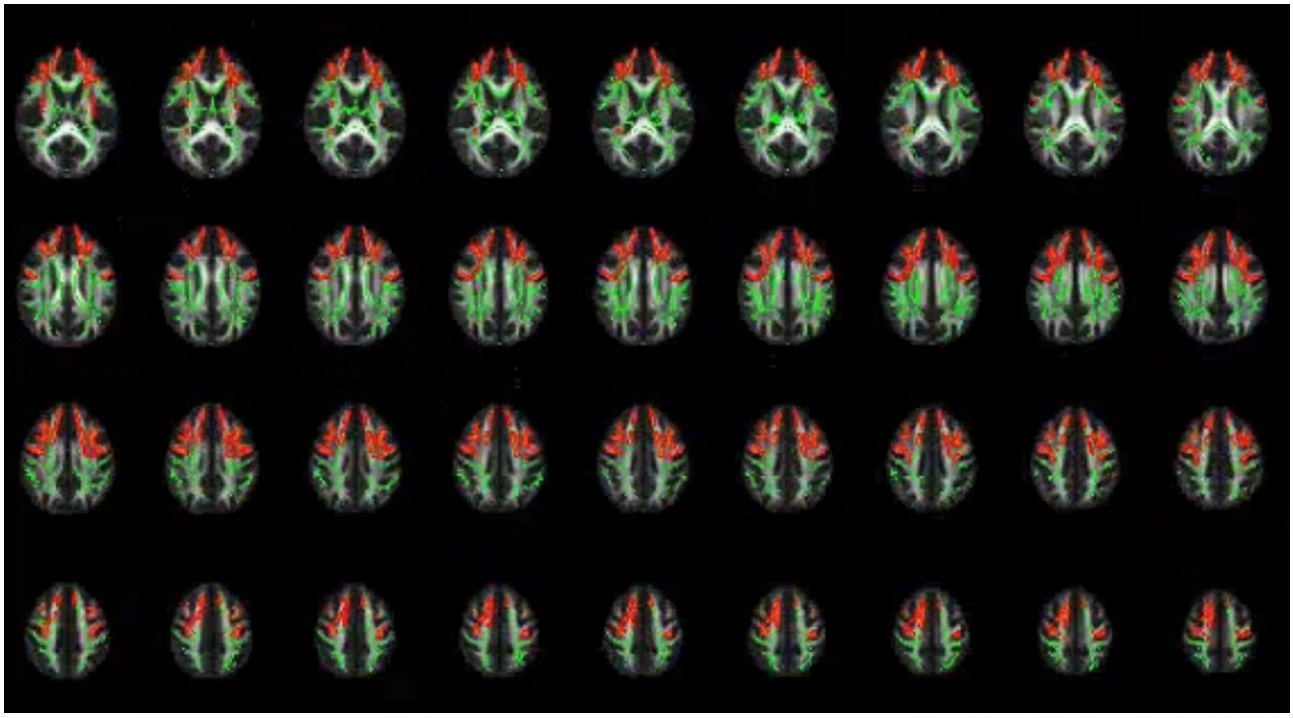

Fig. 2 Lower FA in cyanotic infants compared to acyanotic infants. White matter microstructures show significantly lower FA in cyanotic infants compared to acyanotic infants at different brain scanning levels. Red color indicates voxels where FA is significantly lower (TFCE corrected $P < 0.05$) in the cyanotic group compared to the acyanotic group

Table 3 Multiple liner regression of neurodevelopment outcomes and white matter microstructures in CHD

	R^2	β (95% CI)	*P* value
Adaptability versus ATR-R FA	0.281	0.371(0.005–0.737)	0.047
Adaptability versus fminor FA	0.303	0.385(0.048–0.721)	0.026
Fine motor versus ATR-R FA	0.422	0.354(0.026–0.683)	0.035
Fine motor versus fminor FA	0.418	0.323(0.015–0.630)	0.040
Language versus CGH-R FA	0.393	0.433(0.129–0.737)	0.007
Language versus of fminor FA	0.333	0.350(0.021–0.679)	0.038

Data are presented as R^2, β (95% CI) and P value from a multivariable linear regression model adjusted for sex, age, BW and weight and length when admission

ATR indicates anterior thalamic radiation; CGH, cingulum hippocampus; fminor, forceps minor and R, right

This study demonstrated that CCHD infants exhibited poorer cerebral microstructural development compared to the ACHD group before surgery. Key differences in microstructural properties were located in the right CGH, right ATR, and fminor, though the strength of the correlation between neurodevelopmental outcomes and FA did not differ between different types of CHD.

Consistent with previous study [8], this research suggested that motor developmental deficits were the most common, with CCHD infants performing worse than ACHD in language and motor behaviors. Adaptive and personal-social behavioral problems were also present preoperatively in infants with CHD, which often seen postoperatively or in older children and adolescents [23, 24].

In this study, FA values of the fminor positively correlated with adaptive, fine motor, and language behaviors, which was less known in previous CHD research. The fminor, an associative fiber bundle in the anterior corpus callosum, interconnects the lateral and medial surfaces of the frontal lobes and plays a pivotal role in higher-level language integration and controlling attention skills [25–27], with comprehension, naming, word fluency, and reading positively correlated with quantitative anisotropy of the fminor in post-stroke basal ganglia aphasia studies [28]. Premorbid lesions in the fminor were negatively associated with early subacute language comprehension after aphasic stroke [29]. Lower white matter integrity of the fminor, important for visuomotor integration, could predict visuomotor deficits in Alzheimer's disease [30]. This study first revealed the association between the integrity of the fminor and adaptability, motor, and language behaviors in the CHD population, emphasizing the importance of the fminor in understanding neurodevelopmental deficits.

The association between the integrity of the right ATR and adaptability and fine motor behavior was initially reported in CHD. The ATR carries nerve fibers between the thalamus and prefrontal cortex. Disruption of ATR microstructure has been linked to abnormalities in cognition, response inhibition [31], processing speed, working

Table 4 Multiple liner regression of neurodevelopment outcomes and clinical feathers in CHD

Variables	LA	LV	Hct	HB	SpO2	LPA	RPA	AAo	ARCH
CHD									
Adaptability	**0.403(0.105,0.701)**	**0.453(0.164,0.742)**	-0.269(-0.599,0.062)	-0.249(-0.572,0.075)	0.308(-0.014,0.630)	0.193(-0.150,0.536)	0.147(-0.220,0.515)	**-0.392(-0.718,-0.066)**	**-0.371(-0.722,-0.020)**
Gross motor	**0.332(0.029,0.636)**	**0.513(0.243,0.783)**	-0.248(-0.575,0.079)	-0.226(-0.546,0.094)	0.204(-0.123,0.531)	**0.374(0.056,0.692)**	**0.380(0.040,0.721)**	-0.282(-0.616,0.053)	-0.298(-0.652,0.055)
Fine motor	**0.378(0.112,0.645)**	**0.372(0.104,0.640)**	-0.230(-0.530,0.070)	-0.235(-0.526,0.056)	0.223(-0.073,0.520)	0.260(-0.043,0.562)	0.295(-0.024,0.614)	-0.177(-0.491,0.137)	-0.133(-0.467,0.202)
Language	**0.525(0.265,0.785)**	**0.474(0.201,0.746)**	**-0.386(-0.690,-0.083)**	**-0.317(-0.622,-0.013)**	**0.369(0.067,0.671)**	0.267(-0.059,0.592)	0.332(-0.009,0.672)	-0.197(-0.534,0.139)	-0.144(-0.503,0.215)
CCHD									
Fine motor	**0.449(0.016,1.339)**	0.300(-0.190,1.325)	-0.140(-0.522,0.273)	-0.171(-0.473,0.197)	0.059(-0.348,0.448)	0.079(-0.459,0.645)	0.163(-0.315,0.685)	0.131(-0.437,0.697)	0.262(-0.178,0.719)

Data are presented as beta (95%CI) from a multivariable linear regression model adjusted for sex, age, BW and weight and length when admission.Bold value represents data having statistical significance

SpO2 indicates pulse oxygen saturation; BW, birth weight; HB, hemoglobin; Hct, hematocrit; LA, left atrium; LV, left ventricle; AAo, ascending aorta; ARCH, aortic arch; RPA, right pulmonary artery; LPA, left pulmonary artery

memory [32], and executive function in psychiatric conditions such as hypertension, schizophrenia obstructive sleep apnea and bipolar affective disorder [33–35]. In CHD infants, little is known about alterations of ATR and their association with neurodevelopmental outcomes, particularly advanced nervous functions like cognition. This is the first research on ATR in CHD preoperatively, providing insight into the neurobiological underpinnings of neurodevelopment.

The CGH is a cortico-limbic tract originating from the presubiculum region of the hippocampus and merging with the cingulum, playing a critical role in memory and emotion processing [36, 37]. Decreased CGH structural integrity could suggest alterations in memory function and emotion regulation [38, 39]. In amnestic mild cognitive impairment, alterations in CGH have been observed [40]. Our study found that CGH integrity was positively correlated with language behavior before cardiac surgery, aligning with findings in corrected TOF children [41], emphasizing the need for more attention on neuroimaging and language behavior in early life.

This cohort included TOF, characterized by a smaller aorta and deviated left heart and pulmonary arteries. Our study suggested that better-developed left heart structures predicted both better specific neurodevelopmental outcomes and more mature WM microstructures. A well-developed aorta was negative, while better-developed pulmonary arteries were positively associated with gross motor activity, consistent with WM microstructures.

Previous studies have associated several factors with immature WM microstructures, including CHD subtype and smaller aortic diameter, indicating that reduced antenatal cerebral blood flow affects brain microstructural integrity [16, 42]. However, in our study, a larger aortic diameter was associated with more immature WM microstructures in bilateral CGH, right ATR, and fminor. Given the physiological characteristics of TOF, less-developed left heart structures, small pulmonary arterial diameter, and large aortic diameter result in more deoxygenated blood flowing into the systemic circulation, affecting brain microstructural integrity. Since the brain has limited energy storage capabilities, a continuous supply of oxygen and glucose is crucial, making it vulnerable to ischemia and hypoxia [43].

Few studies investigate the relationship between great blood vessels and neurodevelopment. The diameter of the ascending aortic arch correlated significantly with full-scale IQ and AV valve regurgitation increased the risk of brain damage in patients with hypoplastic left heart syndrome [44]. Our study found that diameter of the ascending aorta negatively correlated with gross motor activity, suggesting that deoxygenated blood has a detrimental effect on neurodevelopment due to the overriding aorta.

Table 5 Multiple liner regression of white matter microstructures and clinical feathers in CHD

Variables	SpO2	RBC	Hct	LA	LV	AAo	ARCH	MPA	RPA	LPA
CHD										
CGH-L	0.269(-0.0790,0.617)	-0.345(-0.698,0.007)	-0.321(-0.667,0.026)	0.213(-0.129,0.555)	0.316(-0.017,0.648)	**-0.460(-0.799,-0.121)**	**-0.430(-0.797,-0.063)**	**0.536(0.228,0.845)**	**0.599(0.267,0.932)**	**0.513(0.189,0.837)**
CGH-R	**0.384(0.070,0.698)**	**-0.393(-0.719,-0.067)**	**-0.374(-0.693,-0.054)**	**0.402(0.101,0.702)**	**0.426(0.129,0.722)**	**-0.513(-0.820,-0.206)**	**-0.370(-0.723,-0.016)**	**0.543(0.258,0.828)**	**0.544(0.224,0.865)**	**0.517(0.216,0.818)**
ATR-R	**0.299(0.009,0.590)**	**-0.351(-0.646,-0.056)**	**-0.306(-0.600,-0.013)**	**-0.306(-0.600,-0.013)**	**0.352(0.078,0.626)**	**-0.491(-0.763,-0.220)**	**-0.472(-0.769,-0.175)**	**0.490(0.232,0.748)**	**0.532(0.251,0.813)**	**0.460(0.187,0.734)**
fminor	0.276(-0.041,0.593)	-0.291(-0.619,0.036)	-0.285(-0.605,0.035)	**0.305(0.002,0.609)**	**0.351(0.053,0.649)**	**-0.463(-0.768,-0.159)**	**-0.470(-0.795,-0.145)**	**0.521(0.244,0.799)**	**0.546(0.239,0.853)**	**0.471(0.173,0.769)**
CCHD										
ATR-R	-0.367(-0.541,0.065)	0.168(-0.280,0.543)	0.158(-0.226,0.441)	0.026(-0.621,0.682)	0.128(-0.502,0.874)	0.236(-0.289,0.648)	0.146(-0.279,0.510)	0.250(-0.188,0.620)	**0.446(0.026,0.750)**	0.233(-0.236,0.660)

Data are presented as beta (95%CI) from a multivariable linear regression model adjusted for sex, age, BW and weight and length when admission.Bold value represents data having statistical significance

ATR indicates anterior thalamic radiation; fminor, forceps minor; SpO2, pulse oxygen saturation; BW, birth weight; RBC, red blood cell; Hct, hematocrit; LA, left atrium; LV, left ventricle; AAo, ascending aorta; ARCH, aortic arch; DAo, descending aorta; MPA, main pulmonary artery; RPA, right pulmonary artery; LPA, left pulmonary artery

Our study suggested that preoperative SpO2 was positively correlated with microstructural growth and neurodevelopment. In fetuses with mixed CHD, ascending aorta oxygen saturations have been found to be lower and correlated with fetal brain size [45]. Decreased systemic oxygen delivery in the neonatal postoperative period is associated with hypoxic-ischemic brain injury [46]. In fetal life, pre-myelinating oligodendrocytes, the most dominant type of oligodendrocytes in the human WM, are vulnerable to hypoxia. They fail to mature into myelin-producing oligodendrocytes due to hypoxia, resulting in impaired myelination of the WM [16, 47]. This study further reinforces the understanding of the relationship between systemic oxygen saturation and neuroimaging in the postnatal and preoperative periods in the CHD population, emphasizing the harmful effect of hypoxia on the developing brain [48].

As Hoffman described, decreased systemic oxygen delivery is associated with childhood neurodevelopmental abnormality postoperatively [46]. Our study found that systemic oxygen saturation was associated with language behavior before surgery, advocating for measures of systemic oxygen delivery to guide perioperative strategies to reduce brain injury and improve neurodevelopmental outcomes.

The underlying pathophysiology for differentiated WM development in CHD is the hypoxic environmental factor. The lack of oxygen delivery and negative impact on brain maturity has been demonstrated in a CHD animal model, suggesting that cerebral hypoxia reduces proliferation and neurogenesis in the subventricular zone in the postnatal brain [45, 49]. Hypoxia due to the pathophysiologic mechanisms of TOF can explain the differences in WM microstructure between ACHD and CCHD.

Oxygen availability is governed by RBC velocity and Hct [43]. HB and Hct are closely related to RBCs and increase when exposed to chronic hypoxia to maintain oxygen supply [50]. Higher Hct values have been significantly associated with reduced reperfusion and greater infarct size after ischemic stroke, possibly due to hyperviscosity and impaired vasomotor reactivity of collateral vessels [51]. Similar mechanisms may operate in CHD infants with higher RBC and Hct levels; future studies are needed to further investigate the effect of RBC and Hct on brain microstructures.

Our study agreed with the view that higher HB levels were associated with declined neurodevelopmental outcomes [44, 52]. Since HB can be used as an oxygen transport or storage factor in neurons, polycythemia vera has been associated with an increased risk of cerebral thrombosis [53]. In limited studies, pulmonary disease (associated with high HB levels) has been linked to cognitive decline in older people [54] and decreased frontal and parietal lobe perfusion on brain imaging [55]. The

mechanisms linking high HB levels to worse cognition are not well understood. HB may be a marker for conditions such as ischemia (via cerebrovascular disease), hypoxia (via hypoxia-inducible factor), and/or oxidative stress (via iron dysregulation) [56]. Our finding of high HB levels being associated with worse language behavior warrants further research given the limited number of cases.

Nevertheless, this study has some limitations. (1) The sample size included in the study was limited. Being an exploratory study, we endeavored to include as many eligible cases as feasible. We plan to incorporate additional cases for validation in the future to enhance the reliability and generalizability of our findings. (2) The study was a single-center study, and no clear correlation between brain microstructural alterations and neurodevelopmental deficits was found in the comparison of CCHD and ACHD groups, which will need to be followed up by a multicenter study. (3) While this study represents a presurgery condition, conducting multimodal brain MRI and neurodevelopmental testing at various time points (including post-surgery and long-term follow up), is crucial for a deeper understanding of morphological changes and neurodevelopmental deficits in CHD patients.

Conclusions

This study enhances the current understanding of neuroimaging and neurodevelopmental outcomes in infants with CHD. We found that CHD infants exhibit early neurodevelopmental deficits, with specific brain microstructures (CGH-R, ATR-R, and fminor) potentially serving as preoperative markers. The anatomy of the heart and great blood vessels, along with hypoxia, were predictive of both WM microstructures and neurodevelopment. Additionally, CCHD infants demonstrated poorer cerebral microstructural development compared to the ACHD group, although no clear correlation between WM microstructural changes and neurodevelopmental deficits was established.

Abbreviations

CHD	Congenital heart disease
ACHD	Acyanotic congenital heart disease
CCHD	Cyanotic congenital heart disease
DTI	Diffusion tensor imaging
BSID	Bayley Scales of Infant Development
NDs	Neurodevelopmental deficits
TOF	Tetralogy of Fallot
SD	Standard deviation
WM	White matter
ATR	Anterior thalamic radiation
CGH	Cingulum hippocampus
Fminor	Forceps minor

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

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Author contributions

MXM and YM designed the study protocol and proofread the manuscript. ZZ and HZQ made substantial contributions to the acquisition, analysis and interpretation of data, drafted and reviewed the article. MSY proofread the manuscript. ZMJ and YM performed brain MRI scans on participants and analyzed the MRI of patients.LY evaluated the levels of neurodevelopmental outcomes of participants. CXY analyzed the results. CY, ZYQ and HL collected the information.Nishant P took charge of the modification of English language. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Data availability

Please contact the author for data requests.

Declarations

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by the Ethics Committee of Children's Hospital of Nanjing Medical University. The study is in accordance with the 1964 Helsinki Declaration and its later amendments. Written informed consent to participate in this study was provided by the legal guardian/next of kin of the participants for the publication of any potentially identifiable radiographic images or data included in this article.

Consent for publication

Not applicable.

Competing interests

The authors have no conflicts of interest to declare.

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