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Original article

Neuroimaging Findings in Infants with Congenital Heart Disease

Somaia A. Elwan[a], Mohamed M. Fahim[b], Zeinab S. abdel razik[a], Eman G. Abd ElRahman[a]

[a] Department of Pediatrics, Benha faculty of medicine, Benha University, Egypt.
[b] Department of Radiology, Benha faculty of medicine, Benha University, Egypt.

Correspondence to: Zeinab S. abdel razik, Department of Pediatrics, Benha University, Egypt.

Email:

zeinabsaad320@gmail.com

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Abstract

Background & Aim: Congenital heart disease (CHD) is the most frequent congenital malformations. Children with CHD remain at risk of neurodevelopmental impairment, characterized by mild cognitive impairment, impaired social and communication skills, inattention and later, deficits in executive function.**This study aimed to** characterize brain lesions using MRI in CHD either cyanotic or acyanotic to assess which lesions are associated more with brain injury. **Methods:** This study was conducted on 30 infants with CHD from the cardiology clinic and general ward at Benha University Hospitals. Patients were subjected to full history taking, complete clinical assessment and investigations as X-ray, Echocardiography and MRI brain. **Results**: In our study, 20% of CHD infants had brain injury on MRI assessment. The most frequent brain injury was arterial ischemic stroke (20%), followed by white matter injury (6.7%), cerebellar hypoplasia (3.3%), and hypoxic injury (3.3%). There was a statistically significant difference between cyanotic and acyanotic heart diseases regarding brain lesions. There was no statistically significant difference in brain lesions regarding type of cardiac lesion. **Conclusion:** MRI provides a good screening method in the detection of brain lesions in infants with CHD, helping to improve the cognitive functions and skills in these patients.

Keywords: Neuroimaging; congenital heart disease; brain MRI

Introduction

Congenital heart diseases (CHD) are the most common congenital defects, affecting approximately 1% of newborns (1). Historically, few infants born with major CHD survived to adulthood, but advances in diagnostic, interventional and surgical techniques over recent decades have led to dramatic increases in survival (2).

However, children with CHD remain at risk of neurodevelopmental impairment, characterized by mild cognitive impairment, impaired social and communication skills, inattention and later, deficits in executive function(3).

The etiology of neurodevelopmental impairment in CHD remains poorly understood. It has become clear that neurological insult in CHD begins, with altered neurological state in infants (4).

Studies of brain injury in presurgical newborns have reported lesions including white matter injury (WMI) and stroke with a prevalence that varies considerably from 19% to 52% of cases (5).

The aim of the present study was to characterize brain lesions in infants with CHD either cyanotic or acyanotic, using MRI, and to assess which CHD are associated more with brain injury.

Patients and methods

This cross sectional observational study was conducted on 30 infants from cardiology clinic and ICU of Benha University Hospitals during the period from March 2021 to September 2021.

Approval of Pediatric Department and Ethics Committee in the Faculty of Medicine, Benha University was taken before preceding the study. Informed verbal or written consents were obtained from the parents before enrollment in the study.

Inclusion criteria:

- Infants with CHD (cyanotic and acyanotic heart disease).
- Both sexes were involved.
- Age from 1 month to 2 years.

Exclusion criteria:

- Evidence of neurological insult.
- Clinical evidence of a congenital syndrome or malformation.
- Suspected or confirmed major chromosomal abnormality (e.g., aneuploidy)

Patients were subjected to full history taking, complete clinical assessment and

investigations as X-ray, magnetic resonance imaging (MRI) and echocardiography.

Echocardiography was done for all cases to confirm CHD at cardiology clinic of Benha University Hospitals using PHILLIPS Affinity 50c Echocardiography machine using a 2.5 MHz phased array.

MRI was performed on a 1.5-Tesla system (Siemens Magnetom Aera, Germany) as soon as the infant can be safely transferred to the scanner and before undergoing surgery. Examinations were supervised by an experienced pediatrician. MRI sequences include a 5s initial slow ramp-up in acoustic noise to avoid eliciting a startle response. T1-weighted and T2-weighted images were motion-corrected post hoc using a dedicated motion-corrected reconstruction.

All patients were sedated during the exam to avoid motion artifacts. The images were stored on the PACS system and reviewed by consultant radiologist and consultant pediatric neurologist in double blind manner. The results are approved when agreement between both the radiologist and the pediatrician occur.

Statistical methods

Data management and statistical analysis were done using SPSS version 28 (IBM, Armonk, New York, United States). Quantitative data were assessed for normality using the Shapiro-Wilk test and direct data visualization methods. According to normality testing, numerical data were summarized as means and standard deviations or medians and ranges. Categorical data were summarized as numbers and percentages. Quantitative data were compared according to the presence of brain lesions using independent t-test or Mann-Whitney U test for normally and non-normally distributed variables, respectively.

Categorical data were compared using Fisher's exact test. All statistical tests were two-sided. P values less than 0.05 were considered significant.

Results

The median age of the studied patients was 11 months, ranging from 1 – 24 months. Regarding gender, about two-thirds were males (60.0%). The median gestational age was 38 weeks, ranging from 34-39 weeks. Most patients were delivered by caesarean section (90%). The mean birth weight was 2.7 ±0.6 kg **(Table, 1).**

About two-thirds of the cases (63.3%) were acyanotic, the most common cardiac lesion was ASD and VSD (20%) for each (T**able, 2).**

The most frequent brain injury was ischemic stroke (20%), followed by white matter injury (6.7%), cerebellar hypoplasia (3.3%), and hypoxic injury (3.3%) **(Table, 3).**

There was statistical difference between cyanotic and acyanotic congenital heart disease patients regarding presence of brain lesions, which was mostly associated with cyanotic congenital heart diseases **(*p*=0.016**, **table, 4).**

There was no statistical difference between patients with and without brain lesions regarding the type of heart lesions by echocardiography, (**Table 5).**

A case study is shown in **figure 1.**

Table (1) General characteristics of the studied patients

General characteristics	Data
Age (months) (mean & range)	11 (1 - 24)
Sex	
Males (number & percentage)	18 (60%)
Females (number & percentage)	12 (40%)
Gestational age (weeks) (mean & range)	38 (34 - 39)
Mode of delivery	
Vaginal (number & percentage)	3 (10%)
Cesarean (number & percentage)	27 (90%)
Birth weight (kg) (mean ± SD)	2.7 ± 0.6

Table (2) Type of heart lesions of the studied patients

Type of heart lesions	**Number (%)**
Cyanotic	11 (36.7)
Acyanotic	19 (63.3)
Type of Echo diagnosis	
ASD	6 (20.0)
COA	2 (6.7)
DORV	4 (13.3)
PDA	4 (13.3)
PS	1 (3.3)
TGA	3 (10.0)
TOF	3 (10.0)
TR	1 (3.3)
VSD	6 (20.0)

ASD: atrial septal defect, COA: Coarctation of the aorta , DORV; Double outlet right ventricle, PDA Patient ductus arteriosus, PS: pulmonary stenosis, TGA: Transposition of the great arteries, TOF: Tetralogy of Fallot, TR: tricuspid regurge, VSD: ventricular septal defect

Table (3) Brain lesions of the studied patients

Brain lesions	Number (%)
White matter injury	2 (6.7)
Arterial ischemic stroke	6 (20.0)
Cerebellar hypoplasia	1 (3.3)
Hypoxic injury	1 (3.3)

Table (4): Comparison between groups with brain lesion and no brain lesion regarding type of CHD

Type of CHD	Brain lesions				P-value
	Absent (n=24)		Present (n=6)		
	No.	%	No.	%	
Acyanotic	18	75.0%	1	16.7%	0.016*
Cyanotic	6	25.0%	5	83.3%	

Fisher's exact test was used, *p<0.05= statistical significant difference

Table (5): Comparison between studied groups with and without brain lesion regarding Echo diagnosis

Echo diagnosis	Brain lesions				P-value*
	Absent (n=24)		Present (n=6)		
	No.	%	No.	%	
ASD	6	25.0%	0	0.0%	
COA	2	8.3%	0	0.0%	
DORV	3	12.5%	1	16.7%	
PDA	4	16.7%	0	0.0%	
PS	1	4.2%	0	0.0%	**0.16**
TGA	1	4.2%	2	33.3%	
TOF	1	4.2%	2	33.3%	
TR	1	4.2%	0	0.0%	
VSD	5	20.8%	1	16.7%	

ASD: atrial septal defect, COA: Coarctation of the aorta , DORV; Double outlet right ventricle, PDA Patient ductus arteriosus, PS: pulmonary stenosis, TGA: Transposition of the great arteries, TOF: Tetralogy of Fallot, TR: tricuspid regurge, VSD: ventricular septal defect

Fisher's exact test was used, *p>0.05= statistical insignificant difference

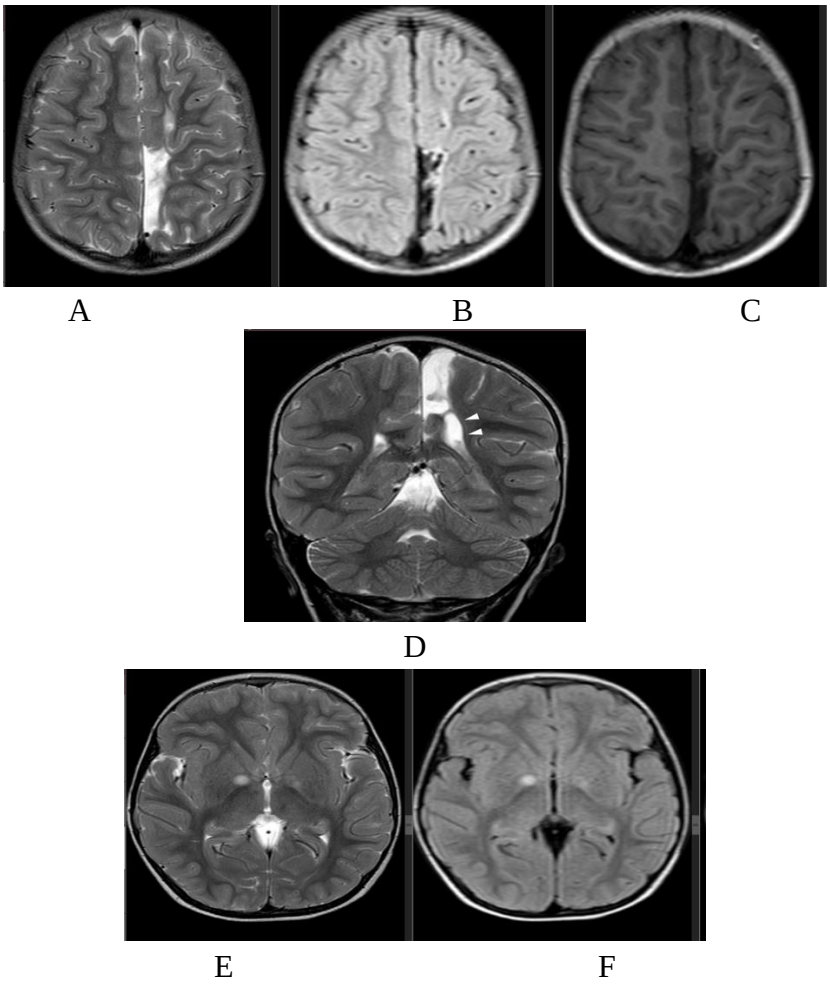

Figure 1: Case 21, brain MRI was done with abnormal findings and many pathological changes.**A.** Axial T2WIs, **B.** Axial FLAIR, **C.** Axial T1WIs &**D.** Coronal T2WIs MR of the brain at the level of the centrum semiovale showing left parietal paramedian cortical and subcortical areas of encephalomalacia displaying bright T2WIs and dark T1WIs and FLAIR signal with marginal bright FLAIR signal related to gliosis. The coronal T2WIs showed associated negative mass effect in the form of exvacudilatation of the left lateral ventricle (arrow heads). **E.** Axial T2WIs.**F.** Axial FLAIR MR of the brain at the basal ganglia level (the same patient) showing bilateral globuspallidi elevated T2WIS/FLAIR signal likely sequel of ischemic-hypoxic injury.

Discussion

Children with CHD who required cardiopulmonary bypass surgery in infancy are at increased risk of adverse neurodevelopmental sequalae (6).The burden of the problem is significant, affecting a wide range of developmental domains including deficits in neuro-motor functions, mild impairments in executive functions, attention and memory, difficulties in social interactions and emotional and

behavioral maladjustment, which impact upon the future educational achievement, employability and quality of life(7).

The current study, shows that 20% of the neonates with CHD had brain injury on MRI assessment. The most frequent brain injury was ischemic stroke (20%) followed by white matter injury (6.7%), cerebellar hypoplasia (3.3%) and hypoxic injury (3.3%).

Our results were similar to a previous study (8) who studied conventional fetal MR imaging. Brain abnormalities were detected in 17 (16.3%) cases. However, the distribution of the lesions was different (isolated mild ventriculomegaly (6/17%), increased extra-axial spaces (4/17%), white matter cysts (2/17%), isolated inferior vermian hypoplasia (2/17%), and white matter signal hyperintensity on T2-weighted images (1/17%)).

On contrary, the percent was high in another study (4). Cerebral lesions were identified in 39% (n=27, 95% CI 28% to 50%) of cases, including white matter injury in 33% (n=23, 95% CI 23% to 45%), cerebellar hemorrhage in 9% (n=6, 95% CI 4% to 18%) and acute ischemic stroke (AIS) in 4% (n=3, 95% CI 1.5% to 12%).

In Bonthrone et.al., cohort study (9); they comprised 18 hypoplastic left heart syndrome (HLHS) fetuses and 30 controls. They observed progressive differences in cortical grey and white matter volumes and subcortical grey matter volumes in the 3rd trimester of pregnancy. There were no differences in lateral ventricle volumes between the groups. Of note, cortical grey and white matter volumes were not significantly reduced in the CHD group prior to 30 weeks gestation.

Low cerebro-placental resistance in fetuses with HLHS was significantly associated with decreased cortical grey matter, white matter, subcortical grey matter. Decreased cortical surface area, absence of antegrade blood flow in the transverse aortic arch were associated with decreased white matter, subcortical grey matter volumes and cortical surface area in the right hemisphere (10).

In a study done by Schellen et.al.,(11) a total of 24 fetuses with Tetralogy of Fallot (TOF), showed significant total brain volume, grey matter volume and subcortical white matter volume reduction, and ventricular volume and external CSF volume increment compared with the control group. There was no difference in cerebellar volume between fetuses with TOF and controls.

However, in another study (12) comprising a cohort of 46 fetuses with mixed CHD diagnoses, with the exception of those with septate defects (VSD/ASD), cerebellar volume was significantly decreased, whereas supratentorial volumes were not reduced.

There was a statistically significant difference between the studied groups in the current study regarding the presence or absence of cyanosis. Brain lesions were more in cyanotic groups (83.3%) versus acyanotic group (16.7 %). These results agreed with another study (13) that included 52 term infants with CHD, who were divided into two groups, cyanotic (*n*=21) and acyanotic (*n*=31). They concluded that infants with cyanotic CHD had significant less brain development and more brain injury than those with acyanotic CHD ($P<0.05$).

Another study reported, a relationship between serial prenatal and postnatal preoperative conventional brain MR imaging studies in a large cohort of fetuses diagnosed with complex CHD. Brain abnormalities were detected in 17% prenatally and in almost twice (32%) postnatally before open heart surgery. Noteworthy, CHD cases with abnormal conventional fetal MR imaging findings had a 90% increased risk of presenting with abnormal neonatal brain MR imaging findings. Although conventional fetal MR imaging was shown to have good specificity, it lacked sensitivity for predicting postnatal brain abnormalities (8).

In a subgroup of cohort study (9), comprising 18 HLHS fetuses and 30 controls, progressive differences in cortical grey and white matter volumes and subcortical grey matter volume were observed in the 3rd trimester of pregnancy. There were no differences in lateral ventricle volumes between the groups. Of note, cortical grey and white matter volumes were not significantly reduced in the CHD group prior to 30 weeks gestation.

MRI studies have shown that brain volumes are reduced in individuals with CHD from the fetal period to adolescence and young adulthood. It appears that these volume reductions are not specific to particular tissues or regions, rather growth of all brain regions is impaired. These tissue volume reductions are accompanied by increase in extracerebral CSF volume. There is some evidence that brain volumes are most reduced in those with cyanotic CHD, although this finding is not observed in all

studies. Reduced cerebral oxygen delivery during fetal life and in the early postnatal period is associated with smaller brain volumes. Other risk factors for impaired brain growth include older age at surgery and perioperative illness severity as indicated by longer times on intensive therapy unit (ITU) (9).

There is increasing evidence that early measures of brain volume and growth are associated with outcome, although large multicentre studies incorporating known clinical risk factors are required to define more precisely the relationship between fetal and neonatal brain volume and subsequent neurodevelopment (9).

The limitations of this study include small size of the study sample that may be due to short period of the study and the general nature of our university hospitals.

Conclusion

MRI provides a good screening method in the detection of brain lesions in infants with CHD, helping to improve cognitive functions and skills in these patients. There is significant increase in the incidence of brain abnormalities in neonates with cyanotic rather than acyanotic CHD.

Recommendation

We recommend having more specialized studies on the subgroups of the CHD in specialized pediatric heart centers.

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