Assessment of the Association Between Congenital Heart Defects and Brain Injury in Fetuses through Magnetic Resonance Imaging

Alina Weissmann-Brenner MD[1,4]*, Anna Mitlin MD[1,4]*, Chen Hoffman MD[2,4], Reuven Achiron MD[1,4], Yishai Salem MD[3,4] and Eldad Katorza MD[1,4]

Departments of [1]Obstetrics and Gynecology, [2]Diagnostic Radiology, and [3]Pediatric Cardiology, Sheba Medical Center, Tel Hashomer, Israel
[4]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT: **Background:** Congenital heart defects (CHD) may be associated with neurodevelopmental abnormalities mainly due to brain hypoperfusion. This defect is attributed to the major cardiac operations these children underwent, but also to hemodynamic instability during fetal life. Advances in imaging techniques have identified changes in brain magnetic resonance imaging (MRI) in children with CHD.

Objectives: To examine the correlation between CHD and brain injury using fetal brain MRI.

Methods: We evaluated 46 fetuses diagnosed with CHD who underwent brain MRI. CHD was classified according to in situs anomalies, 4 chamber view (4CV), outflow tracts, arches, and veins as well as cyanotic or complex CHD. We compared MRI results of different classes of CHD and CHD fetuses to a control group of 113 healthy brain MRI examinations.

Results: No significant differences were found in brain pathologies among different classifications of CHD. The anteroposterior percentile of the vermis was significantly smaller in fetuses with abnormal 4CV. A significantly higher biparietal diameter was found in fetuses with abnormal arches. A significantly smaller transcerebellar diameter was found in fetuses with abnormal veins. Compared to the control group, significant differences were found in overall brain pathology in cortex abnormalities and in extra axial findings in the study group. Significantly higher rates of overall brain pathologies, ventricle pathologies, cortex pathologies, and biometrical parameters were found in the cyanotic group compared to the complex group and to the control group.

Conclusions: Fetuses with CHD demonstrate findings in brain MRI that suggest an in utero pathogenesis of the neurological and cognitive anomalies found during child development.

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KEY WORDS: brain pathology, congenital heart disease (CHD), fetal echocardiography, magnetic resonance imaging (MRI), ultrasound

Congenital heart defects (CHD) are diagnosed in 9 out of 1000 live births. The survival rate of children diagnosed with CHD has increased and ranges from 95% in children with simple defects to 80% in children with complex CHD [1-3]. Several studies examined the association between CHD and neurodevelopmental outcomes [4-7]. Previously it was thought that the neurodevelopmental insult was caused by the surgical interventions these children underwent, mainly because of the decreased blood flow to the brain during surgery [5,6]. However, recent studies proposed that the neurodevelopmental abnormalities existed prior to the surgery and may have been caused by hypoperfusion of the fetal brain, leading to decreased brain metabolism, acidosis, hypoxic ischemic injury, and hemodynamic instability. These conditions could lead to structural brain abnormalities and to cognitive and neurological dysfunction [7-10].

Assessment of fetal brain is performed both by ultrasound and by magnetic resonance imaging (MRI) [11-13]. Our objective was to examine the association between CHD and brain injury using MRI in utero.

PATIENTS AND METHODS

Our cohort comprised 46 pregnant women who underwent fetal brain MRI following the diagnosis of fetal CHD at the Sheba Medical Center between 2011 and 2014. Ethics approval was granted by the institutional review board of the Sheba Medical Center.

All patients underwent sonographic fetal echocardiography. All examinations were conducted using the Voluson E6 or E8 Expert (GE Healthcare, Kretz Ultrasound, Austria), or Pro ultrasound machines (Zipf, Austria) using 4–8 MHz transabdominal transducers or 5–9 or 6–12 MHz transvaginal transducers.

MRI scans were obtained using a 1.5T MR system (Optima scanner; GE Healthcare Technologies, Milwaukee, Wisconsin, USA). Single-shot fast spin echo T2-weighted sequences in three orthogonal planes were used with slice thickness of 3–4 mm, no gap, and a flexible coil (8-channel cardiac coil). The field of view was determined by the size of the fetal head, and was 24 cm for smaller fetuses and up to 30 cm for larger ones.

*The first two authors contributed equally to this work

Other parameters were a matrix of 320/224, echo time (TE) of 90 ms, and repetition time (TR) of 1298 ms. The fast spoiled gradient echo T1 sequence was performed only in the axial plane with a larger field of view of 40 cm, with 4-mm slice thickness and 0.5-mm gap, TR 160 ms, and TE 2.3 ms. Next, a diffusion-weighted imaging sequence was performed with a 40 cm field-of-view, b-values of 0 and 1000 or 700 ms [14].

The variables assessed in the study were: maternal age, medical background, gravidity, parity, nuchal translucency, biochemical screening tests during pregnancy, karyotype exam, sonographic evaluation, fetal echocardiography, fetal MRI, pregnancy outcomes, gestational age at delivery, gender, birth weight, Apgar score, hospitalization in neonatal intensive care unit, clinical evaluation of the newborn, neonatal echocardiography, neonatal cardiac MRI, neonatal brain ultrasound and MRI, operations, and postoperation brain imaging.

Following collection of the data, two classifications of the patients were made according to the cardiac anomaly. Classification of the severity of the CHD was defined as cyanotic and non-cyanotic CHD according to the literature [15]. Classification of situs anomalies, anomalies of the 4 chamber view (4CV), anomalies of the outflow tracts, arches anomalies and anomalies of the veins were determined according to the sweep technique protocol of two dimension five short-axis views [16,17].

The control group comprised 113 fetal MRI examinations performed at our institute between 2011 and 2015. The mean maternal age was 36 years (range 33–40), and 51% of the fetuses were male. Indications for MRI in the control group were brain pathology in previous pregnancy (11%), brain anomaly in a first degree family member with normal sonographic evaluation in the current pregnancy (8%), isolated extracranial anomalies (49%), or maternal cytomegalovirus infection with no intracranial anomalies (32%). These indications for MRI in a control group were previously reported [18,19].

STATISTICAL ANALYSIS

Categorical variables were reported as frequency and percentages. Continuous variables were evaluated for normal distribution using histogram and Q-Q plot and reported as mean and standard deviation or median and interquartile range. Categorical variables were compared using Chi-square test or Fisher's exact test, and continuous variables were determined using Mann-Whitney test or Kruskal-Wallis test. Agreement was determined using Kappa statistics. A P value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 24 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

Forty-six patients underwent fetal echocardiography and fetal brain MRI. Of these, 44 were evaluated after birth by neonatal echocardiography. In two additional cases the pregnancy was terminated and the parents chose not to perform post-mortem evaluation. In those cases, the diagnosis of CHD made during the fetal echocardiograph was used for analysis. The characteristics of the study population and of the pregnancy are shown in Table 1.

One fetus (2.2%) had an abnormal karyotype (Trisomy 21). Anatomical abnormalities were detected by an ultrasound scan in 42 fetuses (91.3%), 15.2% displayed brain abnormalities. Additional defects included hypoplastic lung (4.3%), gastroin-

Table 1. Characteristics of study population

Characteristic	Value
Familial congenital heart disease	4 (8.7%)
Gravidity	2.5 (1–7)
Parity	1.21 (0–4)
Age (years)	31.3 (27.7–35)
Number of fetuses	
Singleton	39 (84.8%)
Twins	7 (15.2%)
Abnormal nuchal translucency	3 (6.5%)
Abnormal second trimester biochemical test	3 (6.5%)
Abnormal amniocentesis	1 (2.2%)
Abnormal CGH	1 (2.2%)
Abnormal early ultrasound scan	24 (52.2%)
Abnormal late ultrasound scan	42 (91.3%)
Fetal echocardiography	
Situs	
Normal	41 (93.5%)
Abnormal	3 (6.5%)
Four chamber view	
Normal	23 (50.0%)
Abnormal	23 (50.0%)
Outflow	
Normal	15 (32.6%)
Abnormal	31 (67.4%)
Arches	
Normal	35 (76.1%)
Abnormal	11 (23.9%)
Veins	
Normal	42 (91.3%)
Abnormal	4 (8.7%)
Complexity of CHD	
Simple	17 (37.0%)
Complex	29 (63.0 %)
Cyanotic CHD	24 (52.2%)
Additional anomalies	
Brain abnormality	7 (15.2%)
Urinary track defects	3 (6.5%)
Face defects	2 (4.3%)
Developmental issues	2 (4.3%)
Other defects	5 (10.9%)
Brain imaging newborn*	
Normal	27 (58.7%)
Lenticulo-striate vasculopathy	1 (2.2%)
Periventricular hyperechogencity in occipital area	1 (2.2%)
Operation	22 (47.8%)

*29 newborns underwent brain imaging

CGH = comparative genomic hybridization, CHD = congenital heart disease

testinal anomalies (8.7%), genitourinary anomalies (6.5%), and anomalies in the portal system (4.3%).

Two pregnancies (4.3%) were terminated because of transposition of the great arteries and agenesis of corpus callosum and because of hypoplastic right heart. One neonate (2.2%) with CHARGE syndrome died 3 weeks following birth. Of the children with CHD, 22 (47.8 %) underwent surgery. The cardiac anomalies in the study population are specified in Table 1.

A cardiac MRI examination was performed on six of the children. Situs inversus was found in two of the children, one had hypoplastic left heart, two had abnormal outflow and additional effects were observed in three of the children. These findings of the cardiac MRI were consistent with the cardiac echocardiography findings in those children.

Fetal MRI revealed normal sulcation in 95.7% of the fetuses. No abnormalities were found in brain stem, face, ears, hypophysis, or optic chiasm. No bleeding or infarctions were detected. Brain MRI imaging was performed on four neonates (8.7%). One neonate (2.2%) was found to have a thin CC, one (2.2%) had unilateral ventricular dilatation and intraventricular hemorrhage, one (2.2%) had sub-arachnoid hemorrhage and one (2.2%) had ischemic injury. The probability of various brain pathologies for each category of CHD are presented in Tables 2 and 3. No significant differences were found in the brain pathologies between the different classifications of CHD including complex CHD and cyanotic CHD.

Various biometrical parameters of the brain were also examined in relation to the different classifications of CHD. The anteroposterior percentile of the vermis was significantly smaller in fetuses with an abnormal 4CV. A significantly higher bi-parietal diameter percentile was found in fetuses with abnormal arches, and a significantly smaller transcerebellar diameter percentile was found in fetuses with abnormal veins.

COMPARISON OF THE STUDY POPULATION TO THE CONTROL GROUP

Comparison between the control group and the simple or complex CHD is presented in Table 4. Significantly higher rates of overall brain pathologies, ventricle pathologies, cortex pathologies, and biometrical parameters were found in the simple group compared to the complex group and the control group.

Table 2. Brain pathology in relation to different classifications of CHD

	Situs eco		Four chamber view		Outflow		Arches		Veins		Miscellaneous	
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
Pathology	9 (22%)	1 (33.3%)	4 (23.5%)	6 (22.2%)	4 (30.8%)	6 (19.4%)	8 (25%)	2 (16.7%)	8 (20%)	2 (50%)	10 (24.4%)	0 (0.0%)
Ventricle pathology	4 (9.8%)	0 (0.0%)	2 (11.8%)	2 (7.4 %)	1 (7.7%)	4 (12.9%)	2 (6.3%)	2 (16.7%)	3 (7.5%)	1 (25%)	4 (9.8%)	0 (0.0%)
CC pathology	1 (2.4%)	0 (0.0%)	0 (0%)	1 (3.7%)	0 (0 %)	1 (3.2%)	1 (3.1%)	0 (0.0%)	1 (3.1%)	0 (0.0%)	1 (3.1%)	0 (0.0%)
Cortex pathology	2 (4.9 %)	0 (0.0%)	1 (5.9%)	2 (7.4%)	1 (7.7%)	2 (6.4%)	2 (6.3%)	1 (8.4%)	2 (5.0 %)	0 (0.0%)	2 (4.9%)	0 (0.0%)
Extra-axial findings	2 (4.9%)	0 (0.0%)	1 (5.9%)	2 (7.4%)	0 (0.0%)	3 (9.7%)	2 (6.3%)	0 (0.0%)	2 (5.0%)	0 (0.0%)	2 (4.9%)	0 (0.0%)
Biometrical parameters	3 (7.3%)	0 (0.0%)	2 (11.8%)	1 (3.7%)	2 (15.4%)	1 (3.2%)	3 (9.4%)	0 (0.0%)	2 (5.0%)	1 (25.0%)	3 (7.3%)	0 (0.0%)
OFD percentile	60 (40–75)	50 (40–50)	60 (45–72.5)	50 (40–75)	60 (40–67.5)	60 (40–75)	50 (40–70)	60 (50–75)	55 (40–73.75)	60 (52.5–71.25)	60 (40–70)	80 (25–80)
BPD percentile	50 (22.5–60)	50 (50–50)	50 (45–70)	50 (20–60)	50 (37.5–70)	50 (20–60)	50 (20–57.5)	55 (50–75)**	50 (21.25–60)	50 (50–50)	50 (22.5–60)	50 (25–50)
TCD percentile	50 (25–65)	60 (20–60)	40 (22.5–77.5)	50 (30–60)	50 (15–55)	50 (30–70)	45 (21.25–67.5)	50 (42.5–67.5)	50 (30–70)	17.5 (6.25–25)***	50 (25–65)	50 (50–50)
Vermis AP percentile	60 (45–80)	25 (20–25)	80 (50–85)	50 (25–75)*	50 (32.5–80)	60 (40–80)	65 (50–80)	55 (26.25–75)	60 (40–80)	65 (31.25–92.75)	60 (35–80)	50 (50–50)
Vermis height percentile	40 (22.5–50)	20 (15–20)	50 (25–50)	25 (20–50)	50 (25–55)	30 (20–50)	40 (25–50)	35 (16.25–61.25)	40 (20–50)	37.5 (25–50)	40 (20–50)	25 (25–25)
Smallest ventricle width (mm)	6 (6–7)	7 (6–7)	7 (6–7)	6 (6–7)	7 (6–7)	6 (6–7)	6 (6–7)	7 (6–7)	6 (6–7)	7 (7–7.5)	7 (6–7)	4 (4–6)
Largest ventricle width (mm)	7 (6–8)	7 (6–7)	8 (6.5–8)	7 (6–8)	7 (6–8)	7 (6–8)	7 (6–8)	7.5 (7–8)	7 (6–8)	8 (7.25–8.75)	7 (6–8)	4 (4–6)
CC percentile	40 (20–50)	25 (10–25)	45 (21.25–57.5)	40 (20–50)	25 (12.5–55)	40 (23.75–50)	40 (15–50)	50 (25–68.75)	40 (20–50)	45 (25–68.75)	40 (20–50)	40 (25–40)

*P = 0.02, **P = 0.015, ***P = 0.01

BPD = bi-parietal diameter, CC = corpus callosum, OFD = occipito-frontal diameter, TCD = trans-cerebellar diameter

Table 3. Brain pathology in relation to complexity of CHD

	Complexity			Cyanotic		
	Simple	Complex	*P* value	Acyanotic	Cyanotic	*P* value
Pathology	5 (35.7%)	6 (19.3%)	NS	6 (35.3%)	4 (14.8%)	NS
Ventricle pathology	2 (14.3%)	3 (9.7%)	NS	2 (11.8%)	3 (11.1%)	NS
CC pathology	0 (0%)	2 (6.7%)	NS	1 (5.9%)	0 (0 %)	NS
Cortex pathology	1 (7.1%)	3 (9.7%)	NS	1 (5.9%)	2 (7.4%)	NS
Extra-axial findings	0 (0.0%)	3 (9.7%)	NS	2 (11.8%)	1 (3.7%)	NS
Biometrical parameters	2 (14.3%)	1 (3.3%)	NS	2 (11.8%)	1 (3.7%)	NS

CC = corpus callosum, NS = not significant

Table 4. Magnetic resonance imaging parameters and pathology comparison between study sub-groups and control population

	Simple	Complex	Control	*P* value
MRI gestational week	33 (32–35)	31 (29–35)	33 (31–35)	NS
Pathology	5 (35.7%)	6 (19.3%)	6 (5.3%)	0.002
Ventricle pathology	2 (14.3%)	3 (9.7%)	2 (1.8%)	0.013
CC pathology	0 (0%)	2 (6.7%)	0 (0.0%)	NS
Cortex pathology	1 (7.1%)	3 (9.7%)	0 (0%)	0.007
Extra-axial findings	0 (0.0%)	3 (9.7%)	0 (0.0%)	0.011
Biometrical parameters	2 (14.3%)	1 (3.3%)	3 (2.7%)	0.046
OFD percentile	58 (47–75)	52 (40–70)	57 (40–75)	NS
BPD percentile	50 (25–71)	43 (20–60)	52 (25–75)	NS
TCD percentile	39 (17–52)	49 (28–70)	54 (30–75)	NS
Vermis anteroposterior percentile	62 (25–90)	55 (40–75)	56 (50–75)	NS
Vermis height percentile	37 (25–50)	37 (18–50)	40 (20–52)	NS
Smallest ventricle width (mm)	6.6 (6–7.25)	6.6 (6–7)	6.9 (6–8)	NS
Largest ventricle width (mm)	7.2 (6.75–8)	7 (6–8)	7.3 (6–8)	NS
CC percentile	33 (12.5–50)	41 (22–50)	39 (20–50)	NS

BPD = bi-parietal diameter, CC = corpus callosum, NS = not significant, OFD = occipito-frontal diameter, TCD = transcerebellar diameter

DISCUSSION

In this study we demonstrated that fetuses with CHD, and specifically those with complex CHD, had significantly more overall brain pathology and more abnormalities in the cortex and in extra-axial findings as determined by MRI, compared to controls. Despite the remarkable improvements in the surgical outcomes and long-term survival in children with CHD, these patients are at increased risk of developmental disorders, disabilities, or developmental delay [1]. It was hypothesized that some of these abnormalities may be related to an in utero insult to the fetal brain due to hypoperfusion caused by decreased blood flow to the fetal brain [8]. Furthermore, increased vulnerability of the white matter was observed in children with CHD [6,11,20-24].

In the present study we showed significantly smaller size of vermis and cerebellum in fetuses with abnormalities in the veins or abnormalities in the 4CV. Similarly, Licht et al. [20] reported a decrease in biometrical parameters in brain MRIs of children with CHD. Mahle [8] also reported microcephaly in 36% of newborns with CHD [8]. Sun et al. [25] reported an association between reduced cerebral oxygenation and impaired brain growth in fetuses with CHD. Limperopoulos and colleagues [5] performed MRI on 55 fetuses with CHD and 50 controls and noted smaller brain volumes and evidence of impaired neuroaxonal development and metabolism.

Fetal third trimester MRIs performed in our study demonstrated normal anatomy of brain stem, hypophysis, optic chiasm, face and ears in all fetuses, and normal sulcation in most fetuses, with no bleeding or infarction. Contrary to our findings, previous studies on neonates with CHD reported evidence of stroke or brain hemorrhage [20]. Continuous hypoperfusion during the neonatal pre-operative period may explain the differences between these findings.

We found no significant differences in the brain pathologies between the CHD classifications including complex CHD and cyanotic CHD. However, when compared to controls, a significantly higher rate of overall pathologies and abnormalities in the cortex and in extra-axial findings were found in the complex CHD compared to simple CHD and controls. Similarly, Mahle [8] reported that newborns with CHD may show symptoms of acidosis, hypoxic ischemic injury, and hemodynamic instability resulting in intraventricular hemorrhage. Kaltman et al. [7] reported altered cerebrovascular resistance in fetuses with complex CHD. Miller and colleagues [6] in their study on 41 newborns with complex CHD identified abnormal brain microstructures and metabolism possibly related to impaired cerebral oxygen and substrate delivery prenatally.

LIMITATIONS

The control group included pregnant patients who underwent fetal brain MRI. This imaging method is not performed on a regular basis during pregnancy; therefore, the control group might have had fetal anomalies. Due to the more effective statistical calculations comparing the study group to controls, we did use a control group and we carefully chose the patients with normal brain anatomy on ultrasound. This modality of control group for normal MRI exam was reported previously [18,19].

CONCLUSIONS

Fetuses with CHD may show abnormal findings in brain MRI, suggesting in-utero pathogenesis of the neurological and

cognitive anomalies found later on in these children. We suggest performance of fetal brain MRI to all fetuses diagnosed with CHD.

Correspondence
Dr. A. Weissmann-Brenner
Dept. of Obstetrics and Gynecology, Sheba Medical Center, Tel HaShomer 52621, Israel
Phone: (972-3) 530-8116
Fax: (972-3) 530-3168
email: alinabrenner@yahoo.com

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Capsule

Human *SNORA31* variations impair cortical neuron-intrinsic immunity to HSV-1 and underlie herpes simplex encephalitis

Herpes simplex virus-1 (HSV-1) encephalitis (HSE) is typically sporadic. Inborn errors of TLR3- and DBR1-mediated central nervous system cell-intrinsic immunity can account for forebrain and brainstem HSE, respectively. **Lafaille** and colleagues reported five unrelated patients with forebrain HSE, each heterozygous for one of four rare variants of *SNORA*31, encoding a small nucleolar RNA of the H/ACA class that are predicted to direct the isomerization of uridine residues to pseudouridine in small nuclear RNA and ribosomal RNA. The authors showed that CRISPR/Cas9-introduced bi- and monoallelic *SNORA*31 deletions render human pluripotent stem cell (hPSC)-derived cortical neurons susceptible to HSV-1. Accordingly, *SNORA*31-mutated patient hPSC-derived cortical neurons are susceptible to HSV-1, like those from TLR3- or STAT1-deficient patients. Exogenous interferon (IFN)-β renders *SNORA*31- and *TLR*3, but not *STAT*1-mutated neurons resistant to HSV-1. Finally, transcriptome analysis of *SNORA*31-mutated neurons revealed normal responses to TLR3 and IFN-α/β stimulation but abnormal responses to HSV-1. Human *SNORA*31 thus controls central nervous system neuron-intrinsic immunity to HSV-1 by a distinctive mechanism.

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