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Congenital Heart Disease and Neurodevelopmental Outcomes in Infants and Adolescents

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Abstract: ***Patients with complicated congenital heart disease are at risk of neurodevelopmental disability. This study aimed to study the correlation between brain development and congenital heart disease in infants. Studies have shown that brain maturation is delayed, and injury may be caused in the white matter or brain volume after the interventions like surgery for congenital heart disease. Secondary research was conducted to find the results of the effects of congenital heart disease on brain development. It was found that white matter has more injury than grey matter. The total brain volume is lower than in control patients. Amongst six different types of congenital heart disease (TOF, DORV, TGA, AoOb, HLHS, HRHS) studied Tetralogy of Fallot showed the most reduced brain volume compared to others. Adolescents with cyanotic heart disease lost more brain volume than those without, particularly in the white matter. In conclusion, it was found that patients with congenital heart disease have smaller brain volumes, smaller cerebellar volumes, and injury in the white matter***

Index Terms: brain stem volume after tetralogy of Fallot, brain volume in infants with CHD, cerebellar volume after interventions, Congenital heart disease, extra cardiac anomaly, hypoplastic left heart syndrome, neurodevelopmental **outcome**

I. INTRODUCTION

In India, CHD is becoming the leading cause of death. In 2016 India reported 27% deaths due to cardiovascular disease (WHO). This essay aims to find the neurodevelopmental needs of children and adolescents with congenital heart disease. I am an International Baccalaureate student and have opted for Biology at a higher level. The syllabus is incredibly vast, and it covers a variety of topics. I was intriguingly fascinated by the topic of Human Physiology and animal physiology topic. However, the syllabus is limited, and I wanted to expand my knowledge about this topic. So, I did some additional research on Human physiology. Reading many research journals was an integral part to gain more knowledge on the topic. However, the most interesting topic I found was congenital heart disease in infants and therefore, I was determined to extend my research in this field.
Congenital Heart disease (CHD) is present at birth and affects the structure of the baby's heart. The disease can range from mild symptoms like extreme fatigue, and rapid heartbeat cyanosis to severe symptoms like shortness of breath and swelling of the legs and ankles. CHD is relatively increasing amongst infants. (NHS) About 1 in 4 babies are born with a heart defect in the United States. (Oster M)

II. METHODS AND RESULTS

A systematic literature search on infant CHD and treatment was undertaken using approximately 60 research journals. The data was collected through secondary research and processed to produce results.

A. Types Of Congenital Heart Disease

1) Atrial Septal Defect: It is a defect present at birth where there is a hole in the septum wall which divides the upper chambers of the heart. It can either close on its own after a short period or may require surgery to close the hole. (Specific Heart defects) 1 in every 1859 babies born in the United States each year is affected by this disease. (Mai CT)

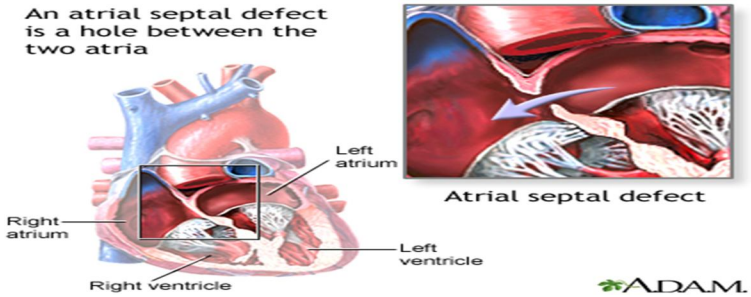


Fig 2.1.1 The above picture shows the Atrial Septal defect

2) *Coarctation of The Aorta:* It is a critical congenital heart disease in which the aorta is narrower than usual because it might not have developed properly during pregnancy. If it is severely narrow, then the baby needs to go under surgery. This disease can prevent normal blood flow to the body. It results in the backflow of blood into the left ventricle of the heart. (Coarctation of the Aorta) 4 out of 10000 babies born in the United States each year have coarctation of the aorta. (Cara T. Mai)

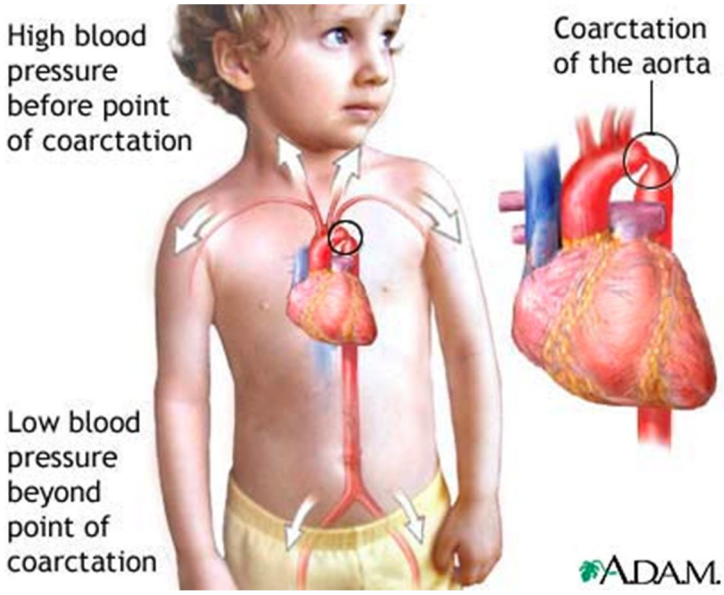


Fig 2.2.1 The figure above represents the Coarctation of the Aorta

3) *Dextro-Transposition of The Great Arteries:* It is a heart defect where the two main arteries the pulmonary artery and the aorta switch their positions. This means that now the blood present in the pulmonary artery will go to the rest of the body instead of the lungs and the oxygen-rich blood in the aorta will go to the lungs instead of the rest of the body. (Specific Heart Defects) 1153 babies are born with TGA every year. (Mai CT)

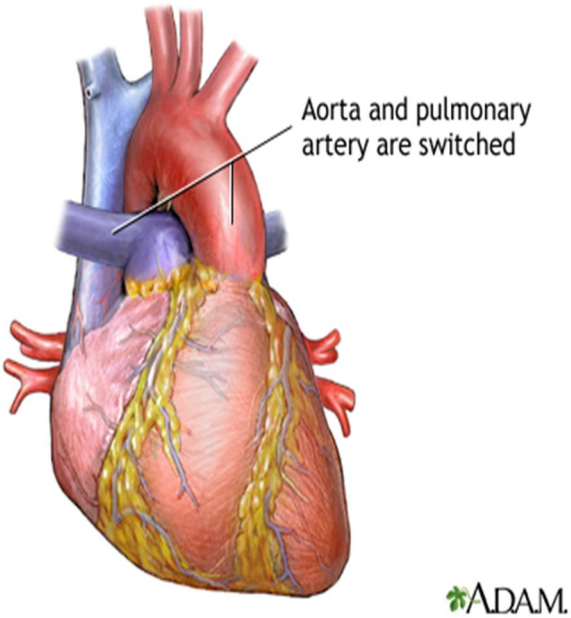
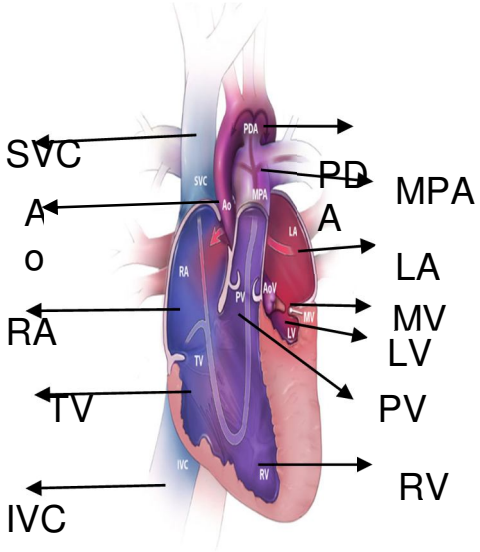


Fig 2.1.3 The above image represents the Dextro- Transposition of the great arteries.

4) *Hypoplastic Left Heart Syndrome:* In this type of heart defect, the left side of the heart does not develop properly during the pregnancy which interrupts the regular flow of blood in the body. (Congenital Heart Disease)1 out of every 3,841 babies born in the United States each year is born with hypoplastic left heart syndrome. (Mai CT)



RA- Right Atrium SVC-Superior Vena Cava TV- Tricuspid Valve RV- Right Ventricle IVC- Inferior Vena Cava MV-Mitral Valve LA- Left Atrium MPA-Main Pulmonary Artery PV- Pulmonary Valve LV-Left Ventricle Ao- Aorta AoV- Aortic Valve PDA- Patent Ductus Arteriosus

Fig2.1.4 The above image shows Hypoplastic left heart Syndrome

5) *Pulmonary Artesia:* It is a heart defect where the pulmonary valve is not at all present between the right ventricle and the pulmonary artery. This is the reason why the blood cannot flow from the right ventricle of the heart to the pulmonary artery so the baby has to go under surgery. (Pulmonary Atresia) Every year around 550 new-born babies have Pulmonary Atresia in the United States. (Cara T. Mai)

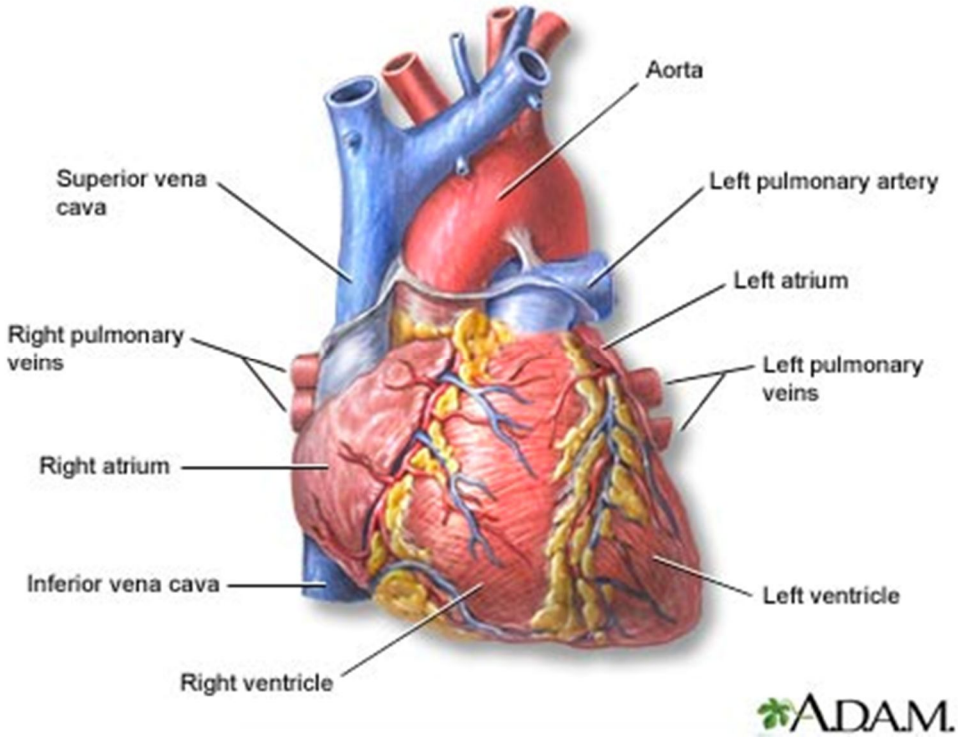
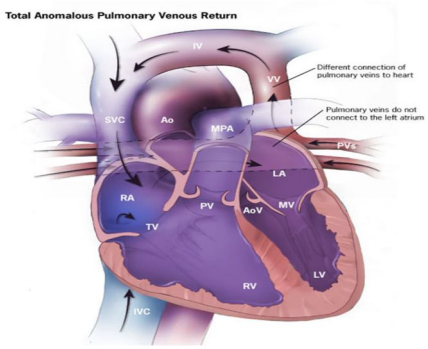


Fig2.1.5 The above image shows Pulmonary Artesia.

6) *Total Anomalous Pulmonary Venous Return:* It is a defect where the oxygen-rich blood goes to the right side of the heart instead of the left ventricle. (Congenital Heart Disease) Every year 504 babies are affected by this disease in the United States. (Mai CT)



RA- Right Atrium SVC-Superior Vena Cava TV- Tricuspid Valve RV- Right Ventricle IVC- Inferior Vena Cava MV-Mitral Valve LA- Left Atrium MPA-Main Pulmonary Artery PV- Pulmonary Valve LV-Left Ventricle Ao- Aorta AoV- Aortic Valve IV- Innominate Vein VV-Vertical Vein PVs- Pulmonary Vein

Fig 2.1.6 shows Total Anomalous Pulmonary Venous Return

7) *Truncus Arteriosus:* It is a defect where the blood vessel between the aorta and pulmonary artery does not separate which results in the mixing of oxygenated blood and deoxygenated blood. (Congenital Heart Disease) Approximately 250 babies are born with Truncus Arteriosus in the United States each year. (Cara T. Mai)

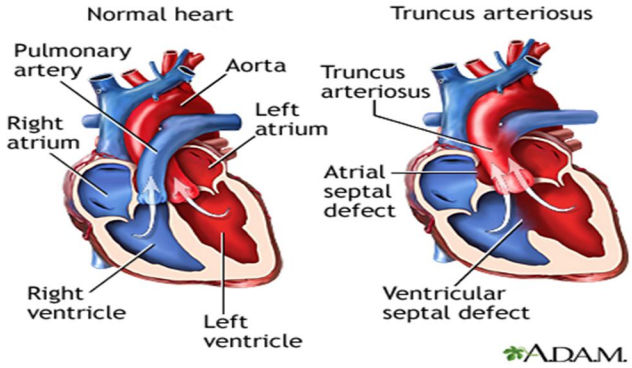


Fig 2.1.7 shows Truncus Arteriosus.

8) *Ventricular Septal Defect:* It is a hole between the walls of the two ventricles as it does not develop completely during pregnancy. Extra blood is forced inside the lungs which puts on pressure on the heart to work more. This can result in high blood pressure and heart failure. (Congenital Heart Disease). Each year 16800 babies are born with this disease in the United States. (Reller MD)\

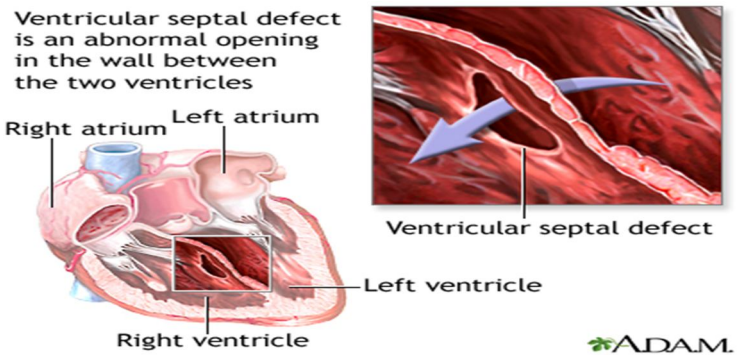


Fig 2.1.8 The above image represents Ventricular Septal Defect.

9) *Tetralogy of Fallot:* There are four types of Tetralogy of Fallot a hole in the wall of two ventricles, narrow pulmonary artery and pulmonary valve, this is *called* pulmonary stenosis, the aortic valve is very large and opens from both the ventricles and the muscular wall of the right ventricle is thicker than normal. (Congenital Heart Disease) Each year 1660 babies are born with this disease in the United States. (Parker SE)

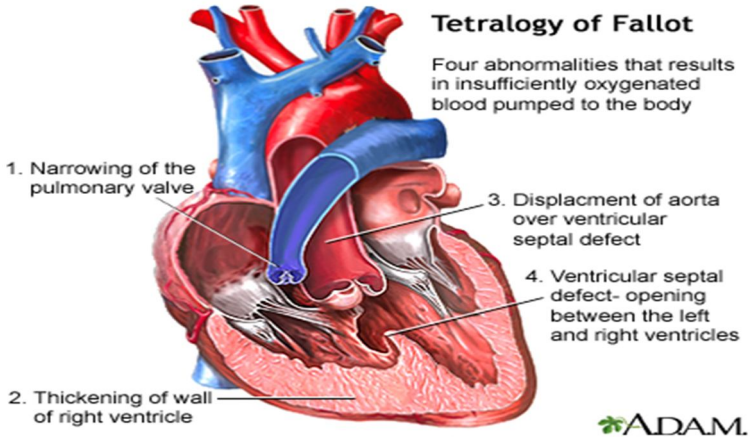


Fig 2.1.9. The above image shows the Tetralogy of Fallot.

III. RESULTS

Infants with CHD have white matter injury shown by the magnetic resonance studies. We could confirm that brain volume decreases in infants with CHD than in the control.

Age and total white matter volume were found to have a positive correlation in CHD patients. This could point to ongoing white matter development in patients that were not detected in controls even after scanning at similar ages.

These results could imply that patients with CHD have a

longer maturation period due to a delay in white matter maturation. They discovered normal cortical thickness but decreased cortical surface areas that were roughly proportional to the number of cortical columns and closely related to the number of radial glia. If each cortical column has a constant number of connections, this will imply a significantly reduced number of axons, which could explain the widespread reduction in white matter volume. A reduced cortical surface, on the other hand, could be the result of axonal loss caused by white matter injury or delayed development. They found that patients with cyanotic CHD had lower grey matter volumes than controls. The limbic cortex, frontal and parietal lobes, and cerebellum showed the greatest reduction in total grey matter. There was no regional preference for white matter reduction. (Michael von Rhein)

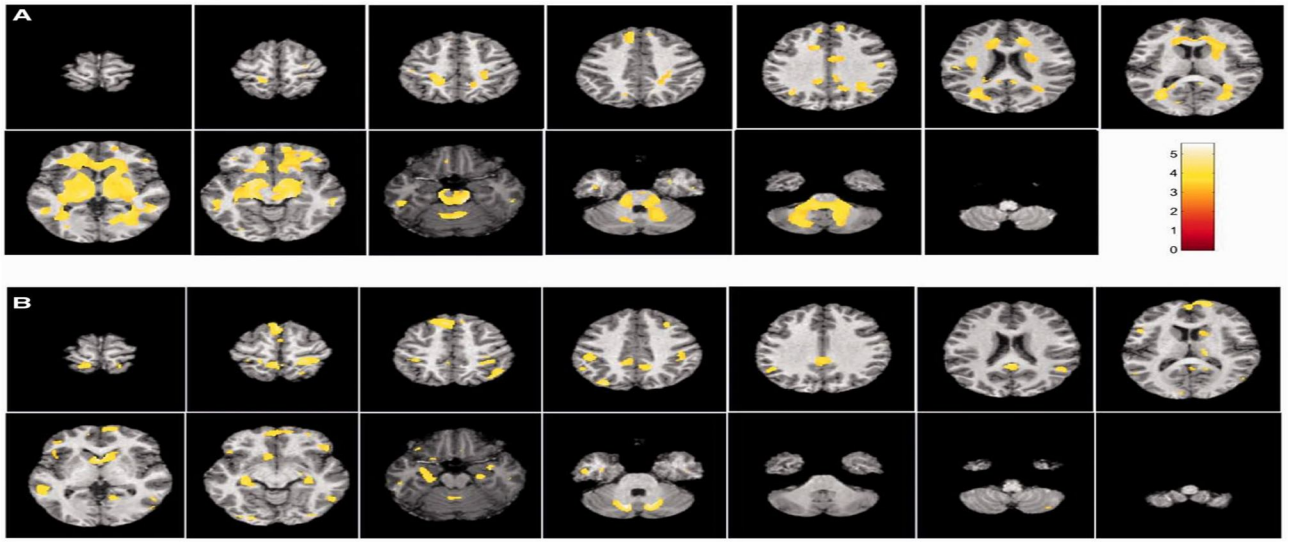


Fig 1 Image A shows the white matter and image B shows the grey matter. It depicts the differences in the brain volume between infants with CHD and control.

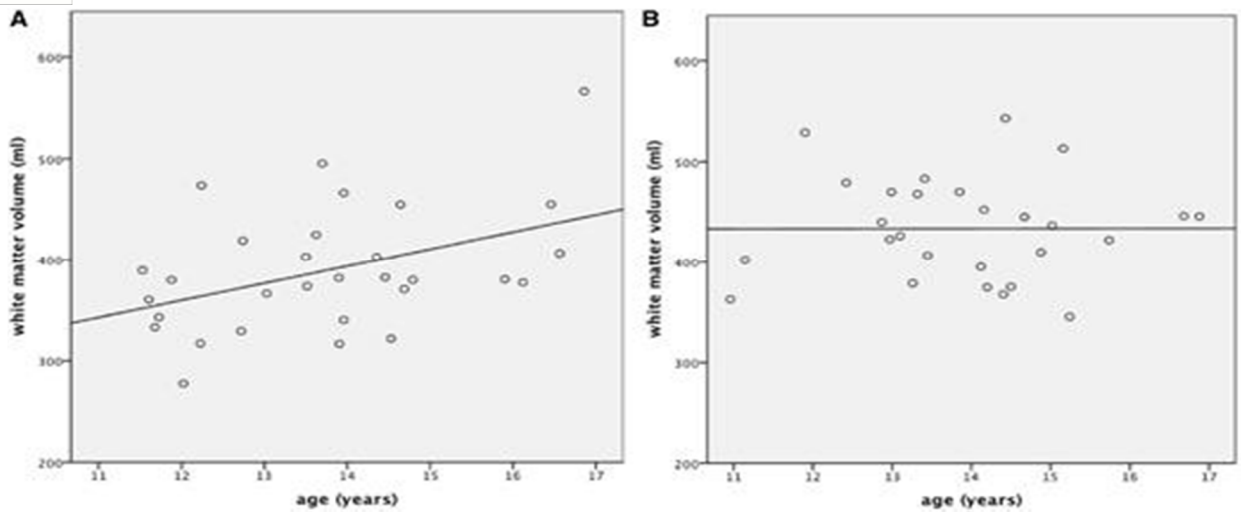


Fig 2 Scatterplots showing white matter plotted against age. **(A)** infants with CHD **(B)** control.

White matter volume and age at scan showed a significant positive correlation in the CHD patient group but not in the control group (beta = 0.30, P<50.001, controlled for total brain volume). In either group, total brain volume and grey matter volumes did not correlate significantly with age. (Majnemer A)

Table 1: Global and regional brain volume in patients and control

	Controls, *n* = 32 Mean (SD)	Patients, *n* = 39 mean (SD)	% Reduction
Total brain volume	1216 (112)	1130 (120)	7.0*
White matter volume	434 (47)	397 (55)	8.5**
Cortical grey matter volume	570 (63)	532 (51)	5.3**
Ventricular volume	13.23 (4.91)	13.85 (6.29)	
Volume gyri total	379 (41)	354 (36)	6.6**
Volume sulci total	190 (22)	174 (19)	8.4**
Surface area gyri total	1165 (129)	1078 (115)	7.5**
Surface area sulci total	828 (96)	765 (90)	7.6**

Reduction in % (control = 100%) brain volume in cm^3, surface area in cm^2, thickness in mm, *P5 < 0.05, **P < 50.01, ***P < 50.001.

Table 2: Global and regional surface area of brain in patients and control

	Controls, *n* = 32 Mean (SD)	Patients, *n* = 39 mean (SD)	% Reduction
Thickness gyri total	2.69 (0.11)	2.69 (0.10)	0
Thickness sulci total	2.40 (0.09)	2.41 (0.07)	0
Surface area frontal lobes	351 (49.7)	326 (39.7)	7.1*
Surface area temporal lobes	327 (46.2)	301 (38.8)	7.9**
Surface area parietal lobes	216 (24.4)	202 (24.0)	6.5**
Surface area occipital lobes	83 (12.9)	78 (9.5)	6
Surface area limbic cortices/ mesocortices	111 (12.4)	100 (9.9)	9.9***

Reduction in % (control = 100%) brain volume in cm^3, surface area in cm^2, thickness in mm, *P5 < 0.05, **P < 50.01, ***P < 50.001.

Table 3: Global and regional

	Controls, *n* = 32 Mean (SD)	**Patients, *n* = 39 mean (SD)**	**% Reduction**
Volume cerebellum	145 (14.1)	136 (12.2)	6.2**
Volume thalami	14.4 (1.2)	13.7 (1.6)	4.9*
Volume basal ganglia	24.5 (1.8)	22.8 (2.5)	6.9**
Volume hippocampi	8.2 (0.8)	7.5 (0.7)	8.5***
Volume corpus callosum	3.09 (0.39)	2.75 (0.47)	11.0***

Reduction in % (control = 100%) brain volume in cm^3, surface area in cm^2, thickness in mm, *P5 < 0.05, **P < 50.01, ***P < 50.001.

IV. DISCUSSION

Infants suffering from hypoplastic left heart syndrome or transposition of the great arteries were assessed with brain magnetic resonance imaging. They were analysed based on total maturation score and head circumferences. The study contingent included 29 infants with hypoplastic left heart syndrome and 13 infants with transposition of the great arteries. It was observed that the mean total maturation score for the contingent was 10.15 ± 0.94, which was lesser than the normative data in infants without congenital heart disease. The development of the structural brain was also delayed by 1 month. The main gender was male in this study which was 64% and the average gestation age was 38.9 ± 1.1 weeks. Mean birth head circumference at birth was 34.6 ± 1.1 cm, and birth weight was 3.37 ± 0.53 kg. The extracardiac anomaly had developed in 12 of 42 patients with TGA and 9 of 29 with HLHS. Total maturation scores were not different between infants suffering from TGA and HLHA. It was also not different between infants with and without ECA. (Daniel J. Licht)

Additionally, there is a growing understanding that CHD patients have smaller-than-expected brains that frequently exhibit white matter damage both before and after surgery, indicating immaturity. They had a mean head circumference that was one standard deviation less than what would be predicted for their gestational age. This is consistent with a prior study from their group that used unique semi-automated MRI techniques to show decreasing brain size with age. Reduced TMS scores, small brain circumferences, a higher incidence of open operculate, and a higher and continued risk for PVL all indicate that in utero brain development is compromised in this population. (Licht DJ)

In another study white matter, cortical grey matter, subcortical grey matter, and ventricular volumes were first examined between control and HLHS foetuses. Volumes changed linearly throughout gestation; however, the slopes were different between the 2 groups. The HLHS group was shown to have considerably reduced gestational volume differences in both white and grey matter ($P < 0.001$), with the difference being progressively bigger after 30 weeks (C. Clouchoux1). It is interesting to note that before 30 weeks GA, neither the white nor the cortical grey volumes showed tissue-specific variations between the 2 groups that were statistically significant ($P = 0.2$ and 0.3, respectively). Although statistically significant ($P = 0.02$), the difference in subcortical grey matter volume between the two groups was less evident. Between the two groups, there was no difference in lateral ventricular volume ($P = 0.6$). In both groups, increasing GA led to a curvilinear change in the GI and surface area of the cortical grey matter. When it was examined, the folding states of the two populations, it was discovered that the GI in the HLHS group was considerably lower than in the controls (Boucher M). Additionally, infants with HLHS had considerably reduced cortical surface areas ($P<0.001$). The gap between the two groups was steadily wider for both metrics as GA increased. The GI and cortical grey matter surface area changed curvilinearly in both groups as GA increased. The folding states of the two populations allowed us to determine that the GI in the HLHS group was significantly lower than in the controls. Infants with HLHS also had significantly smaller cortical surface areas ($P< 0.001$). For both indicators, the difference between the two groups grew as GA rose. (Zilles K)

In intervention of Cardiopulmonary bypass surgery (rectal temperature 32°C) was typically performed with a pump flow rate of 100 to 150 ml/kg per minute in normothermic or mild hypothermic conditions. There are several outcomes of this research- Preoperative cerebral abnormalities are a danger for neonates having congenital heart defects.

1) In about 30% of babies, preoperative cranial ultrasonography findings were found. Mild white matter damage or generalised oedema are examples of abnormalities.
2) The risk of cerebral oedema in infants having balloon-atrial septostomy is high.
3) The early result of neurodevelopment is unrelated to cranial ultrasonography.99 neonates have studied out of which 77 neonates had at least one Preoperative carnival ultrasound. Neonates with preoperative cUS were at a higher chance of surgical risk. Out of these nine infants died. In the end, nineteen out of 66 infants were identified with a genetic disease (25%) and found to have trisomy 21, 22, and 11. There were two deletion syndrome cases and twelve additional genetic disorders. Outcomes were mostly moderate. The majority of new-borns (n=12) had diffuse cerebral oedema, and of the five infants who had PVLs, two of them had cystic PVLs grade II. No infants had a PVL of a higher grade. At 38.6 weeks gestation, one baby with cystic PVL grade II had a ventricular septal defect, and the other had hypoplastic left heart syndrome (40wks gestational age) Two infants had an IVH grade I and three new-borns exhibited ventricular dilatation. All variables were the same, except preoperative BAS. Infants who required BAS had a higher likelihood of developing brain oedema later (9/28 [32.1 percent] vs 3/49 [6.1 percent]; $p=0.006$). Infants with genetic abnormalities considerably outperformed healthy infants in terms of MDIs, PDIs, and neuroscores ($p \leq 0.001$). When children with genetic diseases were eliminated, the medians for the MDI, PDI, and neuro scores were 91 (50–107), 70 (49–113), and 1 (0–7), respectively. At one year, the neurodevelopmental outcome was not correlated with cranial ultrasonography results. Poorer neurodevelopmental outcome was strongly connected with genetic comorbidity (genetic comorbidity $p<0.001$ for all three outcome criteria). (BEATRICE LATAL1)

Table 4: Brain volume and cerebellar volume in infants with different types of CHD

	Brainstem Volume ratio (%)	(IQR) P value	Cerebellar Volume ratio (%)	(IQR) P value	Total Brain volume ratio (%)	(IQR) P value
Tetralogy of Fallot	74.6	(61.1-83.4)	79.7	(69.0-102.0)	85.2	(75.2-96.1)
DORV	85	(69.9-104.3)	91.0	(78.4-110.9)	91.7	(84.9-100.5
TGA	83.5	(71.2-96.7)	91.2	(76.3-107.4)	84.8	(78.7-97.1)
Ao0B	89.5	(78.0-106.7)	94.1	(81.7-101.3)	94.4	(85.8-108.6)
HLHS	80.6	(73.0-111.6)	98.9	(76.7-128.5)	93.1	(84.8-96.5)
HRHS	81.9	(73.2-92.9)	105.7	(83.7-112.7)	88.0	(83.4-94.5)

Figure 1: Brainstem volume in infants with different CHD

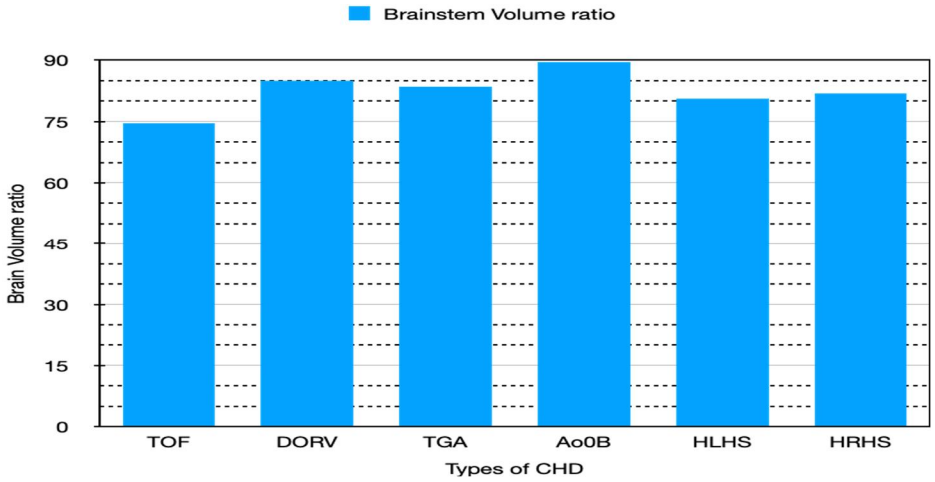


Figure 2: Cerebellar volume ratio in infants with different CHD.

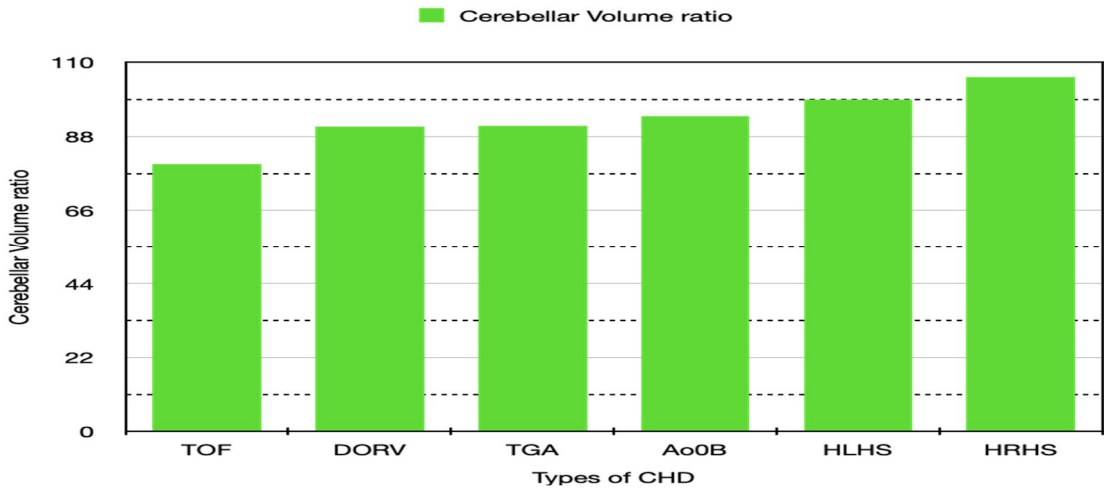
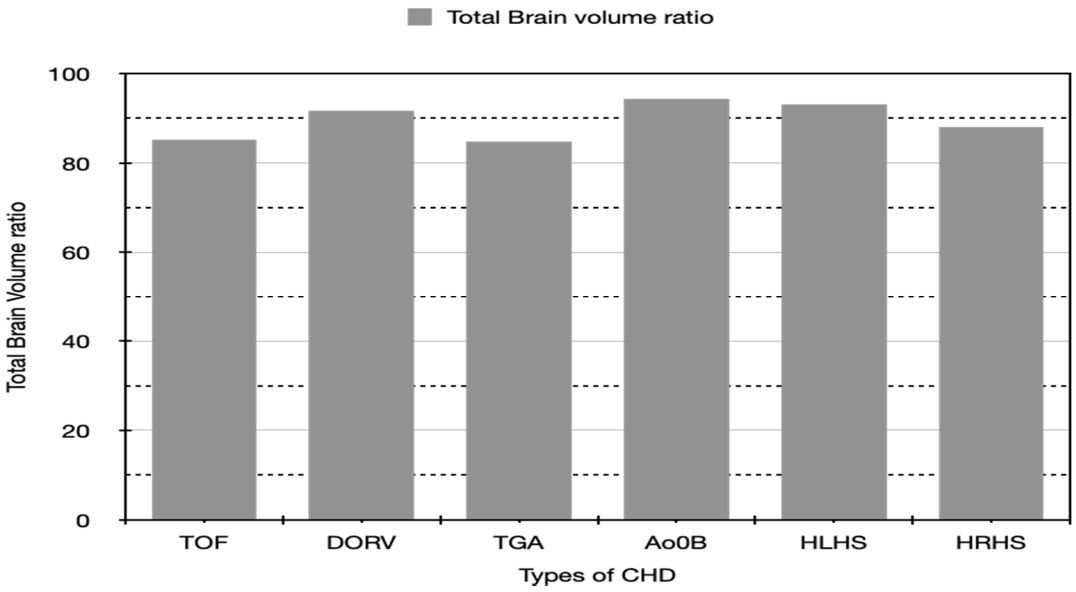


Figure 3: Total Brain volume ratio in infants with different CHD



From midgestational onward, neonates with congenital heart disease have considerably reduced infratentorial brain volumes than controls. This region of the brain contains components that are thought to be essential for proper brain function. These findings show that decreased growth of supra- and infratentorial brain regions develop during the second trimester in neonates with congenital cardiac disease. Among 6 types of CHD infants having tetralogy of Fallot and transposition of the great arteries had the most affected total brain volume reductions. Cerebellar volumes in the Fontan circulation demonstrated high correlations with neurocognition, supporting the cerebellum's function in neurocognitive processes.

Both supratentorial and total brain sizes were smaller in TOF, DORV, TGA, HLHS, and HRHS foetuses but similar in controls and AoOb foetuses. CSF volume was higher in TGA foetuses and lower in HRHS foetuses, but similar in controls and all other forms of CHD foetuses. Brainstem volume in fetuses with AoOb was similar to that of controls but less than that of controls in fetuses with all other forms of CHD. (Gregor O. Dovjak, Hausmaninger and Zalewski, Brainstem and cerebellar volumes at magnetic)

Volumes of the prenatal brain and new-born brain correspond and have a negative link with neonatal ischemia injury in CHD, according to studies (N.H.P. Claessens). In this study, after the infants with structural brain anomalies were eliminated, fetuses having TOF were most likely to have reductions in infratentorial brain volume compared to the control. Postnatal MRI in infants with CHD indicated smaller brain measurements, such as TCD and brainstem area, with the greatest disparities in the frontal lobe and brainstem. Infants with single-ventricle CHD had a smaller brainstem than those with biventricular CHD (Ortinau C). In the current study, TCD was not different from controls, although cerebellar volume was reduced in four of the six kinds of CHD investigated. Impaired growth during pregnancy may precede a more general cerebellar volume reduction, which is also reflected in a smaller TCD postnatally.

Impaired volumetric brain growth in full-term neonates before open-heart surgery was associated with aberrant neurobehavior in infants with complex CHD, and relationships between lower cerebellar volumes and poor behavioural state regulation were seen in a subgroup of cyanotic new-borns. (30. Owen M). Another study on Fontan circulation in adolescents and adults discovered poor neurocognitive outcomes correlated with smaller global brain volumes and white-matter damage, as well as poorer oxygen saturations linked with smaller global brain volumes. (Pediatr) (von rhein M)

V. CONCLUSION

To conclude congenital heart disease influences the neurodevelopmental outcomes of the white matter, total brain volume and cerebellar volume in infants and adolescents.

Comparing global and regional brain volume in adolescent CHD patients with and without overt brain lesions to control subjects the reduction in brain volume was more pronounced in patients with cyanotic heart disease. Lower cerebellar volumes and poor behavioural state regulation were seen in a subgroup of cyanotic new-borns. It was found to be significantly related to neurodevelopmental performance, highlighting the importance of these widespread cortical and subcortical volume reductions for the cognitive outcome. In infants with TGA and HLHS, there is a delay in brain maturation by almost 1 month.

One of the reasons could be the pattern of fetal blood flow which reduces oxygen transport. They are also susceptible to periventricular leukomalacia any time before or after the surgery. This can cause injury in the white matter especially.

We can conclude that brain volume is also significantly affected in infants with CHD. They have smaller brain volumes due to reduced fetal cerebellar oxygen consumption or transportation. Cerebellar volume is reduced in infants with CHD and has a negative link with neonatal ischemia injury. There are poor neurocognitive outcomes correlated with smaller global brain volumes and white-matter damage.

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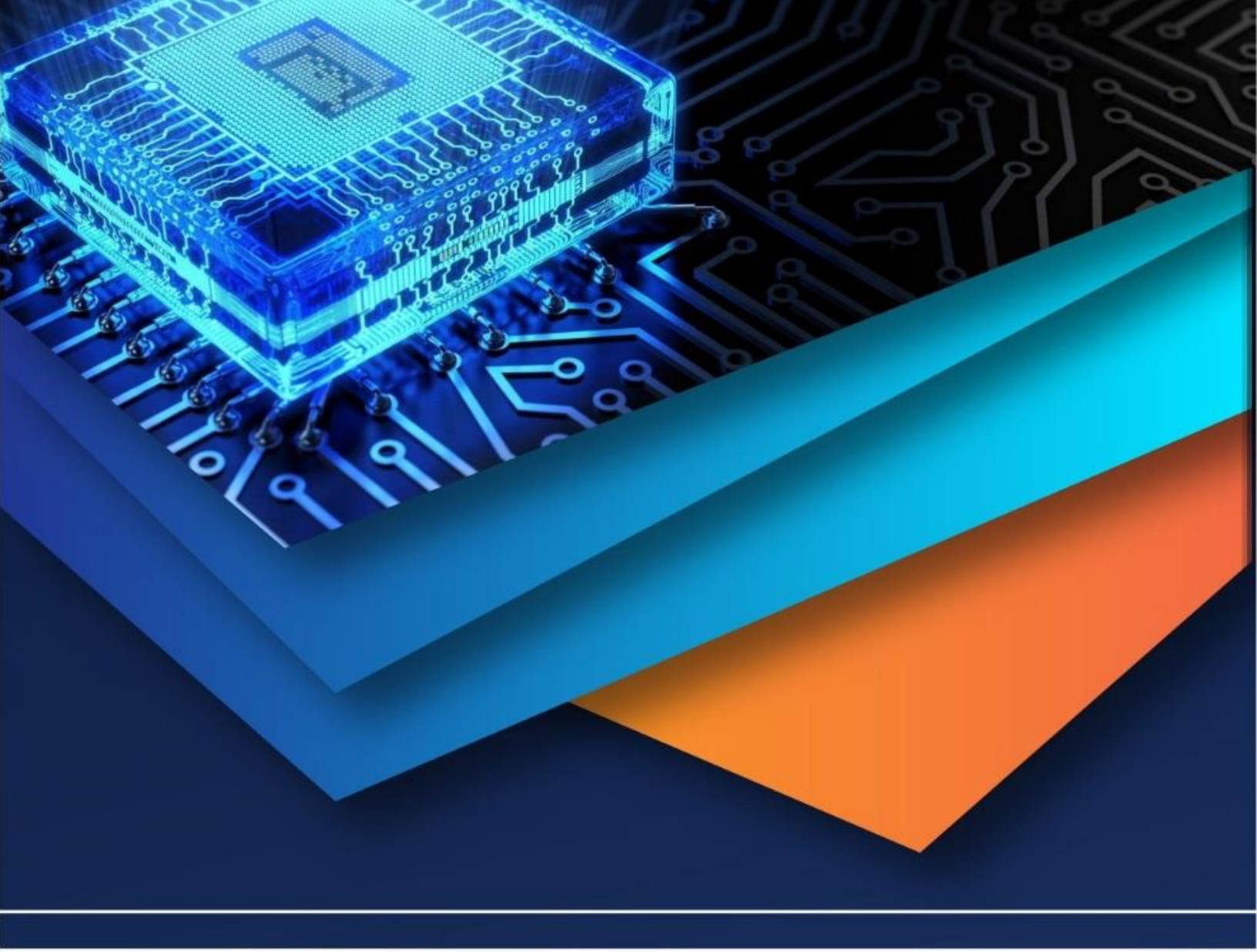

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