Comparison of pre- and postoperative brain MRI findings of neonates undergoing congenital heart surgery-
The impact of brain injury scores on long-term neurological outcome

Inauguraldissertation
zur Erlangung des Grades eines Doktors der Medizin des Fachbereichs Medizin
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In Kooperation mit dem Children's National Hospital in Washington, DC

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1 Preface

Results of the present study were already published:

Kuhn V, Carpenter JL, Zurakowski D, Reitz JG, Tague L, Donofrio MT, Murnick J, Axt-Fliedner R, Limperopoulos C, Yerebakan C. Determinants of neurological outcome in neonates with congenital heart disease following heart surgery. Pediatr Res. 2020 Jul 25. doi: 10.1038/s41390-020-1085-1. Epub ahead of print. PMID: 32711400

2 Introduction

2.1 Brain injuries in children with congenital heart disease

The incidence of moderate or severe congenital heart disease is estimated at 6 per 1000 live births and being therefore the most common birth defect worldwide.[1,2]

Following advances in prenatal diagnosis of congenital heart diseases (CHD), surgical techniques, cardiopulmonary bypass strategies and postoperative intensive care management of the patients, the mortality of children with CHD declined by 24.1% between 1999 and 2006.[3] The overall mortality after congenital cardiac surgery remains less than 3%.[4] Nowadays, approximately 85% of the children diagnosed with CHD reach adulthood.[5]

While the mortality rate has dropped significantly in the last few decades due to the previous described advances, the focus of the current clinical research has been short- and long-term neurological outcome of infants with CHD. One of the most common extracardiac complication in these patients remains brain injuries,[6] which may significantly affect their short and long-term neurodevelopmental outcome.

Many studies have examined perioperative risk factors impacting brain function, such as birth weight, age at surgery and lowest blood pressure postoperatively. However, bypass strategies, duration of deep hypothermic circulatory arrest (DHCA) or aortic cross clamp time do not seem to have an impact on postoperative brain injuries. [7,8] Other literature suggested that patient characteristics, such as the specific cardiac lesion or genetic disorders, have a major impact on brain injuries and thus on long-term outcome. [9]

While earlier research focused on postoperative brain injuries that were suspected to be the result of open heart surgery, a growing number of studies have recently shown a significant incidence of both, brain injury and abnormal brain development, already before surgery in neonates with CHD.[8,10,11] Abnormalities described include alteration in brain development [12,13,14] and evidence of acute injuries [15, 16], some of which are hypothesized to have occurred prenatally.[17]

White matter injury (WMI) is the most common subtype cerebral injury found in neonates with CHD.[18] Andropoulos et al. demonstrated that brain immaturity in neonates with CHD is significantly associated with pre- and postoperative brain injury, especially WMI. [8]

Fetal studies have shown abnormal brain development and cerebral blood flow in fetuses with CHD. [19,20,21,22] Limperopoulos et al. provided the first in vivo evidence that impairment of fetal brain growth in fetuses with CHD has its onset in the third trimester. [23] McQuillen et al. suggest that failures in brain oxygen and nutrient delivery due to the underlying heart defect and alterations in fetal blood flow lead to the impairments of fetal brain growth. [24] Moreover, oligodendrocytes which have high activity levels in the 3rd trimester are excessively vulnerable for hypoxia/ischemia, infection, hyperoxia or anesthetic drugs, which increases the risk of hypoxic and oxidative injuries to the white matter in CHD patients due to decreased brain oxygen delivery caused by the underlying cardiac defect.[25]

Supporting this assumption, Graupner et al. demonstrated that those fetuses with retrograde arch flow, as found in cases of severe left-sided obstructive lesions show significant smaller head circumferences compared to fetuses with antegrade cerebral blood flow. [26]

Sun et al. also encourage the assumption that a reduction in cerebral oxygen saturation is associated with smaller fetal brain size. Moreover, they demonstrated that blood flow and oxygen saturation in the umbilical vein is diminished in fetuses with CHD in comparison with controls, which leads to a reduction in cerebral oxygen delivery. The study group supports the hypothesis that maternal hyperoxygenation could have a positive effect on the fetal brain development. [27] However, randomized controlled trials are warranted to strengthen the therapeutic effect of this strategy. [28]

Graupner et al. could demonstrate that fetuses with congenital heart disease have lower middle cerebral artery pulsatility indeces and lower cerebroplacental ratios within doppler examinations. Therefore, they conclude that these fetuses, especially those with low oxygen saturation in the ascending aorta, common in cases of severe left-sided obstructive lesions, show a cerebral redistribution in the third trimester compared to healthy fetuses. [29]

2.2 Neurodevelopmental outcome in children with congenital heart disease

Impairments in neurodevelopmental outcome are frequently seen in patients with CHD.[6] Despite considerable recent efforts to improve long-term outcome of the patients, either through advances in surgical techniques or through mitigation of possible risk factors, an enhancement of either motor function or cognitive function in patients with CHD were not seen in the last two decades.[30]

The term “developmental disorder and disabilities” (DD) is commonly used to describe the existence of mental or physical impairments which usually leads to an abnormal everyday function, whereas “developmental delay” is used to describe that the developmental level and achieved skills of a child, such as fine and gross motor skills, language and communication, problem solving behavior or personal-social skills, is not consistent with the expected course and differ in comparison to healthy controls.[31]

Children with mild CHD, such as atrial septal defect (ASD) or ventricular septal defect (VSD), have a low prevalence of mild or severe developmental DD. The more complex CHD the higher the prevalence of mild or severe developmental DD. In the group of children with palliated single ventricle CHD or severe two-ventricle CHD, i.e. hypoplastic left heart syndrome (HLHS) and transposition of the great arteries (TGA), respectively, only a minority of patients do not possess any disabilities.[32]

2.2.1 Neurodevelopmental disorder and disabilities

Fine and gross motor delays are common impairments in children with CHD and usually manifest during the first year of life.[33] During preschool age impairments in motor skills still persists but disorders in language, especially expressive language, and memory functioning predominate.[34] Behavioral problems, such as hyperactivity or impulsivity, problems in peer interaction and emotional problems are frequently seen in school- age children with CHD.[35,36] Almost half of the patients show learning difficulties at school, which also affect their academic performance.[33,32]

Limperopoulos et al. demonstrated that more than half of the patients with CHD already show neurobehavioral abnormalities before cardiac surgery. Anomalies described preoperatively includes hypotonia, hypertonia, motor asymmetries or feeding difficulties. Importantly, most of the patients with abnormalities after surgery had already been described as abnormal preoperatively.[10] It seems that neurologic abnormalities preoperatively remains a strong predictor of impaired neurodevelopmental outcome at 1 and 5 years of age.[36]

2.2.2 Risk factors of neurodevelopmental disorder and disabilities

Majnemer et al. could find some predictor variables for developmental DD. A palliative surgery and duration of DHCA seem to play an important role on neurologic findings, such as hypotonia, microcephaly, motor asymmetries or hemiplegia, development of fine and gross motor delays, as well as difficulties in receptive language. Moreover, they could show that parental stress leads to behavioral problems at the age of 5 years.[36] For decades, duration of DHCA was seen as one of the main risk factor for an abnormal neurologic outcome, however, the Boston Circulatory Arrest Trial could demonstrate, that neurodevelopmental outcome is not significantly impaired by the duration of DHCA as long as it is less than 41 minutes.[37] Furthermore, the socioeconomic status of the families seems to be a significant factor in terms of the neurodevelopmental outcome and therefore lower-income families should be supported in the care of their chronically ill children.[33] But still, it is not possible to determine specific risk factors which lead to a worse neurodevelopmental outcome, since many modifiable and nonmodifiable factors have an impact on the long-term outcome of the patients.

Clancy et al. demonstrated that 11,5% of the children who underwent cardiac surgery had postoperative seizures detected by Electroencephalography (EEG) without a clinical correlation.[38] Since most of the children are sedated and intubated after surgery, most of the seizures cannot be detected clinically but by using EEG.[33] Some studies could show that the occurrence of postoperative seizures detected by EEG predict neurologic abnormalities. [34,39]

Approximately one third of the children born with CHD have an underlying genetic disorder.[40] CHD with underlying genetic abnormalities or syndromes are nearly always associated with developmental DD.[41] Even more, B. Latal could show that most of the children with CHD and genetic disorder have an IQ one to two standard deviations bellow the mean (mean IQ=70), whereas children with CHD and without genetic disorder perform within the normal IQ level (mean IQ=90).[33]

The American Heart Association and the American Academy of Pediatrics published an “algorithm for surveillance, screening, evaluation, and management of developmental disorders and disabilities” in 2012. As a first step, children with CHD should be stratified into a low-risk and a high-risk group for developmental DD. Patients at high-risk are infants undergoing open heart surgery or with cyanotic CHD not requiring open heart surgery and all patients with other comorbidities, like prematurity, genetic disorders, seizures or history of extracorporeal membrane oxygenation (ECMO) support. Patients at high-risk for developmental DD should be referred for a formal developmental and medical evaluation. If a developmental DD is diagnosed a supportive therapy or intervention should be initiated. Surveillance is indicated for patients at low-risk or at high-risk with no identified DD. Periodic reevaluations should be performed for all patients.[32]

Multiple studies have demonstrated a high incidence of both brain injury and abnormal neurodevelopmental outcome in CHD patients, yet little is known about the direct impact of structural brain injury on neurodevelopmental outcome in this population.

2.3 Physiology and management of HLHS

2.3.1 Definition

HLHS is one of the most common diagnosis among the single-ventricle anomalies and responsible for 20-25% of deaths in patients with CHD.[42]

HLHS is characterized by the underdevelopment of left heart structures and which are therefore incapable of supporting the systemic circulation (Figure *1*). The diagnosis can be subcategorized based on the morphology of the left heart valves into aortic and mitral stenosis, aortic and mitral atresia, aortic atresia and mitral stenosis, aortic stenosis and mitral atresia.[43]

In the prenatal period the blood from the right ventricle is directed through the ductus arteriosus into the aorta, where it can either flow antegrade down the descending aorta or retrograde through the carotid arteries into the head vessels. Following birth the pulmonary vascular resistance declines significantly, which leads to the effect that most of the right ventricular output flows into the pulmonary circulation and a small percentage flow through the patent ductus into the systemic circulation. A closure of the ductus after birth leads to an inadequate systemic blood flow resulting in severe hypoxemia, acidosis and death.[43] Without intervention the diagnosis HLHS is almost always fatal.[44]

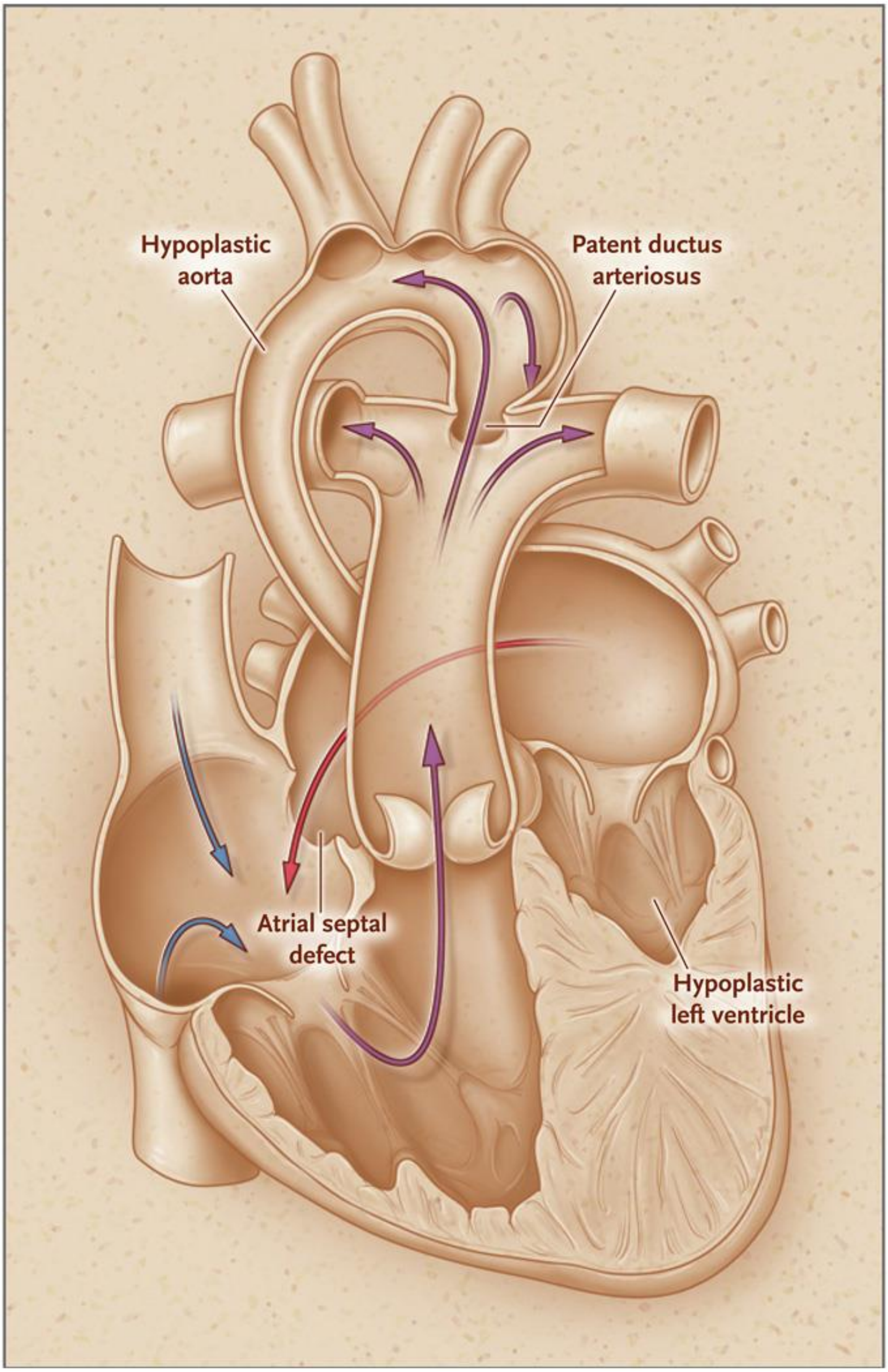

Figure 1: Hypoplastic left heart syndrome

(Reproduced with permission from Ohye et al.[45], Copyright Massachusetts Medical Society)

2.3.2 Diagnosis and Therapy

Due to advances in fetal echocardiography most of the patients with HLHS can be diagnosed prenatally.[46] The prenatal diagnosis rate of HLHS vary between 39-75% [47,48], whereby the prenatal detection rate of HLHS in pregnancy who underwent a fetal echocardiography is reported to be 97%.[49] A prenatal diagnosis allows the multidisciplinary team, composed of surgeons, fetal echocardiographers and cardiologists, an early counseling of the parents and a better preparation of the perinatal management of the neonates, including obstetrical service close to a cardiac center.[50]

Postnatal confirmation of the prenatal diagnosis or new postnatal diagnosis is usually made by echocardiography.

Nowadays, there are different approaches for HLHS repair, whereby there are two major strategies of treatment: a three-step surgery, which leads to an univentricular circulation, or heart transplantation, which is restricted due to the insufficient number of donor hearts.[51] However, every neonate diagnosed with HLHS regardless of the surgical approach needs early institution of prostaglandin E1 to keep the ductus arteriosus Botalli open and ensure a sufficient systemic perfusion.[50] After preoperative stabilization, the neonates are usually undergoing stage 1 surgery within the first week of life.

The three-step surgery, which is used in the most centers starts with the Norwood procedure, that is first described by Norwood et al. 1983. [52] During the first stage procedure (Norwood operation) a neoaorta will be reconstructed, by connecting the hypoplastic aortic arch and the main pulmonary artery, the so-called DKS (Damus–Kaye–Stansel) anastomosis and arch reconstruction, using cardiopulmonary bypass. To ensure the pulmonary circulation in the first stage operation, the reconstruction of the neoaorta can either be combined with a Sano shunt (connecting the right ventricle and pulmonary artery) or with a modified Blalock-Taussig (BT) shunt (connecting the subclavian artery and pulmonary artery).[53] The mortality after stage 1 procedure decreased to 10-20% in the last decades and depends on the expertise of the centers and can reach up to 40%.[54,55]

The second stage surgery is usually 4-6 months after stage 1 and is called bidirectional Glenn operation. The systemic to pulmonary arterial shunt will be removed and the superior vena cava will be connected to the right pulmonary artery. The procedure can be done with or without cardiopulmonary bypass.[56] The mortality following stage 2 procedure has been reported between 2-5%.[43]

The final surgery is usually done 2-3 years after stage 2 and is called the Fontan procedure. In the final stage, the inferior vena cava will be connected to the pulmonary artery using either an intraatrial tunnel, placed in the lateral wall of the right atrium, an extracardiac conduit or an intra-extracardiac conduit. The final result of the three- stage surgery is an almost complete separation of the pulmonary and systemic circulation, expect when there is a fenestration in the Fontan conduit.[57]

The single ventricle reconstruction trial demonstrated a 3- years transplantation- free survival of 61% after the Norwood procedure with a modified BT- shunt and a 6- years transplantation free survival of 59%.[58,59]

An alternative of the stage 1 Norwood procedure is the so called "hybrid procedure", first described in 1992 by Gibbs et al. [60] This approach is a combination of surgery with a banding of the pulmonary arteries and an atrial septostomy and a catheter intervention with a stenting of the arterial duct.[60]

Akintuerk et al. established the Giessen hybrid stage I procedure in 1998 based on the idea of Gibbs et al. [61] This approach is a combination of catheter intervention with a balloon atrioseptostomy and a stenting of the ductus to keep it patent, and a surgical intervention, whereby the pulmonary blood flow will be restricted by bilateral pulmonary artery banding. The reconstruction of the hypoplastic aorta is accomplished during the Glenn procedure at the age of 4-6 months.[62] Some benefits of the hybrid approach may be a better survival rate compared to the Norwood procedure (78% versus 64%) [63] particularly in high-risk patientis and a possible better neurodevelopmental outcome [64], since the high- risk surgery with cardiopulmonary bypass (CPB) is shifted from the neonatal period, to an older age.

2.3.2.1 Prenatal intervention

In fetuses with an underdeveloped left ventricle and an aortic stenosis a prenatal catheter intervention could bring some benefits in terms of the postnatal outcome and even make a biventricular repair feasible. An in-utero aortic valvuloplasty, which improves the flow through the left heart and therefore might avoid the development of hypoplastic left heart structures, can be done by experienced obstetrical and interventional catheter teams. But since the risk of fetal dismiss after the intervention is still high and the percentage of biventricular repair low, this approach is used in just a few selected centers around the world and by a stringent patient selection.[65] The percentage of biventricular repair after successful in utero aortic valvuloplasty is reported to be 30%.[66]

Since an intact or highly restrictive atrial septum leads to severe hypoxia after birth a prenatal balloon dilatation of the restrictive septum can also be performed.[67]

2.4 Physiology and management of d-TGA

2.4.1 Definition

Dextro-transposition of the great arteries (d-TGA) is one of the most common diagnosis among the cyanotic heart defects (approximately 6 %).[68]

In patients with d-TGA the aorta arises from the morphologic right ventricle, which is connected to the morphologic right atrium and the pulmonary artery arises from the morphologic left ventricle, which is connected to the morphologic left atrium, that leads to two parallel circulations (Figure 2).

In one of the circulations- the systemic circulation- the blood volume from the body flows through the right atrium and right ventricle into the aorta and back to the body, bypassing the lung. Therefore, the body is not supported with oxygenated blood. Within the second circulation- the pulmonary circulation- the blood volume from the lungs flows through the left atrium and ventricle into the pulmonary artery back into the lungs, without supporting the body with the oxygenated blood.

A distinction is made between simple and complex transposition. The simple transposition is defined as the isolated finding of atrioventricular concordance and ventriculoarterial discordance, whereas the complex transposition is combined with other malformations, such as a VSD. [69]

To ensure the survival of the patients of d-TGA at least one point of mixing the oxygenated and deoxygenated blood should be present. During the first few days after birth the point of intracardiac mixing is usually the patent ductus arteriosus.[69] After the closure of the ductus there should be an associated VSD or ASD and otherwise a balloon atrial septostomy, introduced by Rashkind 1966 [70], should be performed as soon as possible. Untreated the diagnosis of TGA usually leads to death within the first days of life.

Another type of TGA is the acyanotic defect levo- Transposition of the great arteries (l-TGA), also called as congenital corrected TGA (cc-TGA). It is described by transposed great arteries, as well as a transposition of the morphologic right and left ventricle with the corresponding atrioventricular valves.[69] In this kind of congenital heart defect, the blood volume from the body flows through the morphologic right atrium, to the morphologic left ventricle and through the pulmonary arteries into the lungs. The oxygenated blood from the lungs flow through the morphologic left atrium, into the morphologic right ventricle into the aorta and the body. These patients are usually acyanotic, since the deoxygenated venous blood from the systemic circulation returns into the lungs and the oxygenated blood flows into the systemic circulation. Patients with l-TGA are at risk for heart failure due to the decline of the right ventricular function, which supports the high-pressure arterial system. [71]

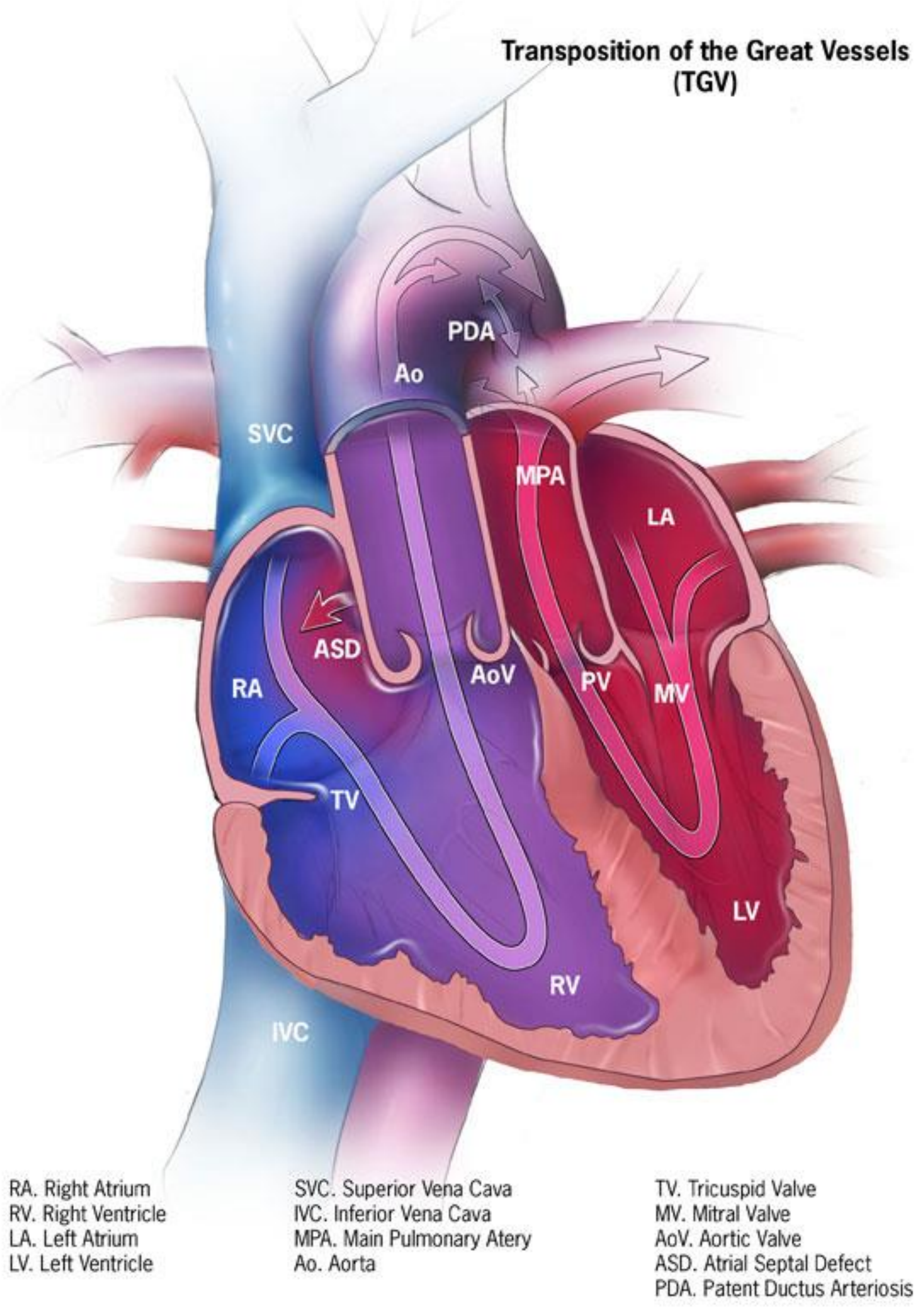

Figure 2: d-Transposition of the Great Arteries

(This image is in the public domain and thus free of any copyright restrictions [72])

2.4.2 Diagnosis and Therapy

An increase rate of diagnosis are made prenatally by fetal echocardiography, which could also predict the need of emergent postnatal balloon atrial septostomy, by evaluating the intra-atrial communication, which is essential for the survival of neonates with TGA, and could therefore improve the postnatal outcome.[50] Other benefits of prenatal diagnosis are the better counseling of the parents and a better preparation of the perinatal management.[73]

The postnatal diagnosis is usually made by echocardiography within 24 hours after birth due to the finding of a hypoxic and acidotic newborn.[74]

Since the neonates with d-TGA are dependent on an intracardiac mixing point, as described previously, soon after birth either an infusion of prostaglandin E1 to keep the ductus arteriosus open or an atrial septostomy is indicated.[69]

The procedure of choice to achieve an anatomical and physiological repair is the arterial switch procedure, which is usually done within the first two weeks of life. [74] It should better not be delayed after the first month of life, because after 4-6 weeks the left ventricle, which supports the pulmonary circulation and has therefore a low pressure load, may not be capable to acutely take over the high pressure load of the systemic circulation after the procedure.[75]

In the arterial switch operation, the ductus arteriosus will be ligated and both great arteries will be separated from their initial position. Thereupon the aorta will be connected to the morphologic left ventricle and the main pulmonary artery to the morphologic right ventricle. Coronary arteries are translocated to the neo-aorta.[74] Cardiopulmonary bypass is required during surgery. The hospital survival is reported to be close to 100%.[76] A recently published study demonstrates an overall survival of 95% 10, 20 and 25 years after an arterial switch operation.[77]

If a child is referred to the hospital for TGA repair later than 4-8 weeks of age and the left ventricle muscle mass may be inadequate to take over the systemic blood pressure after a one-stage switch operation, a (rapid) two- stage arterial switch operation is indicated, described by Jonas et al. in 1986. In the stage- one procedure, a modified Blalock shunt from the subclavian artery to the pulmonary artery is placed to prevent severe desaturations between stage-one and stage-two. Moreover, a pulmonary artery band around the main pulmonary artery is placed to increase the left ventricular pressure, which leads to an increase of the left ventricular muscle mass. In average 9 days after stage-one an arterial switch procedure, including the removal of the band and the Blalock shunt, can be performed.[78]

Three other procedures are available, which are usually done in the presence of contraindication for the arterial switch procedure like severe pulmonary stenosis. These approaches are namely the Rastelli procedure introduced in 1969, the Réparation à l'Etage Ventriculaire (REV) described 1982 and the Nikaidoh procedure first described 1984.

In the Rastelli procedure, a patch is used to create an intracardiac connection from the left ventricle, through the VSD into the aorta and an extracardiac conduit is placed to connect the right ventricle and the pulmonary artery.[69] Longtime follow- up shows a survival of 82% at 5 years of age and just 52% after 20 years of age, with a risk of 44% for reoperation due to left ventricle obstruction (16%) or obstruction of the extracardiac conduit (69%).[79]

Whereby the connection between the right ventricle and the pulmonary artery is built by placing an extracardiac conduit in the Rastelli procedure, in the REV procedure this connection is built by directly implanting the pulmonary trunk into the right ventricle. Otherwise the connection between the left ventricle and the aorta is the same as in the Rastelli procedure.[69] Five-year survival after REV procedure is reported to be 84%. The REV procedure is also associated with a high percentage of reintervention due to pulmonary valve regurgitation and right ventricular outflow tract obstruction (10%).[80]

The Nikaidoh procedure is usually used for more complex forms of d-TGA with VSD and pulmonary stenosis. This procedure avoids the creation of an intracardiac tunnel between the left ventricle and the aorta. Instead, the aorta is translocated with a direct connection through the VSD to the left ventricle and the coronary arteries to the translocated aortic root. The pulmonary artery is connected to the right infundibular area and the right ventricular outflow tract is reconstructed using a patch too.[81] Survival rate after Nikaidoh procedure is estimated to be around 95-100% after 20 years of life with 47% reoperation rate, mostly due to right ventricular outflow tract obstruction [82] or deterioration of the aortic valve function. [83]

3 Aim of the study

In this study we compared pre- and postoperative brain MRI findings using brain injury scores and determine the effect of a complex congenital heart surgery during the neonatal period and the postoperative course on morphological and physiologic findings in the brain.

As a second aim we evaluated whether pre- and postoperative brain injuries correlate with neurodevelopmental outcome in the first 2 years of life in infants with CHD. It has already been shown that there are many intra- and postoperative factors, which influence the neurodevelopmental outcome of children with CHD. [84,85] However, the impact of brain injuries on short and long-term neurodevelopmental outcome in these patients remain largely unexplored.

4 Methods

Of note: Parts of this chapter were already published.[86]

This study was approved by the Children's National Medical Center Institutional Review Board in Washington DC, as well as the Ethics committee at Justus-Liebig University, Giessen. It was a retrospective study with one patient cohort receiving CPB with DHCA.

4.1 Patient Cohort

All patients with a diagnosis of HLHS and d-TGA- born between 2009 and 2017- who underwent a complex congenital heart surgery at Children’s National Hospital in Washington DC within their first month of life were included.

All subjects with HLHS, who underwent other than a Norwood procedures and subjects with d-TGA, who underwent other than an arterial switch operation, were excluded.

Other exclusion criteria were: gestational age (GA) less than 36 weeks at birth, lab genetic abnormalities known to be associated with abnormal neurological, congenital brain abnormalities or multiple congenital anomalies.

Only subjects with pre- and postoperative brain MRIs with diagnostic-quality T1- and T2-weighted images, which were not affected by motion or other artifacts, were enrolled in the study, overall 53 patients.

4.2 Clinical Data

Medical records for all subjects were reviewed to extract the clinical data: Perioperative data, collected from electronic medical records included GA, APGAR scores, birth weight and head circumference, age at time of preoperative MRI, length of stay in the intensive care unit (ICU), length of hospital stay, duration of intubation and mortality.

Intraoperative data, including age and weight at intervention, time of CPB, aortic cross-clamp time, time of DHCA and type of procedure were also recorded.

4.3 MR Imaging

MRI studies were done pre- and postoperatively on either a 1.5 T (Discovery MR450; GE Healthcare, Waukesha, Wisconsin or Siemens Avanto, Erlangen, Germany) or 3.0 T scanner (Discovery MR750; GE Healthcare, Waukesha, Wisconsin). Scans were obtained clinically as per the institutional routine in all patients. The scans included standard T1- and T2-weighted images, diffusion-weighted imaging, susceptibility-weighted images and magnetic resonance spectroscopy. Postoperative scans were most commonly done in the days prior to discharge once the patients were stable and pacing wires were removed.

4.4 MRI Analysis- Brain Injury Score

MRIs were scored by two clinicians familiar with brain injury associated with CHD, one a pediatric neuroradiologist, the other a pediatric neurologist. Scores were assigned retrospectively and outside of regular clinical practice but because the images were not deidentified, clinicians were not considered blinded. Pre- and postoperative MR images were graded according to a scoring system devised by Andropoulos et al.[8]

Brain injuries were divided in 8 different categories: WMI, infarction (ischemic stroke), intraparenchymal hemorrhage (IPH), punctate lesions (PL), elevated lactate on magnetic resonance spectroscopy (MRS), intraventricular hemorrhage (IVH), subdural hemorrhage (SDH) and dural sinus venous thrombosis (DVST). Each severity of the injury was scored- depending on the total size of the abnormality- 0 for none, 1 for mild, 2 for moderate and 3 for severe.

For the Total Injury Score (TIS) the scores in each category were multiplied by an outcome significant multiplier: 3 for WMI, infarction, or intraparenchymal hemorrhage; 2 for punctate lesions or increased lactate on MRS; and 1 for intraventricular hemorrhage, subdural hemorrhage, dural sinus venous thrombosis (See Table *1*).

A TIS of 0 represents no injury; a score of 1 to 5 mild injury, 6 to 10 moderate injury and >10 severe injury.

Category	***Score***	***Outcome significant multiplier***	***Definition***	***Size (total mm, all lesions)***
WMI	0	3	None	0
	1	3	≤3 lesions, <2mm	1-5mm
	2	3	>3 lesions, >2mm	6-15mm
	3	3	10% white matter	>15mm
Infarction (stroke-ischemic)	0	3	None	
	1	3	< 1/3 of vascular territory of ACA, MCA, or PCA in one hemisphere	
	2	3	1/3- 2/3 vascular territory	
	3	3	>2/3 vascular territory	
IPH	0	3		0
	1	3		1-5mm
	2	3		6-15mm
	3	3		>15mm
PL (0-2mm discrete, isolated lesions; emboli from platelet/fibrin clot, air, other particulate material)	0	2	none	0-2mm
	1	2	1-3 lesions	All ≤ 2mm
	2	2	4-6 lesions	All ≤ 2mm
	3	2	>6 lesions	All ≤ 2mm
Elevated Lactate on MRS	0	2	Lac/Cr ratio ≤0.15	
	1	2	Lac/Cr ratio 0.16-0.5	
	2	2	Lac/Cr ratio 0.5-1	
	3	2	Lac/Cr ratio >1	
IVH	0	1	none	

	1	1	Subependymal/ germinal matrix hemorrhage/ choroid plexus hemorrhage	1-5mm
	2	1	IVH—isolated	6-15mm
	3	1	IVH with ventricular dilation	>15mm
SDH	0	1	Subdural blood above tentorium; minimal SDH below tentorium (usually birth related)	
	1	1	Minimal just above tentorium	
	2	1	Spread to interhemispheric fissure in occipital area	
	3	1	Larger hemorrhage; interhemispheric to parietal or frontal area; any mass effect	
DVST	0	1	none	
	1	1	R or L transverse alone	
	2	1	Bilateral R and L	
	3	1	Straight and/or sagittal sinus	

Table 1: Brain Injury Scoring System [8]

4.5 Outcome Scores

At the Children's National Hospital in Washington, patients with CHD including surgery with CPB are scheduled for appointments with a pediatric neurologist and developmental psychologist after discharge as part of the Cardiac Neurodevelopmental Outcome (CANDO) program. Based on assessments from these clinical appointments, two different outcome scores were assigned to quantify the neurodevelopmental outcome of the patients.

4.5.1 Pediatric Version of the Glasgow Outcome Scale–Extended

The Glasgow Outcome Scale-Extended (GOS-E) is the most commonly used score to measure the outcome of adults after traumatic brain injury in clinical trials.[87] Beers et al.

modified the GOS-E score to measure the Outcome of patients < 17 years of age after brain injuries.[88]

The Pediatric version of the GOS-E (GOS-E Ped) is a measure of functional outcome of patients <17 years of age after brain injuries. It evaluates the functional independence inside and outside home, capacity for school, participation in social and leisure activities and psychological problems, which affects the interaction with family or friends.

The GOS-E Ped was divided into 4 different categories: 1= good recovery, 2= moderate disability, 3= severe disability, 4= death.

1- "No physical or psychical limitations affecting the daily live" or "psychological problems occasionally (less than weekly) effecting the interaction with family or friends/ patient participating a bit less in social and leisure activities than before (at least half as often)"
2- "Psychological problems frequently effecting the interaction with family or friends", "patient participating much less in social and leisure activities than before (less than half as often)", "reduced capacity for school"
3- "Patient does not behave age appropriately outside home", "patient need frequent help at home" and "patient is not able to follow simple commands or communicate"
4- death

4.5.2 Pediatric Stroke outcome measure

The Pediatric Stroke outcome measure (PSOM) is a measure of neurologic deficits, using 5 categories: sensorimotor function, expressive language, language comprehension, behavior/state regulation and cognition.[89] Each category has 4 different scores: 0 for no deficit, 0.5 for mild deficit, 1 for moderate deficit and decreased function, or 2 for severe deficit and missing function.

To describe the severity of the outcome the following criteria were used:

- Normal: 0-0.5 in all subscales
- Mild: 1 in 1-2 subscales and <1 in remaining subscales
- Moderate: 1 in ≥3 subscale or 2 in 1 subscale and <2 in all remaining subscales
- Severe: 2 in ≥2 subscales

Normal to mild deficits were classified as good outcome, moderate and severe deficits were classified as poor outcome.

4.6 Statistical Analysis

Univariate analyses were performed with the Mann-Whitney U-test for continuous (non-normally distributed) variables, Student t-tests for normally distributed variables and Fisher's exact test for categorical or binary variables to evaluate differences between HLHS and d-TGA groups. Changes for HLHS and d-TGA in ordinal brain injury scores between preop and postop were assessed by the Wilcoxon signed-ranks test and presented as median scores and interquartile ranges (IQR). Diagnosis, duration of DHCA, ICU length of stay, duration of ventilation and preoperative total injury score were analyzed as candidate predictors of adverse neurologic outcome. Backwards stepwise multivariable logistic regression modeling with the likelihood ratio test used to assess significance (threshold of $p < 0.05$ was used for entry and $p < 0.10$ for removal from the model) was used to define risk factors for worse GOS-E and PSOM scores and derive odds ratios and 95% confidence intervals. It was also used to identify independent risk factors for moderate to severe postoperative brain injuries (Total brain injury score ≥6). Receiver operating characteristic (ROC) curve analysis was applied to identify optimal cut- off values of continuous predictor variables using the Youden J-index. To identify candidate predictors of moderate to severe postoperative WMI, infarction and intraparenchymal hemorrhage the subcategories were analyzed as binary categories. PSOM scores were grouped as normal/mild deficits (Score 0 to 1) and moderate/severe deficits/death (Score 2 to 4). GOS-E scores were divided into good recovery (Score 1) and moderate to severe disabilities (Score 2 to 4). Statistical analysis was performed using IBM SPSS Statistics (version 24.0, IBM Corporation, Armonk, NY). Two-tailed values of $p<0.05$ were considered statistically significant without any adjustments for multiple testing and multiple endpoints and therefore should be regarded as exploratory evidence.

5 Results

Of note: Parts of this chapter were already published.[86]

Fifty-three patients met our criteria and were included in the study. Twenty-four with the diagnosis of HLHS and twenty-nine with the diagnosis d-TGA underwent open heart surgery in the time between 2009 and 2017 at Children's National Hospital in Washington DC, USA. The characteristics of the cohort are summarized in Table 2.

The patients with HLHS were younger at the day of surgery ($p=0.005$), had a longer duration of DHCA ($p<0.001$), longer duration of ventilation ($p=0.004$) and a longer stay on cardiac ICU ($p<0.001$) and in the hospital ($p<0.001$), whereas the patients with d-TGA had a longer time on CPB ($p<0.001$) and a longer aortic cross-clamp time ($p<0.001$). Intra- and postoperative parameter are presented in Table 3.

Twenty three of 29 patients with d-TGA (79%) required balloon atrial septostomy (BAS) before surgery (age= 973 ± 2090 minutes).

Two patients (8%) in the group of HLHS required ECMO after surgery and one patient in the group of d-TGA (3%) ($p=0.586$). Two patients with HLHS had a cardiac arrest after surgery, of which one required ECMO. No patient with d-TGA had a postoperative cardiac arrest. All patients with postoperative ECMO or cardiac arrest survived the first 2 years of live.

Four patients (17%) in the group of HLHS died, three within the first year of life (17, 19 and 35 weeks of age) and one at 82 weeks of age. 100% in the group of d-TGA survived the first 2 years of live.

Parameter	HLHS, Mean ± SD	d-TGA, Mean ± SD	p value
Male	16 (67%)	18 (62%)	0.780
Prenatal diagnosed	23 (96%)	20 (69%)	**0.015***
Birth weight (g)	3152 ± 578	3250 ± 565	0.681
Gestational age at birth (weeks)	38 ± 1	38 ± 1.2	0.130
Average age at preop MRI (days)	2.7 ± 2.1	2.8 ± 1.5	0.286
Average age at surgery (days)	5.4 ± 2.5	6.6 ± 2.4	**0.005***
Average weight at surgery (g)	3124 ± 550	3403 ± 595	0.509
Average time between surgery and postop MRI (days)	37 ± 22	16 ± 13	**<0.001***

d-TGA: d-Transposition of the great arteries; HLHS: hypoplastic left heart syndrome; MRI: magnetic resonance imaging

*Statistically significant

Table 2: Characteristics of The Cohort

Parameter	HLHS Median (IQR)	TGA Median (IQR)	p value
CPB time (minutes)	145 (133-169)	188 (158-206)	**<0.001***
Aortic cross clamp time	41 (0-50)	114 (106-125)	**<0.001***
DHCA time (minutes)	50 (42-56)	9 (8-12)	**<0.001***
ICU length of stay (days)	28 (19-47)	13 (10-23)	**<0.001***
Hospital length of stay (days)	56 (34-79)	19 (16-34)	**<0.001***
Duration of ventilation (days)	15 (7-35)	7 (4-10)	**0.004***

CPB: Cardiopulmonary bypass; DHCA: deep hypothermic circulatory arrest; ICU: intensive care unit

*Statistically significant

Table 3: Intra- and Postoperative Parameter

5.1 Brain Injury Score

All patients had pre- and postoperative brain MRI studies as soon as the neonates were clinical stable and could safely transported to the MRI examination. The preoperative MRI examination was done at day of life 2 ± 1.8 and the postoperative scan 25 ± 20.4 days after surgery.

Preoperative brain injuries were present in 53% of all patients (40% HLHS; 63% d-TGA). The most common preoperative brain injuries in the group of HLHS were IVH (20%), WMI (20%) and infarctions (16%), whereas subdural hemorrhage (27%) and WMI (23%) were the most frequently seen injuries in patients with d-TGA. The median preoperative total brain injury score for the HLHS group was 0 (IQR 0-3) and 1 (IQR 0-3) for the d-TGA group.

Sixteen patients (30%) had no preoperative and only postoperative lesions noted on MRI (9 HLHS, 7 d-TGA). New lesions (defined as an increase in number or size of preoperative lesions or new type of lesion) were seen in 30 out of 53 patients (57%). The incidence of postoperative brain abnormalities was 72% in patients with HLHS and 77% in patients with d-TGA. The most common new postoperative brain injuries were WMI (33%) and infarction (33%) for HLHS patients and punctuate lesions (26%) and SDH (22%) for d-TGA patients. The median postoperative total brain injury score for the HLHS group was 4 (IQR 1-8) and 3 (IQR 1-5) for the group of d-TGA.

Pre- and postoperative brain MRI findings are presented in Table 4. Examples of different brain lesions in MRI are present in Figure 3-6.

Differences based on the TIS were not seen between the groups, neither preoperatively ($p=0.436$) nor postoperatively ($p=0.195$). (Figure 5)

A significant increase of the TIS from preoperative to postoperative within a group was seen in both groups (HLHS: $p=0.006$; d-TGA: $p=0.017$). (Figure 5)

A diagnosis of HLHS correlated with an increased risk for moderate to severe postoperative infarction (size > one-third of a vascular territory in one hemisphere) ($p=0.017$). The length of stay in ICU was significantly associated with a moderate to severe total injury score (total score ≥6) on postoperative brain MRI ($p<0.001$). Among the 17 patients with a moderate to severe postoperative total injury score (≥6), the median (IQR) cardiac ICU time was 33 days (21-55 days) compared to 14 days (10-22 days) for the other 36 patients with postoperative injury scores less than 6 ($p<0.001$).

Of note, BAS was not associated with an increased risk for preoperative brain injury in the d-TGA group. Specifically, patients with d-TGA, who underwent a BAS, neither show a higher preoperative total brain injury score ($p=0.934$), nor a higher preoperative prevalence of WMI (p=0.380), infarction (p=0.910) or intraparenchymal hemorrhages (p=0.070) compared to patients without BAS.

Parameter	HLHS n, %	d-TGA n, %33	p value	Total
Any preoperative finding	10 (40%)	19 (63%)	0.108	29 (53%)
Preoperative WMI	5 (20%)	7 (23%)	1.000	12 (22%)
Preoperative infarction	4 (16%)	2 (7%)	0.394	6 (11%)
Preoperative IP hemorrhage	1 (4%)	0 (0%)	0.455	1 (2%)
Preoperative punctate lesions	2 (8%)	3 (10%)	1.000	5 (10%)
Preoperative elevated lactate in MRS	0 (0%)	3 (10%)	0.242	3 (5%)
Preoperative IVH	5 (20%)	2 (7%)	0.226	7 (13%)
Preoperative SDH	2 (8%)	2 (7%)	1.000	4 (7%)
Preoperative DVST	0 (0%)	0 (0%)	1.000	0 (0%)
Any postoperative finding	18 (72%)	23 (77%)	0.762	41 (75%)
Postoperative WMI	12 (48%)	7 (23%)	0.087	19 (35%)
Postoperative infarction	8 (32%)	3 (10%)	0.088	11 (20%)
Postoperative IP hemorrhage	2 (8%)	1 (3%)	0.586	3 (5%)
Postoperative punctate lesions	4 (16%)	13 (43%)	**0.04***	17 (31%)
Postoperative elevated lactate in MRS	0 (0%)	1 (3%)	1.000	1 (2%)
Postoperative IVH	6 (24%)	6 (20%)	0.754	12 (22%)
Postoperative SDH	1 (4%)	8 (27%)	**0.031***	9 (16%)
Postoperative DVST	0 (0%)	0 (0%)	1.000	0 (0%)
Any new post-operative finding	12 (48%)	14 (47%)	1.000	26 (47%)

DVST: Dural sinovenous thrombosis; IP: intraparenchymal; IVH: intraventricular hemorrhage; MRS: magnetic resonance spectroscopy; SDH: subdural hemorrhage; WMI: white matter injury

*Statistically significant

Table 4: Pre- and Postoperative Brain Injuries

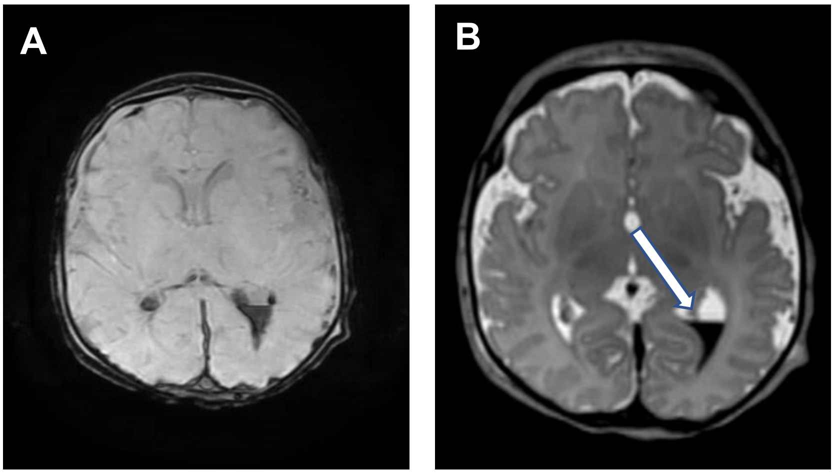

Figure 3: Example of an intraventricular hemorrhage on axial SWAN sequence (A) and axial T2-weighted image (B)

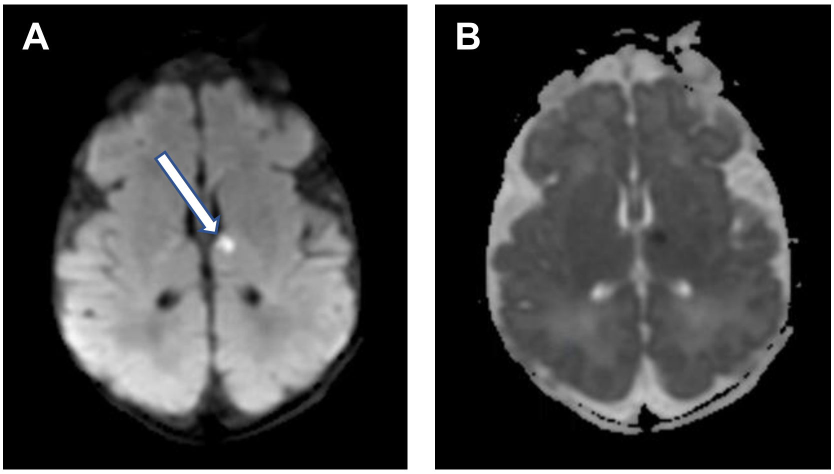

Figure 4: Example of an acute ischemic lesion on Diffusion weighted image (A) and Apparent diffusion coefficient (B)

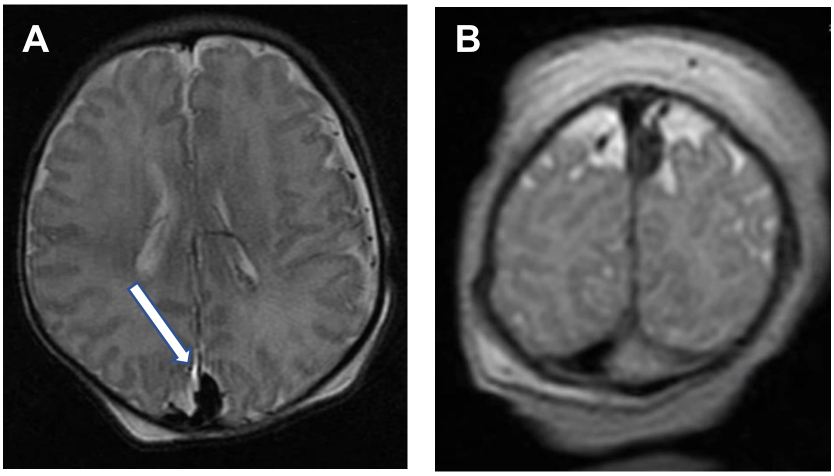

Figure 5: Example of a subdural hemorrhage on axial (A) and coronal (B) T2- weighted image

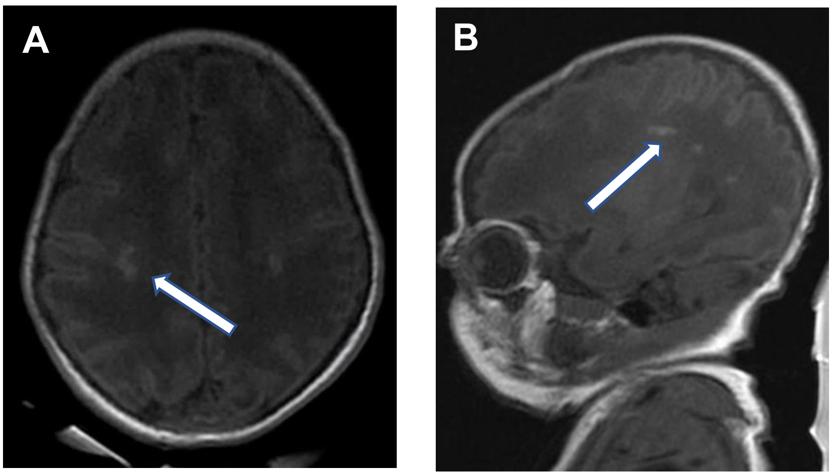

Figure 6: Example of white matter lesions on axial (A) and sagittal (B) T2- weighted image

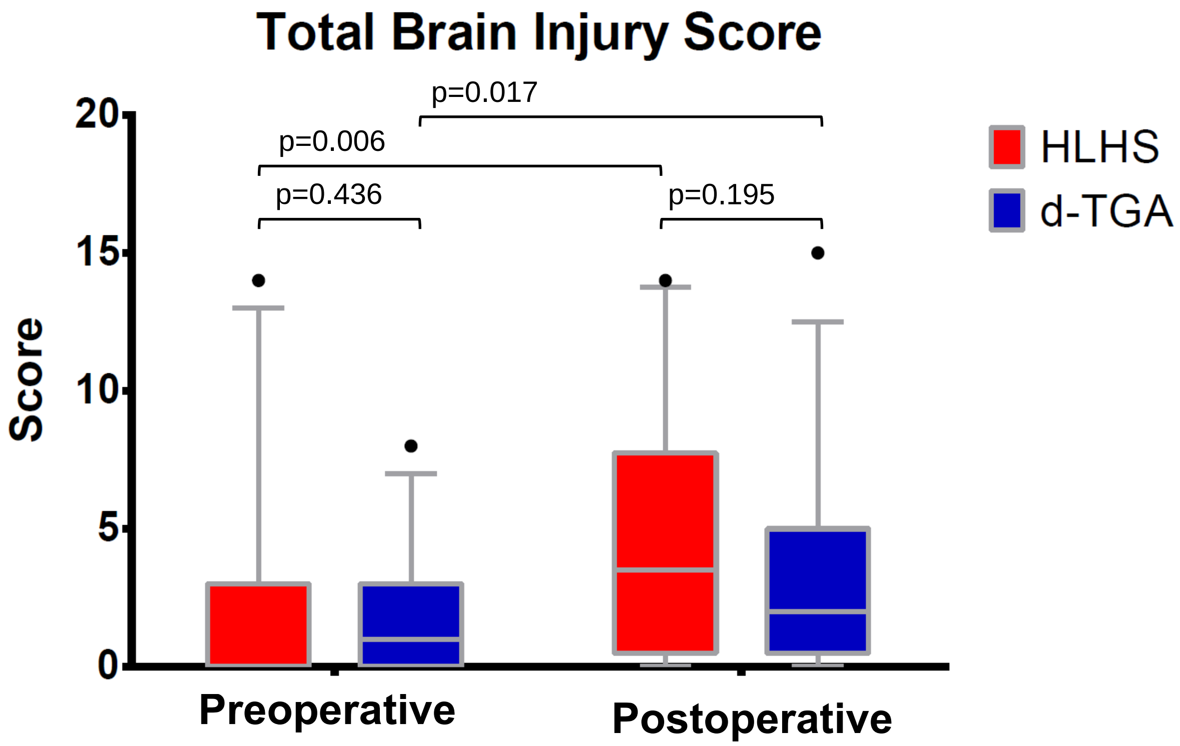

Figure 5:Box and whiskers plot of Total Injury Scores in HLHS and d-TGA

5.2 Neurological Outcome

Eight patients were lost for follow-up. Forty-five out of 53 patients (85%) underwent a neurologic assessment between 5 month and 23 months of age. The median age of neurologic assessment was 10 ± 6 months.

An abnormal assessment was seen in 49% of the patients, whereby 82% of the HLHS patients and 17% of the d-TGA patients had an abnormal examination ($p<0.001$).

PSOM and GOS-E scores were highly correlated with each other ($r_s=0.916$, $p<0.001$).

The mean GOS-E scores were 3.86 ± 2.122 in patients with HLHS and 1.54 ± 0.932 in patients with d-TGA ($p<0.001$). The mean PSOM scores were 1.82 ± 1.296 for the HLHS group and 0.25 ± 0.608 for the d-TGA group ($p<0.001$). (Figure *6*Figure *6*)

The multivariate regression analysis showed a significant correlation between DHCA longer than 40 minutes (odds ratio [OR] =11.6; 95% CI, 2.0-74.7; p=0.005) and total duration of ventilation more than 12 days (OR= 17.9; 95% CI, 2.8-113.3; $p<0.001$) and moderate to severe deficits based on PSOM scores. (Figure *7*Figure *7*)

DHCA more than 40 minutes (OR= 14.3, 95% CI, 2.5-84.7, $p<0.001$) and a total duration of ventilation more than 12 days (OR= 13.9; 95% CI, 2.3-84.0; p=0.002) were predictive for moderate to severe disabilities based on GOS-E scores. (Figure *8*Figure *8*)

Of note, 75% of the patients with DHCA time more than 40 minutes showed a Total Injury Score ≥1 on postoperative brain MRI.

ICU length of stay more than 24 days (PSOM: p=0.724; GOS-E: p=0.860) and moderate to severe preoperative brain injuries (PSOM: p=0.359; GOS-E: p=0.787) were neither predictive for worse PSOM scores nor for worse GOS-E scores.

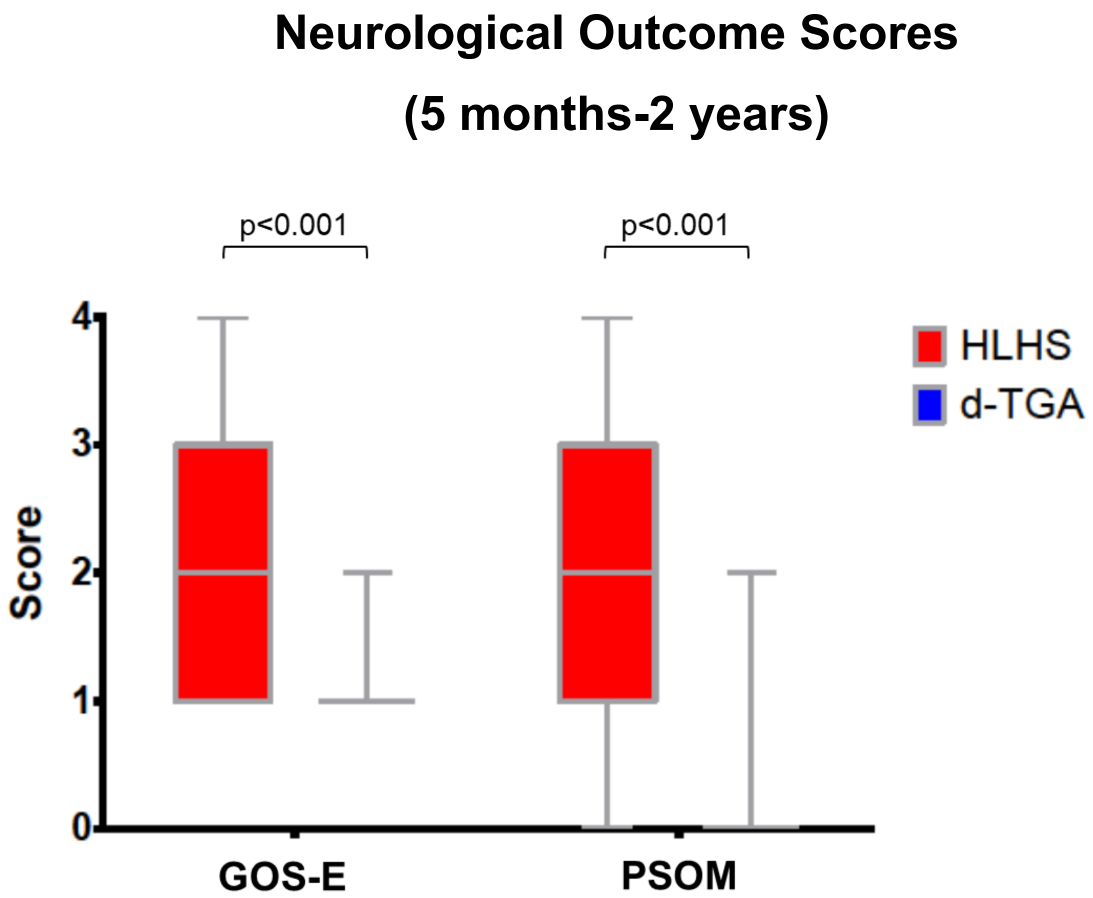

Figure 6: Box and whiskers plot of neurological outcome scores in HLHS and d-TGA

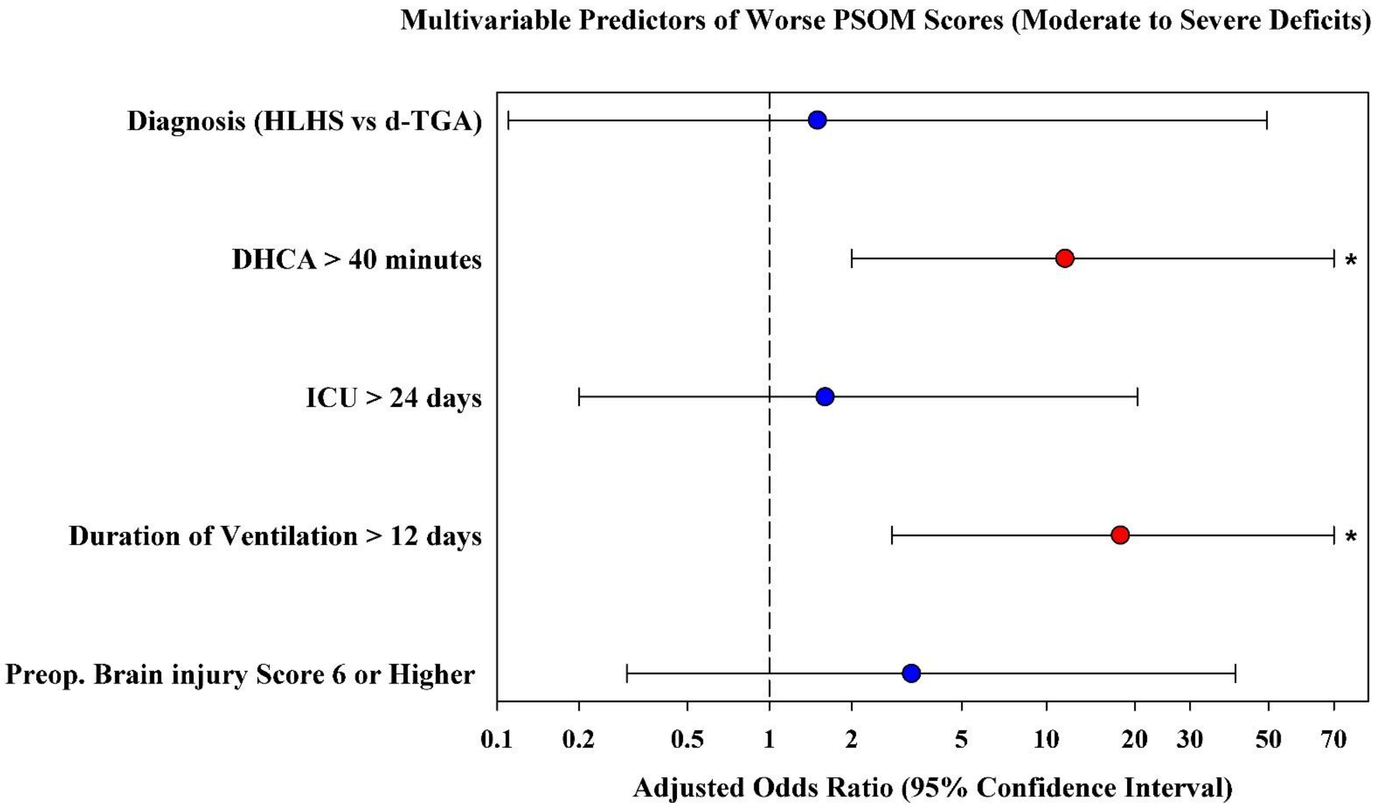

Figure 7: Multivariable predictors of worse PSOM Scores

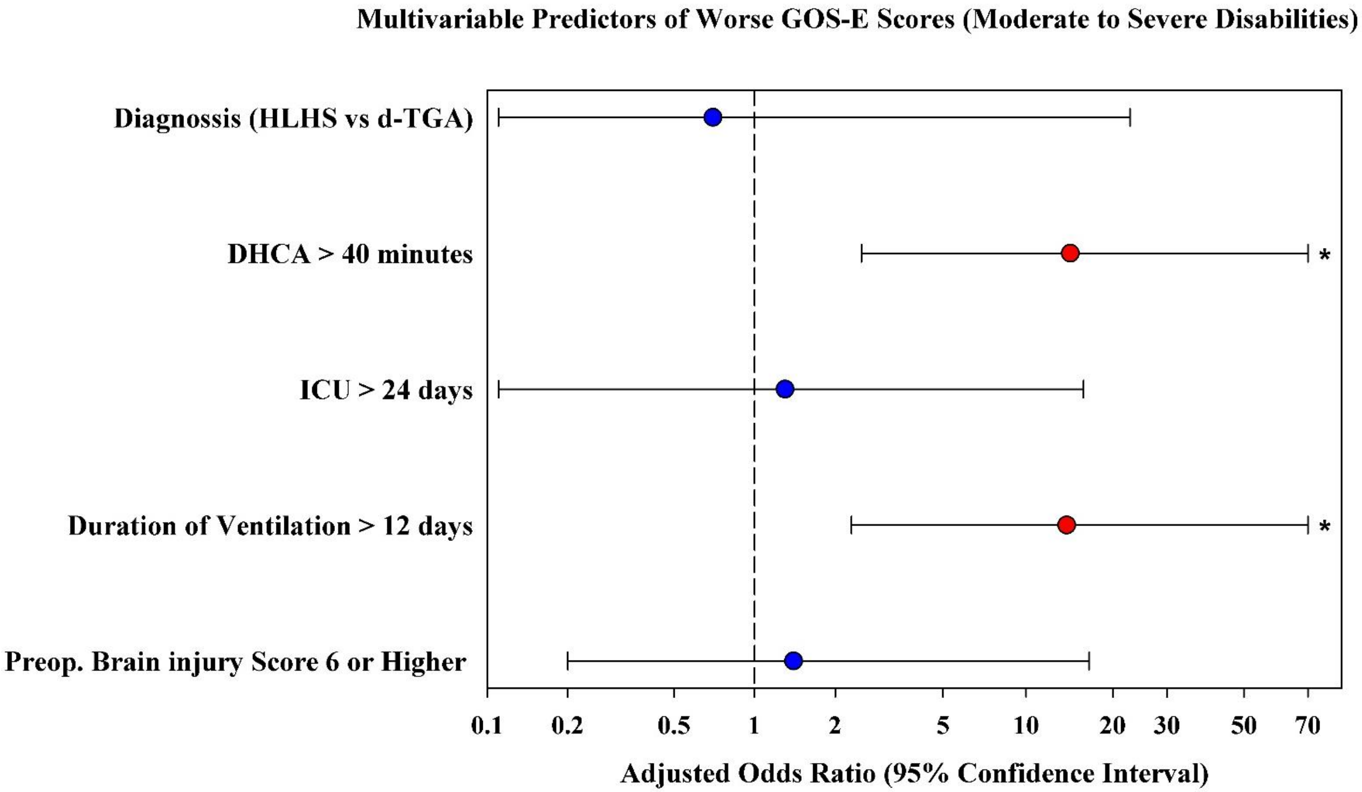

Figure 8: Multivariable predictors of worse GOS-E Scores

6 Discussion

Of note: Parts of this chapter were already published.[86]

In this retrospective study, we evaluated the impact of patient characteristic, clinical factors and structural brain injury severity on neurological outcome within the first 2 years of life. Abnormal brain MRI findings were present in 53% of the patients prior to surgery and 73% after surgery. New postoperative findings were seen in 55%. The most common brain MRI findings were IVH, WMI and infarctions in the group of HLHS and WMI in patients with d-TGA. The incidence of perioperative brain injuries in our study is concordant with other studies. [8,16,90] The severity of brain injuries does not differ between both groups, neither preoperatively nor postoperatively, even though patients with HLHS have more perioperative risk factors, such as younger age at surgery, longer timer of deep hypothermic circulatory arrest or longer duration of intubation.

49% of the total group had an abnormal neurologic assessment in the time between 5 month and 2 years of age. Independent risk factors for adverse neurological outcome in our cohort were DHCA >40 minutes and longer duration of ventilation, which is also consistent with previously published studies. [37,90,91]

6.1 Perioperative brain injuries

In 2007, McQuillen et al. reported a high rate of new postoperative brain lesions with WMI predominance in their study of sixty-two patients with CHD. New acquired brain injury in their study cohort were primarily seen in patients with single ventricles who underwent a Norwood procedure. [16] In our study, we also noted a high rate of new postoperative lesions (57% of the patients), including a high prevalence of WMI. However, in our cohort, new postoperative lesions subtypes varied based on the CHD diagnosis. Specifically, infants with either HLHS or d-TGA were found to have similar total brain injury scores but differences in injury subcategories were noted. For example, a greater incidence of hemorrhage in the d-TGA group was noted on the postoperative scans. Microhemorrhage, intraventricular hemorrhage and subdural hemorrhage were most commonly seen, all which historically are less likely to impact neurological outcome. [8,92] Newly acquired postoperative injuries found in the HLHS cohort, were primarily WMI and infarction. A possible explanation for this finding could be due to the fact that the postoperative MRI scan of patients with d-TGA was done 11 days after surgery on average and thus the hemorrhages were still present, whereas the scans in the HLHS group were done 30 days postoperative and therefore some of the hemorrhages could already be absorbed by the body.

Prior studies have shown an increased risk of infarction after BAS [74,93], but this association is not consistent in the literature. [15,94,95] Kelly et al. suggest that the patients who undergo BAS have the greatest burden of hypoxia and are therefore at higher risk of brain injuries. [96] Perhaps the failure to consistently demonstrate increased injury in this vulnerable population relates to the timing of the BAS and the associated supportive care received. BAS was not associated with an increased risk for preoperative brain injury in our cohort, including infarction, white matter injury and hemorrhage which may be a reflection our center's high rate of early BAS and cardiac focused perinatal care.

McQuillen et al. suggested that preoperative brain injuries are more common in patients with two-ventricle lesions, whereas new postoperative MRI abnormalities are more frequently seen in patients with single- ventricle lesions.[16] This could support the assumption that prenatal or preoperative factors, possibly more present in the group of single-ventricle lesions, but not yet defined, make the brain more susceptible for further injuries during surgery. In our study we could find more patients with preoperative brain injuries in the group of d-TGA indeed, but we could not identify more patients with new postoperative injuries in the HLHS group. This can be explained in part by the small sample size of just 24 patients with HLHS in our cohort.

We found a significant increase of the total injury score in both groups from pre- to postoperative, that confirms the finding of Andropolous et al. [8] This finding would emphasize the previously described assumption that prenatal or preoperative factors, not yet defined, make the brain more susceptible for further injuries during surgery. However, none of our assessed risk factors correlated with the increase of the severity of brain injuries. Andropoulos et al. and McQuillen et al. suggested that the severity of postoperative brain injuries could be associated with the technique of the CPB.[8,16]

6.2 Neurological outcome

Independent risk factors for adverse neurological outcome in our cohort were DHCA >40 minutes and longer duration of ventilation, which is also consistent with previously published studies.[37,90,91]

Kosiorek et al. recently showed that also in a population of patients who underwent open heart surgery without DHCA prolonged mechanical ventilation is an independent risk factors for worse neurological outcome. [97]

In univariate analysis, infants with HLHS were identified to have worse developmental outcome compared to those with d-TGA but CHD subtype did not predict outcome in the multivariate analysis. These groups differed significantly in terms of operative and perioperative management and therefore infants with HLHS as a group had longer duration of pre- and postoperative ventilation and longer stay in ICU. The discrepancy of developmental outcome comparing patients with single ventricle CHD and d-TGA has also been identified by other studies using univariate regression analysis.[90,98,99] However, similar to our study, these studies were also unable to confirm this finding in a multivariate regression analysis. [90,99] In repeated analyses, the clinical factors appear to surpass the CHD diagnosis as stronger predictors of adverse neurodevelopmental outcome.[90,99] Perhaps, future larger studies using a more substantive tool for measuring outcome, like the Bayley Score of Infant Development and/or multivariate regression analyses may better determine the association between CHD diagnosis and adverse outcome.

Many studies in the last two decades have defined risk factors associated with adverse neurologic outcome in children with CHD.[8,91,93,99,100]

Historically there have been concerns that the use of DHCA increases the risk of perioperative brain injury and adverse neurological outcome in children with CHD. However, there are a growing number of studies that suggest a limited period of DHCA does not affect the neurological outcome.[37,101] Investigators from the Boston Circulatory Arrest Trial concluded that only a duration of DHCA beyond 41 minutes affects the neurological outcome.[37] Our results support the concept that DHCA greater than 40 minutes is an independent risk factor for poor neurologic outcome.

While several studies have investigated potential risk factors for perioperative brain injury and adverse neurological outcome, the relationship between structural brain injury and abnormal neurological outcome is still not well understood.

Beca et al. performed the largest study to date, investigating the impact of brain injuries on neurologic outcome.[102] In this multicenter study they examined 153 infants with mixed CHD diagnosis, who underwent congenital heart surgery with or without CPB and evaluated the neurodevelopmental outcome at 2 years of age using the third edition of the Bayley Scales of Infants and Toddler Development (Bayley-III). Brain MRI findings were classified as focal infarction, WMI or hemorrhage. A correlation between the Bayley Scales and brain injuries was not found. They found that the diagnostic group was the strongest predictor for new postoperative WMI. Similar to the results of our study, Beca et al. showed that single ventricle patients are at greatest risk for new postoperative WMI.

More recently, Claessens et al. reported an association between perioperative brain injury, especially WMI, and reduced brain volumes and adverse cognitive, behavioral and motor outcome at 2 years of age.[103] These findings confirm the findings of Andropoulos et al., who also described an association between new postoperative WMI and worse cognitive outcome at 12 months of age in a group of varying types of CHD.[91] Compared to Beca et al., who analyzed brain injury only as dichotomous predictor, Claessens et al. also included brain volumes and cortical measures, such as the inner cortical surface and a gyrification index. Neonates with worse neurodevelopmental outcome showed smaller brain volumes and decreased cortical measures in this study.[102]

While much has been learned regarding specific influences on neurodevelopmental outcome and perioperative brain injury, such as the duration of DHCA, ICU length of stay, duration of ventilation or nonmodifiable patient characteristics, the impacts of altered cerebral development and acquired brain injury on the neurodevelopmental outcome of CHD patients are complex and multifaceted. Inconsistencies in the literature may indicate variations amongst CHD subtypes and the postnatal care received that still need to be explored.

Of note is that, Peyvandi et al. recently suggested that the timing of neurodevelopmental assessment could influence the predictive value of brain injuries on neurological outcome. They showed that only clinical factors, such as cardiac lesion, BAS and maternal education, were associated with worse 12 months Bayley Scales. However, brain injury scores were significantly associated with lower Bayley Scales at 30 months follow-up.[104] Also, McGrath et al. pointed out, that neurodevelopmental status at 1 years of age modestly predict the status at school age and long-term follow-ups are necessary to predict the risk for adverse developmental outcome. They demonstrated that children with d-TGA with deficits at 8 years of age frequently have a normal performance at 1 year of age.[105] These findings could be an explanation why we could not find an association between brain injuries and the developmental outcome within the first 2 years of life in our cohort. A correlation could possibly be demonstrated on follow-ups beyond 24 months of age when cognitive and language skills are more accurately tested. Also, patients with HLHS are typically undergo multiple surgeries with CPB. Therefore, neurodevelopmental testing in the first 2 years of life may underestimate the cumulative impact of hospital time and of multiple surgeries on performance at school-age. Moreover, assessment of neurodevelopmental outcome using the Bayley Score of Infant Development, the gold standard for the assessment of outcome of infants, may have allowed for a better correlation between brain injuries and neurodevelopmental outcome within the first 2 years of life.

6.3 Limitation

The present study has several limitations. It was a single center study with a retrospective study design and a small sample size, which limits the statistical power of the analysis. Furthermore, we do not have a control group of either healthy neonates or CHD patients without DHCA or CPB. Only patients with pre- and postoperative MRI scans were included. Therefore, the sickest neonates may be excluded, either because they were not stable enough to undergo a preoperative MRI scan or they died after surgery and for this reason did not undergo a postoperative MRI examination. Moreover, preoperative brain MRI exams were first included into our routine clinical practice in 2009. The consistency of these screening MRIs improved as the program developed and became more standardized. As a result, the patients receiving clinically indicated brain MRIs may have included more screening MRIs over time.

Also, in order to capture a homogeneous group of patients for comparison of clinical variables, we did not include patients born prior to 36 weeks gestation. Because we did not include babies born at <36 weeks in our analysis, our findings may not be applicable to all d-TGA and HLHS patients treated with surgery in the neonatal period.

Also, as our patients were not sedated for their MRI study, they needed to be clinically stable before the scan could be obtained safely. Consequently, the time between surgery and the postoperative MRI scan is variable. The MRI scans for d-TGA patients were on average 2 weeks earlier compared to the HLHS group. The inconsistency in the timing of the postoperative scan may have impacted certain aspects of the scoring, especially in the subcategories IVH, MRS and subdural hemorrhage, which were more commonly seen in the d-TGA group. Also, WMI lesions can become less visible with time.

Eight patients were lost for follow-up and did not have outcome scores assigned which is a significant portion of total patients in this small cohort and may have impacted the analysis. Also, the age range used for assigning neurological outcome covers a broad range of early development that likely impacted sensitivity of the testing. Follow up assessments were made over a broad range of ages (5 months to 23 months). Due to normal developmental progressions, assessment in infancy is less sensitive at detecting deficits than those obtained in toddlers. Also, due to the retrospective design of the study, the Bayley Score of Infant Development, a more substantive tool for measuring development, was not used. To compensate for the inherent limitations of a retrospective assessment, we chose to two complimentary measures of outcome; the PSOM which emphasizes the neurological examination and the GOS-E Peds which focuses on functional outcome. Also, scores were assigned by a single clinician so that scores could be consistently assigned across the spectrum of ages. Finally, neurodevelopmental outcome has been shown to be associated with socioeconomic status (SES). No SES variable was included in this analysis which may have impacted outcomes. Furthermore, the reoperation and re-intervention rate of patients with CHD could have a substantial impact on the neurodevelopmental outcome, which were not included in our analysis. Further larger studies are in preparation and will consider the reoperation and re-intervention rate.

6.4 Conclusion and Perspectives

In this study of neonates undergoing surgery for HLHS or d-TGA, prolonged mechanical ventilation and extended duration of DHCA were associated with worse early neurological outcome scores. Brain injury was commonly seen by MRI before and after surgery but no correlation between the total brain injury score and adverse neurological outcome was seen in the first 2 years of life. Neurological outcome seems to be more affected by the clinical course than by the CHD diagnosis itself.

Future studies that include neurodevelopmental assessments beyond 24 months of age may shed further light on the impact of brain injury in the neonatal period on more longterm neurodevelopmental outcome. Moreover, other studies should include patients who underwent open heart surgery with and without DHCA, as well as with and without CPB to investigate the effect of different surgical approaches on MRI findings and neurologic outcome.

Nagaraj et al. demonstrated that neonates with CHD have lower regional and global cerebral blood flow before open heart surgery compared with healthy controls. [106] Potential approaches for further studies could be to compare pre- and postoperative cerebral blood flow and determine factors influencing the brain perfusion. Moreover, the association of impaired brain perfusion and worse neurologic outcome should be investigated.

The role of the placenta-heart axis and their impact on the fetal brain development in pregnancies carrying fetuses with CHD is still mostly ununderstood.[107] Prior studies could show that placental abnormalities, such as infarction, calcification or histologic chorioamnionitis are frequently seen in in pregnancies carrying fetuses with CHD.[108] It is also reported that the placenta in CHD is smaller compared to healthy controls.[109]

However, more studies are needed to examine the effect of placental and cardiac dysfunction on brain development and long-term neurodevelopmental outcome.

7 Summary

Objectives: To determine the impact of surgical and therapeutic risk factors on pre- and postoperative brain MRI findings and to evaluate the association of patient characteristics, perioperative risk factors and brain imaging abnormalities on neurologic outcome in patients with hypoplastic left heart syndrome (HLHS) or d-transposition of the great arteries (d-TGA) who underwent cardiac surgery including cardiopulmonary bypass as neonates.

Methods: We performed a retrospective analysis to identify neonates with HLHS and D-TGA who underwent cardiac surgery at a single center between 2009 and 2017. Patients born <36 weeks' gestation, those with genetic abnormalities known to be associated with abnormal neurodevelopment, congenital brain abnormalities or multiple congenital anomalies were excluded. Andropoulos' Brain Injury Scores were calculated from pre- and postoperative brain magnetic resonance images (MRI). Patient characteristics, perioperative risk factors and brain MRI findings were correlated to outcome assessments performed on patients between 5 months and 2 years of age. Neurologic deficits were quantified using the Pediatric Stroke Outcome Measure (PSOM) and functional outcome was evaluated using the Pediatric Version of the Glasgow Outcome Scale–Extended (GOS-E). The risk factors for worse neurodevelopmental outcome were assessed using multivariate logistic regression.

Results: Twenty-four neonates with HLHS and twenty-nine neonates with D-TGA were identified and met our enrollment criteria. Preoperative brain MRI was abnormal in 53% of the patients and postoperative MRI findings were abnormal in 72% of the patients. Both groups showed a significant upward change in median total brain injury score from the preoperative to postoperative study (HLHS: p=0.006; d-TGA p=0.017).

Duration of ventilation more than 12 days and deep hypothermic circulatory arrest (DHCA) longer than 40 minutes were associated with worse PSOM and GOS-E scores. MRI measures of brain injuries were not associated with worse outcome by PSOM or GOS-E.

Conclusion: For HLHS and d-TGA patients, duration of mechanical ventilation and DHCA are associated with adverse neurologic outcome. Neonatal brain MRI commonly demonstrates acquired brain injuries, but the clinical impact of these abnormalities are not often seen before 2 years of age.

8 Zusammenfassung

Ziele: Bewertung des Einflusses von operativen und therapeutischen Risikofaktoren auf prä- und postoperativen Auffälligkeiten in MRT Befunden des Gehirns und die Beurteilung der Assoziation von Patientenmerkmalen, perioperativen Risikofaktoren und Auffälligkeiten des Gehirns auf das neurologische Outcome der Patienten mit hypoplastisches Linksherzsyndrom (HLHS) und d-Transposition der großen Gefäße (d-TGA) nach einer Operation am offenen Herzen.

Methodik: In dieser retrospektiven Studie wurden alle Patienten mit HLHS und d-TGA eingeschlossen, die sich in ihrem ersten Lebensmonat einer Herzoperation mit Herz-Lungen-Maschine am Children's National Hospital in Washington, DC im Zeitraum von 2009-2017 unterzogen haben. Patienten die vor der 36. Schwangerschaftswoche geboren wurden, chromosomale Anomalien oder andere angeborenen extrakardialen Pathologien zeigten, wurden ausgeschlossen. Hirnauffälligkeiten im MRT wurden mit Hilfe von Andropoulos' „Brain Injury Scores" beurteilt. Patientendaten, perioperative Risikofaktoren und Hirnauffälligkeiten wurden mit der Beurteilung des neurologischen Outcomes, welches in der Zeit vom 5. Lebensmonat bis zum 2. Lebensjahr erhoben wurde, korreliert. Das neurologische Outcome wurde mit Hilfe der zwei Fragebögen: „Pediatric Version of the Glasgow Outcome Scale–Extended (GOS-E)" und dem "Pediatric Stroke Outcome Measure (PSOM)" beurteilt.

Ergebnisse: 24 Neugeborene mit HLHS und 29 Neugeborene mit d-TGA entsprachen den Kriterien und wurden in die Studie eingeschlossen. 53% der Patienten zeigten präoperative Hirnauffälligkeiten und 72% der Patienten zeigten auffällige Befunde in den postoperativen MRT Befunde. Beide Gruppen zeigten einen signifikanten Anstieg des „Total Injury Scores" von prä- zu postoperativ (HLHS: p=0.006, d-TGA: p=0.017).

Eine Dauer der mechanischen Beatmung von mehr als 12 Tagen und eine Zeit der tiefen Hypothermie an der Herz-Lungen-Maschine von mehr als 40 Minuten waren mit schlechteren PSOM und GOS-E Werten assoziiert. Auffälligkeiten im kranialen MRT korrelierten nicht mit einem schlechteren Outcome.

Schlussfolgerung: Sowohl bei Patienten mit HLHS als auch bei Patienten mit d-TGA waren die Dauer der Beatmung, als auch die Dauer der Tiefen Hypothermie an der Herz-Lungen-Maschine mit einem schlechteren neurologischen Outcome assoziiert. Häufig zeigen die Befunde des kranialen MRTs von Neugeborenen mit angeborenen Herzfehlern Hirnschädigungen, wohingegen die Auswirkungen auf die Klinik dieser Auffälligkeiten in den ersten 2 Lebensjahren meist nicht nachgewiesen werden können.

9 Abbreviation

ASD atrial septal defect
BAS balloon atrial septostomy
Bayley-III the third edition of the Bayley Scales of Infants and Toddler Development
BT Blalock Taussig
CHD congenital heart disease
CPB cardiopulmonary bypass
DD disorder and disabilities
DHCA deep hypothermic circulatory arrest
d-TGA dextro-Transposition of the great arteries
DVST dural sinus venous thrombosis
ECMO extracorporeal membrane oxygenation
EEG electroencephalography
GA gestational age
GOS-E Glasgow Outcome Scale-Extended
GOS-E Ped Pediatric version of the Glasgow Outcome Scale- Extanded
HLHS hypoplastic left heart syndrome
ICU intensive care unit
IPH intraparenchymal hemorrhage
IQR interquartile ranges
IVH intraventricular hemorrhage
l-TGA levo- Transposition of the great arteries
MRI magnetic resonance imaging
MRS magnetic resonance spectroscopy
OR odds ratio
PL punctate lesions
PSOM Pediatric Stroke outcome measure
REV Réparation à l'Etage Ventriculaire
ROC receiver operating characteristic
SDH subdural hemorrhage
SES socioeconomic status
TGA transposition of the great arteries
TIS Total Injury Score
VSD ventricular septal defect
WMI white matter injury

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12 Reverences

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14 Publication list

14.1 Congress Contributions

14.1.1 Oral Presentation

17th World Congress in Fetal Medicine, 24th June 2018, Athens/ Greek

"Analysis of pre- and postoperative brain injury scores of children with complex congenital heart disease"

2nd Science Day, FB 11 JLU, 17th November 2018, Giessen

"Pre- and Postoperative Brain Injury Scores of Children with Congenital Heart Disease"

6th Giessen Symposium "Prenatal Medicine & Fetal Therapy", 12th January 2019, Giessen

"Brain Injury Scores of Neonates with Complex Congenital Heart Disease"

48th Annual Meeting of the German Society for Thoracic and Cardiovascular Surgery, 18th February 2019, Wiesbaden

"Brain Injury Scores of Neonates with Complex Congenital Heart Disease"

33rd Annual Meeting of the European Association for Cardio-Thoracic Surgery, 5th October 2019, Lisbon/Portugal

"Determinants of Neurological Outcome of Neonates with HLHS or D-TGA following Congenital Heart Surgery"

14.2 Publications

Kuhn V, Carpenter JL, Zurakowski D, Reitz JG, Tague L, Donofrio MT, Murnick J, Axt-Fliedner R, Limperopoulos C, Yerebakan C. Determinants of neurological outcome in neonates with congenital heart disease following heart surgery. Pediatr Res. 2020 Jul 25. doi: 10.1038/s41390-020-1085-1. Epub ahead of print. PMID: 32711400.

Kuhn V, Yerebakan C. Brain and Congenital Heart Disease-Together in Good Times and Bad. Semin Thorac Cardiovasc Surg. 2020 Jun 29:S1043-0679(20)30209-4. doi: 10.1053/j.semtcvs.2020.06.018. Epub ahead of print. PMID: 32610195.

Vorisek CN, Kurkevych A, **Kuhn V**, Stessig R, Ritgen J, Degenhardt J, Enzensberger C, Wolter A, Götte M, Khalil M, Akintürk H, Axt-Fliedner R. Prenatal Diagnosis and Postnatal Outcome of Eight Cases with Criss-Cross Heart - A Multicenter Case Series. Ultraschall Med. 2020 Jul 16. English. doi: 10.1055/a-1205-0289. Epub ahead of print. PMID: 32674186.

Meister M, Axt-Fliedner R, Graupner O, **Kuhn V**, Wolter A, Götte M, Enzensberger C. Atrial and Ventricular Deformation Analysis in Normal Fetal Hearts Using Two-Dimensional Speckle Tracking Echocardiography. Fetal Diagn Ther. 2020;47(9):699-710. doi: 10.1159/000508881. Epub 2020 Jul 2. PMID: 32615558.

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