Pre- and Postoperative Brain Magnetic Resonance Imaging Findings and Their Relationship to Neurodevelopment in Newborns with Congenital Heart Disease

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1 Introduction

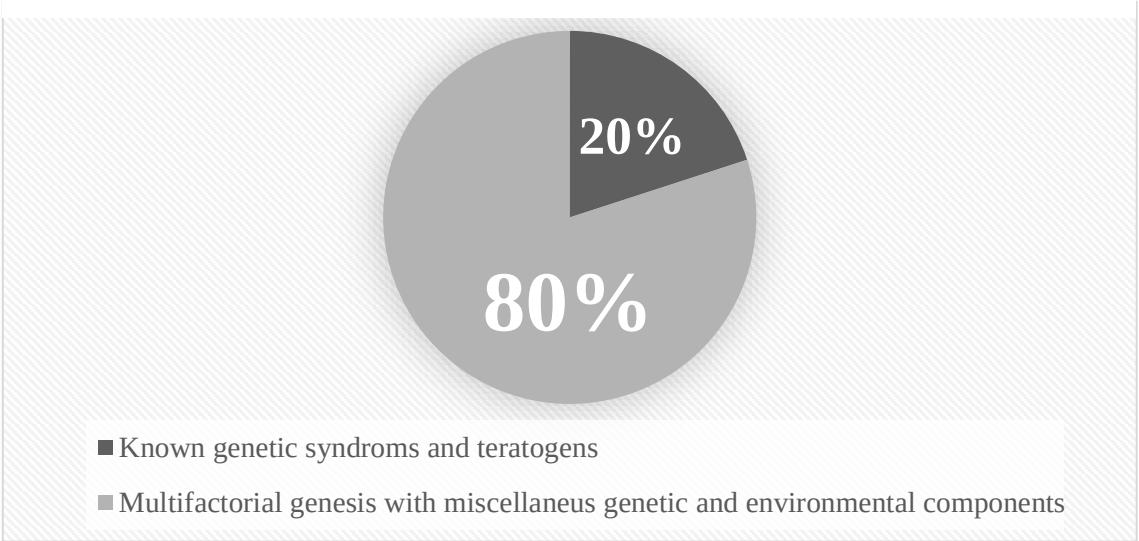
1.1 Congenital Heart Disease

Congenital heart disease is by far the most common type of birth defect universally, diagnosed in about 1% of live births (Bernier *et al.*, 2010; Van Der Linde *et al.*, 2011; Liu *et al.*, 2019). CHD is a general term for a range of cardiac defects present at birth. The prevalence of severe CHD is estimated at around 1.5 per 1 000 births (Reller *et al.*, 2008; Liu *et al.*, 2019). In all newborns with CHD, more than one-third will need surgical intervention in the neonatal period (Marino *et al.*, 2012; Latal, 2016). Although heart surgery may palliate or emend a cardiac defect, there are many psychological and neurodevelopmental challenges for the child and the parents. In addition, adaptation after the surgical event together with comprehensive surveillance and evaluations may significantly diminish the quality of life in these patients. All things considered, increased morbidity and mortality associated with CHD represent a major global health problem.

1.1.1 Pathogenesis

There are several factors contributing to pathogenesis of congenital heart diseases. First of all, genetic syndromes and teratogen exposure are well-researched factors contributing to approximately 20% of CHD cases (Figure 1).

Figure 1. Pathogenesis of CHD



The remaining 80%, however, has a multifactorial genesis involving miscellaneous genetic and environmental components, e.g., pregestational diabetes, maternal rubella, or medication taken during pregnancy, such as retinoic acid and lithium (Blue *et al.*, 2012).

1.1.2 Mortality

Over the last decades, infant mortality related to CHD has declined (Boneva, R. S., Botto, L. D., Moore, C. A., Yang, Q., Correa, A., & Erickson, 2001). This phenomenon is an aftermath of tremendous advances in cardiothoracic surgical techniques, diagnostic technologies, and postoperative care (Holst *et al.*, 2017). Consequently, a steadily growing population of patients with CHD reaching adulthood emerged. As a matter of fact, in 2010, adults accounted for two-thirds of the general CHD population (Marelli *et al.*, 2014). According to estimates, 69% of infants with a critical CHD and 95% of infants with a non-critical CHD survive to 18 years of age (Oster *et al.*, 2013; Mazor Dray and Marelli, 2015).

1.1.3 Morbidity

Undoubtedly, increased survival is a major success. However, recent studies have shown that morbidity remains high. Lifelong burdens include atrial arrhythmias, pulmonary hypertension, and a recurrent need for cardiac surgery (Ionescu-Ittu *et al.*, 2010; Lowe *et al.*, 2011; Mandalenakis *et al.*, 2018). Neurodevelopmental disabilities are seen in up to 50% of surviving children across a wide range of domains (Limperopoulos *et al.*, 2000; Limperopoulos C, Majnemer A, Shevell MI, Rosenblatt B, Rohlicek C, Tchervenkov C, 2001; Wernovsky, Shillingford and Gaynor, 2005).

1.2 Neurodevelopmental Outcome

The definition of the term neurodevelopmental outcome may vary across studies. Typically, this composite term refers to neurological outcomes concerning motor, sensory and cognitive functions. Neurodevelopmental outcomes can be divided into short-term and long-term.

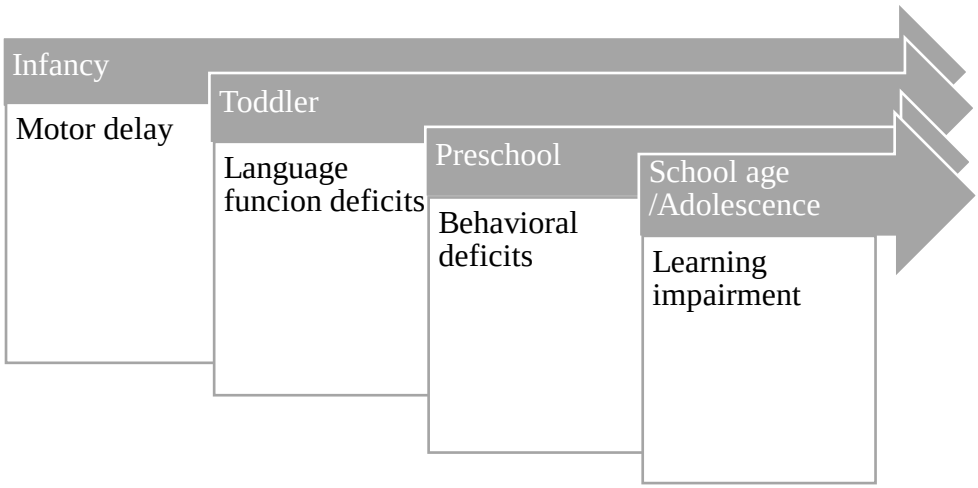
1.2.1 Short-term outcome

Studies show that motor milestones in children with CHD are delayed in the first year of life and as a result these patients score lower on the Bayley Scales of Infant Development (Limperopoulos *et al.*, 2000; Snookes *et al.*, 2010; Gaynor *et al.*, 2015). A major contributor to this impairment is generalized muscular hypotonia. Overall, in these early stages motor development appears to be more affected than cognitive development. Within the first three years of age, motor functions tend to improve, however, they persist in pre- and school years (Karl *et al.*, 2004; Sananes *et al.*, 2012; Liamlahi *et al.*, 2014; Mussatto *et al.*, 2014). Furthermore, some studies have indicated that preschool- and school-age children with CHD have lower (but still within normal range) overall IQ scores than healthy peers (Miatton *et al.*, 2006; Donofrio and Massaro, 2010). Domains that are particularly affected are: language, memory, and processing. Additionally, poor school performance of children with CHD can be explained by deficits in fine motor and visuomotor domains (Karl *et al.*, 2004; Liamlahi *et al.*, 2014). In addition, children with CHD are more likely to have behavioral deficits, predominantly consisting of internalizing symptoms (Latal *et al.*, 2009). Depression, anxiety, and withdrawal are typical examples of internalizing symptoms. Nevertheless, externalizing symptoms, in the form of hyperactivity and inattention, are also frequently reported maladjustments after open-heart surgery, seen in around 40% of the CHD population (Shillingford *et al.*, 2008; Liamlahi *et al.*, 2014). Although IQ scores in this specific population are (lower but) within normal range, above mention challenges may still affect the peer interaction.

Behavioral difficulties have multifactorial character and can be traced to delayed maturation of emotion-related self-regulation mechanisms that are contributed by either subtle cerebral injuries or delayed cerebral maturation. Other significant determinants are

parental factors such as overprotection, maternal anxiety or posttraumatic stress disorder (Latal *et al.*, 2009). Finally, communication skills may be affected by delayed acquisition of language milestones, especially in the motor aspects of speech (Karl *et al.*, 2004). Importantly, although reading difficulties persist in school-age children and adolescents, they are not more affected than other functional areas (Bellinger *et al.*, 2011, 2015). The temporal occurrence of delayed milestones described above is schematically depicted in the Figure 2.

Figure 2. Temporal occurrence of delayed milestones



1.2.2 Long-term outcome

Most of the developmental studies in the CHD pediatric population focus on short-term outcomes in the early stages of life, i.e., early childhood or early school-age. The scarcity of long-term studies may be explained by technical difficulties in conducting them with a high rate of drop-out and demand for continuous funding.

Nevertheless, there is evidence that academic performance and social interaction may be impacted in preterm-born children (Hack, 2009). Furthermore, adolescents with CHD predispose to impairments in executive, visuoperceptual, as well as fine and gross motor functions. Overall, lower intellectual performance in the adult CHD population results in impaired executive functions, poorer educational performance, and a lower level of

education. As a result, they are at higher risk of unemployment and have lower quality of life (Zomer *et al.*, 2012; Tyagi *et al.*, 2014).

Careful consideration should be given when interpreting developmental impairments in children with CHD as certain skills mature during childhood and may not be apparent at the early stages. Overall, it is still unclear how developmental impairments evolve over time.

1.2.3 Predictors of Adverse Neurodevelopmental Outcome

Poor neurological outcome in CHD has complex and multifactorial causation. It comprises patient-specific (non-modifiable) factors as well as partly modifiable parameters.

Type and severity of CHD, low birth weight as well as lower socioeconomic status are identified as strong, non-modifiable predictors of adverse neurodevelopmental sequelae in CHD (Gaynor *et al.*, 2007; Hövels-Gürich, 2016; Naef *et al.*, 2017). Other well researched patient-specific factors are gene mutations expressed in heart and brain causing cerebral dysgenesis. In comparison to healthy fetuses, those with CHD have smaller total brain volumes as well as impaired neuroaxonal maturation and metabolism (Limperopoulos *et al.*, 2010). Furthermore, it is reported that loss of total brain volume observed in infants with CHD, especially reduction of white matter, may lead to language impairment and abnormal neurobehavior (Owen *et al.*, 2014; Rollins *et al.*, 2017).

Additionally, recent neuroimaging studies link altered brain maturation in full-term CHD neonates with increased susceptibility to brain injury, especially white matter injury (WMI), and worse neuropsychological performance at 2 years of age and in adolescents (Licht *et al.*, 2009; Andropoulos *et al.*, 2010; Beca *et al.*, 2013; Heinrichs *et al.*, 2014). Structural brain injury in early infancy also predisposes to worse neurodevelopmental outcomes in CHD patients (Andropoulos *et al.*, 2014).

Apart from innate factors mentioned above, the neurocognitive outcome is also determined by a clinical course such as the use of cardiopulmonary bypass (CPB), exposure to deep hypothermic circulatory arrest (DHCA) for more than 40 minutes,

extended stay in intensive care unit (ICU) and prolonged mechanical ventilation (Wypij *et al.*, 2003; Rivkin *et al.*, 2013; Wernovsky and Licht, 2016; Morton, Ishibashi and Jonas, 2017; Kuhn *et al.*, 2020). While these determinants are increasingly acknowledged, little is known about how acquired brain injury, and perioperative parameters influence specific CHD subpopulations.

1.3 Brain Maturation

Brain development is a highly complex process requiring the timeliness of series of organizational events, eventually creating an intricate circuitry of the human brain. The process begins in the third gestational week and persists into adulthood (Stiles and Jernigan, 2010). Initially, the brain has a smooth structure. At the 8th gestational week appears the first fissure, the interhemispheric fissure, which marks the beginning of the gyrification process (Chi, Dooling and Gilles, 1977). Importantly, the alterations in the brain's gross anatomy translate into major changes at the cellular level, including neuronal proliferation, migration, and myelination. As those features can be accurately assessed on MR images, maturation assessment became a routine radiological practice in neonates.

Several studies focused on the quantitative assessment of cerebral maturation by analyzing myelination, cortical folding, and other features (Nicholas, Mcardle and Richardson, 1987; Knaap *et al.*, 1996). Finally, Childs et al. introduced a semiquantitative scoring system, the total maturation score (TMS), developed, and validated in healthy preterm neonates (Childs *et al.*, 2001). In addition to the assessment of progressive myelination and cortical folding, the new scoring system was supplemented with other parameters such as the distribution of the subependymal germinal matrix and progressive involution of glial cell migration.

The usefulness of the scoring system was then confirmed by another study examining brain maturation in preterm neonates with punctate white matter lesions (Ramenghi *et al.*, 2007). The study concluded that myelination and cortical infolding were the most significant parameters. Furthermore, TMS proved to be applicable for another cohort,

full-term infants with complex CHD. The study described significantly lower mean TMS in infants with CHD, an equivalent of a 1-month delay in structural brain development (Licht *et al.*, 2009). Some studies indicate that brain immaturity is a risk factor for MRI abnormalities, especially WMI, and adverse neurodevelopmental outcomes (Andropoulos *et al.*, 2010; Beca *et al.*, 2013).

1.4 Brain Injury

According to a growing number of literature, brain anomalies are seen in both pre- and postoperative neuroimaging, which emphases the vast impact of CHD on brain development and its susceptibility to injury. Modern medicine provides us with various techniques to detect early neurological pathologies, such as electroencephalography or cranial ultrasound. Owing to further technical advances, especially magnetic resonance imaging (MRI) and its growing number of modalities, additional, quantifiable information may be gathered.

1.4.1 Pre- and Postoperative Brain Injuries

23%-57% of newborns with CHD are found to have evidence of preoperative brain injuries, mostly in the form of white matter injury (WMI) or focal strokes (Dent *et al.*, 2006; McQuillen *et al.*, 2007; Andropoulos *et al.*, 2010; Dimitropoulos *et al.*, 2013; Cordina *et al.*, 2014; Kelly *et al.*, 2019). Periventricular leukomalacia (PVL), detected in 17-28% of preoperative brain MRI, is a form of WMI that typically occurs in the border zone at the end of arterial vascular distributions, adjacent to the lateral ventricles (Mahle *et al.*, 2002; Licht *et al.*, 2004). Another study performed by McQuillen reports stroke to be the leading pathology, followed by WMI (McQuillen *et al.*, 2007).

The high incidence of WMI, especially PVL, in neonates with CHD resembles a characteristic pattern seen in preterm infants and is atypical in term newborns exposed to hypoxia-ischemia of different pathogenesis (Miller *et al.*, 2005; Woodward *et al.*, 2006). This discovery indicates that a part of the acquired brain injuries in the population with

CHD could be associated with an abnormal cerebral vascular system, and/or brain development. To the pathogenesis of PVL contribute an underdeveloped cerebral vascular bed supplying blood to the white matter, immature autoregulation of cerebral blood flow and vulnerability to ischemia of the oligodendrocytes (OL) representing the region (Johnston *et al.*, 2001). Especially the presence of late OL progenitors in the periventricular white matter, which are more susceptible to hypoxia-ischemia than mature OLs, found to be correlating with a higher incidence of PVL. The period of the predominance of late OL progenitors coincides with a critical period for brain development, and the highest vulnerability for PVL (23-32 GW). The decrease in the incidence of PVL was observed at about 32 GW, not surprisingly, corresponding with beginning of myelination in the periventricular white matter (PVWM) (Back *et al.*, 2001).

Postoperative brain injury was seen in 35% of cases, most commonly as WMI (McQuillen *et al.*, 2007). New PVL was found in 48% and stroke in 19% of postoperative MRIs (Mahle *et al.*, 2002).

1.4.2 Surgical Techniques and Their Influence on Neurologic Sequelae

Although the occurrence of brain injuries preoperatively is significant, the focus of many studies shifted to intraoperative factors. The explanation of this interest is its adjustable nature, as an alteration of parameters or a technique may improve the neurodevelopmental outcome.

A potential risk factor contributing to brain injury is exposure to mechanical support during surgery such as DHCA and continuous cardiopulmonary bypass (CPB). DHCA allows a thorough repair under bloodless conditions and reduces exposure to the foreign surfaces of the bypass circuit. However, in order to create the bloodless surgical field, there is an obligate period of global cerebral ischemia followed by reperfusion. In contrary to DHCA, CPB facilitates continuous brain and body perfusion at the cost of exposing the blood to foreign surfaces. The exposure may lead to a systemic inflammatory response causing increased capillary permeability, excessive fluid accumulation in tissues, and organ failure. A common non-neurological sequel of the

inflammatory response to CPB is pulmonary and ventricular dysfunction (Skaryak *et al.*, 1996; Schultz *et al.*, 2006).

An interesting study that conducted an extensive developmental analysis on children with transposition of the great arteries (TGA) is the Boston Circulatory Arrest Study. In this study infants underwent the arterial switch operation (ASO) either with solely DHCA or primarily with continuous low-flow CPB. Data indicated that children undergoing a procedure with DHCA perform worse on evaluation in comparison to cohort exposed to CPB. Specifically, prolonged DHCA was associated with a higher risk of postoperative clinical seizures and ictal activity on EEG (Jane W Newburger *et al.*, 1993) as well as delayed motor development at 1 year of age (Jane W. Newburger *et al.*, 1993; Bellinger *et al.*, 1995). Further investigation at 2.5 and 4 years of age showed developmental delays in motor and language functions (Bellinger *et al.*, 1997, 1999). In contrast, neurologic evaluations at 8 years failed to present a significant difference between the two strategies (Pigula *et al.*, 2000; Bellinger *et al.*, 2003).

According to the final analysis of the Boston Circulatory Arrest Study, each method has its own unique, subtle impact on the CHD cohort (Ungerleider and Gaynor, 2004). Fine motor skills, visual-motor tracking, expressive language, and phonologic awareness were impaired in the DHCA group. The CPB group, on the other hand, demonstrated attention and behavioral deficits. Both study groups, however, did not vary significantly in IQ, memory, visual-spatial, or visual-motor skills.

2 Aims of the Study

Infants with CHD are at high risk for adverse neurodevelopmental outcome. While determinants like extended stay in ICU and prolonged mechanical ventilation are increasingly recognized in literature to affect the CHD population, little is known about neurodevelopmental sequelae within CHD subpopulations.

This study was initiated to illustrate perioperative variables and abnormal brain magnetic resonance imaging findings in a specific CHD subpopulation of infants who were not exposed to deep hypothermic circulatory arrest during their first open-heart surgery. A secondary aim of this research was to determine the impact of clinical characteristics, perioperative course and neuroimaging abnormalities on neurological outcome in this population of CHD patients

I hypothesized that perioperative clinical variables and structural neuroimaging abnormalities would influence the neurologic outcome in this specific population of CHD infants.

3 Methods

3.1 Study Cohort

The study was a retrospective analysis of infants with CHD undergoing open-heart surgery with or without CPB in their first 10 weeks of life. The study population consisted of consecutive patients with CHD born between 2009 and 2017 who underwent open-heart surgery at Children's National Medical Center (CNMC) in Washington, DC. Solely patients with preoperative (postnatal) and postoperative brain MRI exams were included in the study. Patients with multiple congenital anomalies or a syndrome associated with cerebral or neurodevelopmental impairments were excluded from the study. Further exclusion criteria were prematurity (gestational age (GA) less than 37 weeks at birth), and surgery performed with DHCA.

This study was approved by the Children's National Medical Center Institutional Review Board in Washington, DC.

3.2 Clinical Data

The CNMC's electronic medical records were analyzed for essential clinical data, and patient characteristics. Demographics collected consisted of gestational age, cardiac diagnosis, sex, birth weight, APGAR scores, head circumference and age at time of pre-/postoperative MRI. Intraoperative and perioperative data included age at intervention, type of surgical procedure, use of CPB, ICU length of stay, postoperative seizures as well as duration of mechanical ventilation. A postoperative seizure was characterized as any electrographic seizure captured on EEG throughout the hospitalization where the heart surgery was performed. Clinical events suspicious of seizure without EEG validation were excluded due to the struggle in correct identification of seizures clinically in this age group (Murray *et al.*, 2008). Mortality, neurologic and neurodevelopmental data were also evaluated.

3.3 MRI Acquisition

Pre- and postoperative MRI examinations were acquired 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). MRI exams included T1- and T2-weighted images, SWI, DWI, and MR spectroscopy (minimum required sequences: DWI, T2, T1). Prior to discharge, typically after the patient's medical condition stabilized and the pacing wires were removed, postoperative neuroimaging exams were scheduled. All MRI scans were performed as part of primary healthcare.

3.4 MRI Studies

MRI scores were assessed outside of routine medical care, without relating to clinical data other than patient's age and sex.

3.4.1 Brain Maturation

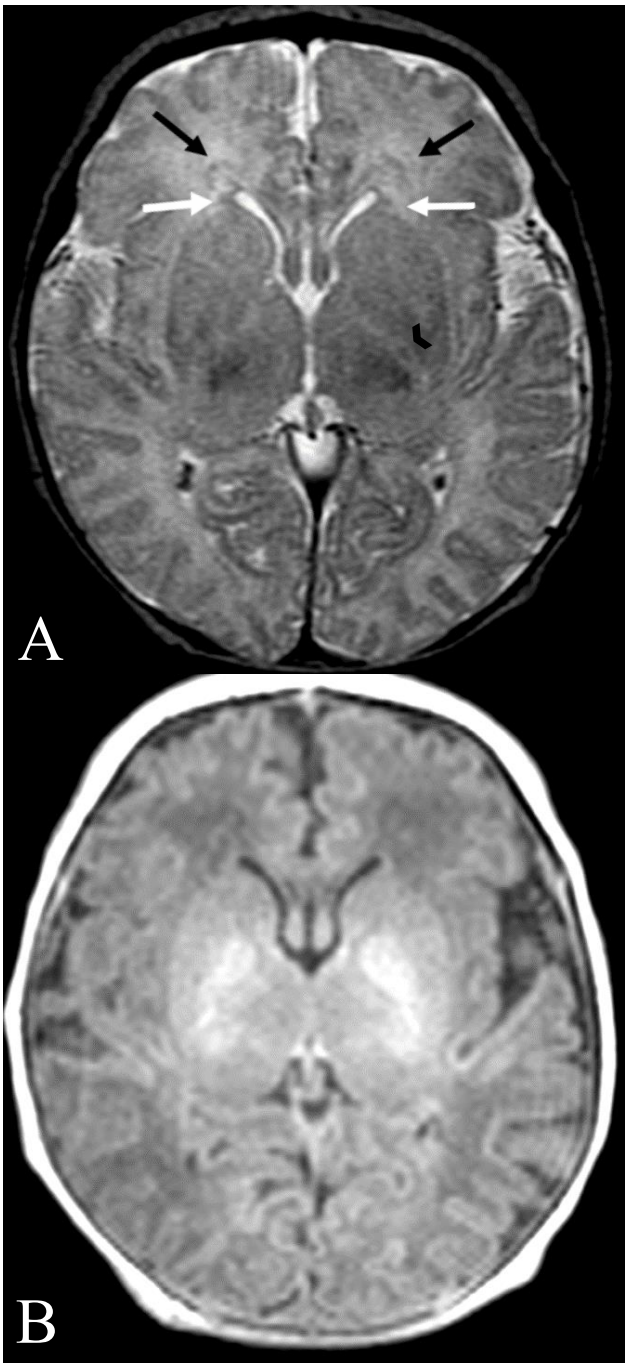
Brain maturity was evaluated on preoperative brain MRIs by a board-certified pediatric neuroradiologist. The total maturity score (TMS) was assigned according to the scoring system described by Childs et al. (Table 1)(Childs *et al.*, 2001). The TMS evaluation includes an assessment of myelination (M), cortical and insular infolding (C), white matter intensity on T1 sequences, involution of the germinal matrix (GM), and presence of bands of migrating glial cells (B). Myelination is scored separately on T1- and T2-weighted images then averaged to give the myelination score. In Childs et al. original paper, the cortical infolding score consisted of the average of individual scoring items: cortical infolding, insular infolding, and white matter intensity in T1 score. As the white matter intensity score is a subjective feature and may vary based on MRI scanning technique, it was excluded from the calculation. The TMS is produced from the sum of the four scores: myelination, cortical infolding, involution of the germinal matrix, and presence of bands of migrating glial cells (Figure 3).

Table 1. Brain maturation scoring system adapted from (Childs et al., 2001)

	Myelination (M):
M1	Myelination evident in brain stem, cerebellar peduncle, inferior colliculus, cerebellar vermis
M2	+ Subthalamic nuclei, globus pallidus, ventrolateral thalamus
M3	+ Caudal portion of the posterior limb of the internal capsule (PLIC)
M4	+ Complete PLIC
M5	+ Optic radiation
M6	+ Corona radiata
M7	+ Anterior limb of internal capsule
	Cortical infolding (C):
C1	Frontal and occipital cortex completely smooth, insula wide open; thin bright cortical rim on T1, generally low-intensity white matter (WM) on T1
C2	Frontal cortex still very smooth, some sulci evident in occipital cortex; insula still wide with almost smooth internal surface; WM low intensity on T1
C3	Frontal and occipital cortex similar number of convolutions; frontal sulci still quite shallow; internal sur- face of insula more convoluted; WM still somewhat low intensity on T1
C4	Frontal and occipital cortex folded and rich in sulci; frontal sulci obvious along interhemispheric fissure; occipital WM separated into strands by deeper sulci; insula more convoluted and infolded; WM still slightly low intensity on T1
C5	Frontal and occipital WM separated into strands by deeper sulci; insula completely infolded; WM still distinguishable from gray matter on T1
C6	As above but WM now isointense with gray matter on T1
	Germinal matrix (GM)
GM1	Matrix seen in posterior horn, at caudothalamic notch (CTN) and anterior horns of lateral ventricles
GM2	Matrix evident at CTN and anterior horns only
GM3	Matrix at anterior horns alone
GM4	No matrix evident

	Bands of migrating glial cells (B)
B1	Broad band with additional narrower bands
B2	Broad band alone
B3	Narrow band alone
B4	No bands seen

Figure 3. TMS - infant of 38 weeks` gestation at the time of the MRI scan, TMS=11.5



A: axial T2-weighted image. Especially frontal horn germinal matrix (white arrows, GM=2) and broad bands of migrating glial cells (black arrows, B=2) are well seen in this example. Myelination can be seen to have started in the caudal portion of posterior limb of the internal capsule (arrowhead, M=3).

B: axial T1-weighted image. Cortical: The frontal and occipital white matter separated not strands by deeper sulci (C=5). Insula: more convoluted and infolded (C=4).

3.4.2 Brain Injuries

Brain injuries were assessed by two clinicians, either a pediatric neuroradiologist or a pediatric neurologist. Brain injury scores were assigned in accordance with the Andropoulos classification system on preoperative and postoperative brain MRIs (Table 2) (Andropoulos *et al.*, 2010). This classification system grades brain injury according to eight categories: white matter injury (WMI), infarction (ischemic stroke), intraparenchymal hemorrhage (IPH), punctate lesions (PL), elevated lactate on MR spectroscopy (MRS), intraventricular hemorrhage (IVH), subdural hemorrhage (SDH) and dural sinovenous thrombosis (CSVT). Each category is scored for severity: 0 = none, 1 = mild, 2 = moderate and 3 = severe. Subscores are multiplied by a proposed outcome significance multiplier: 3 (WMI, infarction, or IPH), 2 (PL, or MRS), or 1 (IVH, SDH, or CSVT). The Total Brain Injury Score (TBIS) is the sum of weighted subcategories. A TBIS of 0 was considered as no injury and within range 1 - 5 as mild injury, within range 6 - 10 as moderate injury, and >10 as the highest measure of severe injury (Table 3).

Table 2. MRI Brain Injury Scoring System adapted from (Andropoulos et al., 2010)

Category	Score	Outcome significance multiplier	Definition	Size
WMI	0	3	None	0
	1	3	Mild: ≤3, <2 mm	1–5 mm
	2	3	Moderate:>3, >2 mm	6–15 mm
	3	3	Severe: 10% WM	>15 mm
Infarction (stroke—ischemic)	0	3	None	0
	1	3	< 1/3 of ACA, MCA or PCA vascular territory in one hemisphere	1–5 mm
	2	3	1/3 – 2/3	6–15 mm
	3	3	>2/3	>15 mm
IP hemorrhage	0	3		0

(stroke—hemorrhagic)				
	1	3		1–5 mm
	2	3		6–15 mm
	3	3		>15 mm
Punctate lesions	0	2	None	0
	1	2	1–3 lesions	all ≤ 2mm
	2	2	4–6 lesions	all ≤ 2mm
	3	2	>6 lesions	all ≤ 2mm
Increased Lactate on MRS	0	2	None to Lac/Cr ratio of 0.15	NA
	1	2	Lac/Cr ratio of 0.16–0.5	
	2	2	2 Lac/Cr 0.5–1	
	3	2	Lac/Cr>1	
IVH	0	1	0	
	1	1	Subependymal/ germinal matrix hemorrhage/ choroid plexus hemorrhage	1–5 mm
	2	1	IVH—isolated	6–15 mm
	3	1	IVH with ventricular dilatation	>15 mm
SDH	0	1	SDH above tentorium; minimal SDH below tentorium frequently secondary to birth process and not considered abnormal	
	1	1	Minimal just above tentorium	
	2	1	Spread to interhemispheric fissure in occipital area	

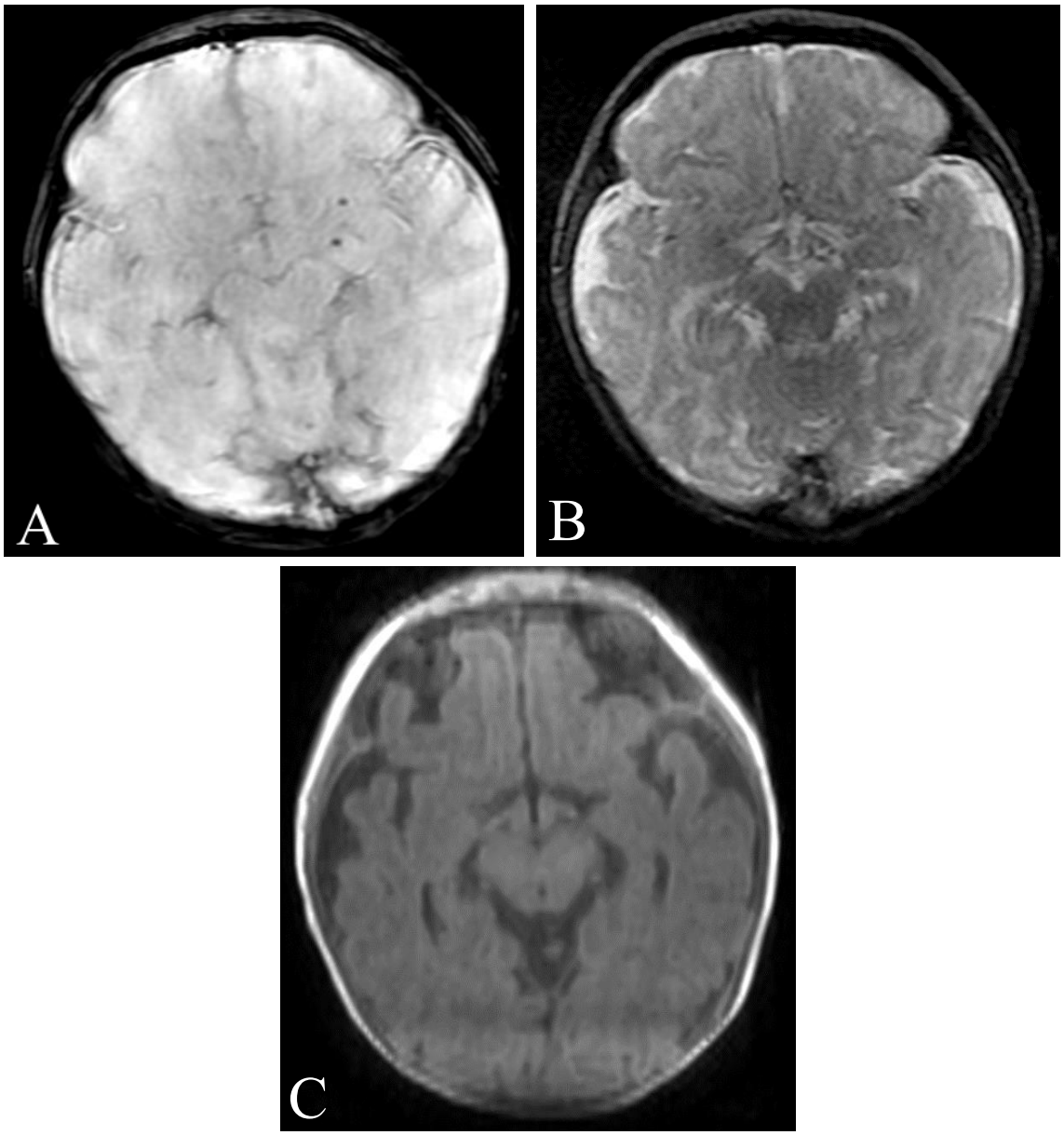
	3	1	Larger hemorrhage; interhemispheric to parietal or frontal area; any mass effect	
CSVT	0	1	Flow voids in dural venous sinuses, confirmed by MR venogram	0
	1	1		R or L transverse alone
	2	1		Bilateral R and L
	3	1		Straight and/or sagittal sinus

Table 3. TBIS Severity Score adapted from (Andropoulos et al., 2010)

TBIS	Severity
0	no injury
1-5	mild injury
6-10	moderate injury
>10	severe injury

Figure 4 and Figure 5 show exemplary assessments of brain injuries according to Table 2.

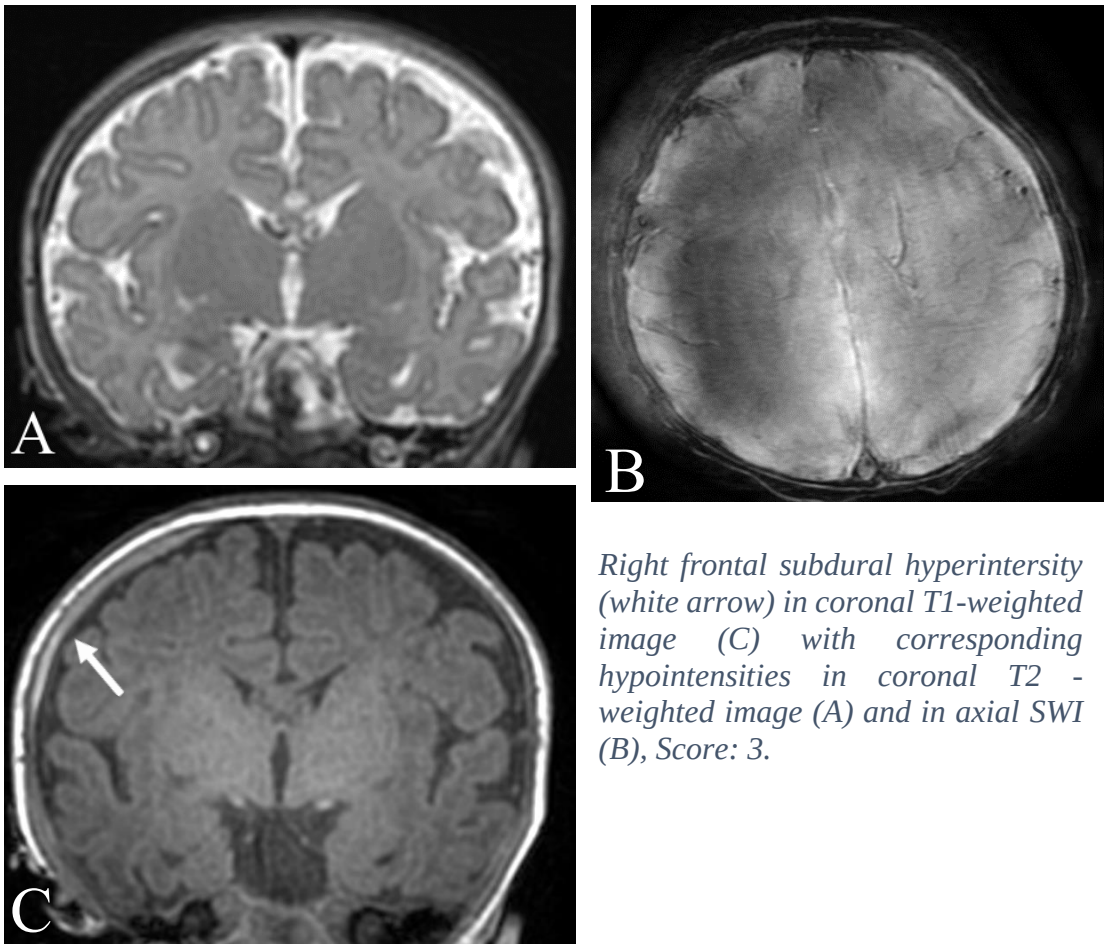
Figure 4. Postoperative punctate lesions



A: axial SWI image.
Two punctate hypointensities in left limbic system and left frontal lobe.
B: axial T2-weighted image.
Typically for punctate lesions, there are barely visible hypointense signals in T2 (white arrows).
C: axial T1-weighted image.
Corresponding to SWI and T2 hypointensities, there are barely visible hyperintensities on T1 image.

Two punctate lesions - Score: 1.

Figure 5. Postoperative epitentorial SDH



Right frontal subdural hyperintersity (white arrow) in coronal T1-weighted image (C) with corresponding hypointensities in coronal T2 - weighted image (A) and in axial SWI (B), Score: 3.

3.5 Neurological Outcome Tools

At Children's National pediatric patients with CHD are offered neurodevelopmental assessments as part of cardiac follow-up care, established as the Cardiac Neurodevelopmental Outcome Program (CANDO). Evaluations are conducted by a group of specialists, including a speech therapist, pediatric neurologist, occupational therapist, and developmental psychologist. For this study, CANDO clinical assessments were used to determine the neurodevelopmental outcomes through two approved measures in pediatric patients, the Pediatric Stroke Outcome Measure (PSOM) and the Pediatric version of Glasgow Outcome Scale-Extended (GOS-E Peds).

3.5.1 PSOM

The PSOM evaluates neurological impairments and function across five subscales: left and right sensorimotor, language production, language comprehension, cognition, and behavior (Figure 6). Each domain was scored: 0 = no deficit, 0.5 = mild deficit without functional deficit, 1 = moderate deficit with decreased function or 2 = severe deficit with missing function (Gabrielle *et al.*, 2000). Subscores were applied to produce a total severity score extending from 0 (normal) to 3 (severe impairments). Finally, severity score was generated from subscores, ranging from 0 (normal) to 3 (severe deficits) (Table 4) (Felling *et al.*, 2020). For this study, the poor neurologic outcome was defined as a total severity score >1 or death.

Table 4. PSOM Interpretive Neurological Assessment adapted from (Felling et al., 2020)

Severity	Total PSOM criteria	Outcome
Normal (0)	0-0.5 point in all subdomains	Good
Mild deficits (1)	1 point in 1-2 subdomains and <1 in remaining subdomains	
Moderate deficits (2)	1 point in ≥3 subdomains OR 2 points in 1 subdomain and <2 points in all remaining subdomains	Poor
Severe deficits (3)	2 points in ≥2 subdomains	

Figure 6. PSOM adapted from (Gabrielle et al., 2000)

SUMMARY OF IMPRESSIONS Score SOI-Score PSOM-SNE - Adapted from (Gabrielle *et al.*, 2000):

A. Sensorimotor Deficit (ANY motor or sensory abnormality including Cranial Nerve Deficits, Visual, and Hearing deficits)

Severity	**R side**	**L side**
None	0	0
Mild but no impact on function	0.5	0.5
Moderate with some functional limitations	1	1
Severe or Profound with missing function	2	2
Not Tested	n/t	n/t

Select the Sensorimotor Deficits You Observed (select all that apply)

□ Global developmental delay □ Global hypotonia or hypertonia

□ Hemiparesis □ Hemifacial weakness □ Hemiataxia □ Dysarthria □ Other Motor deficit

□ Hemisensory deficit □ Other Sensory deficit

□ Difficulty with vision □ Difficulty with drinking, chewing or swallowing

□ Other, describe:

B. Language Deficit – Production (exclude dysarthria)

Severity	**Score**
None	0
Mild but no impact on function	0.5
Moderate with some functional limitations	1
Severe or Profound with missing function	2
Not Tested	n/t

Describe the Language Production Deficits You Observed Here:

C. Language Deficit - Comprehension

Severity	**Score**
None	0
Mild but no impact on function	0.5
Moderate with some functional limitations	1

Severe or Profound with missing function	2
Not Tested	n/t

Describe The Language Comprehension You Observed Here:

D. Cognitive or Behavioural Deficit (specify which)

□ Cognitive □ Behavioural

Severity	**Score**
None	0
Mild but no impact on function	0.5
Moderate with some functional limitations	1
Severe or Profound with missing function	2
Not Tested	n/t

Describe the Cognitive or Behavioural Deficits You Observed Here:

_____

TOTAL SCORE: ____/10

3.5.2 GOS-E Peds

The GOS-E Peds adjusted by Beers et al. is a functional outcome scoring system adapted to evaluate younger patients (birth to 16 years of age) after a brain injury (Beers *et al.*, 2012). The GOS-E Peds examines five domains: independence inside and outside home, school performance, engagement in social and leisure activities as well as psychological issues affecting friendships and family (Figure 7). The results of the GOS-E Peds interview were scored as 1 = upper good recovery, 2 = lower good recovery, 3 = upper moderate disability, 4 = lower moderate disability, 5 = upper severe disability, 6 = lower severe disability, 7 = vegetative state and 8 = death. For this study, poor functional outcome was defined as GOS-E Peds > 2, a score most compatible with PSOM > 1.

Figure 7. GOS-E Peds adapted from (Beers et al., 2012)

PEDIATRIC GLASGOW OUTCOME SCALE–EXTENDED:

Information obtained (select one):

- ☐ In person,
- ☐ By phone,
- ☐ From records

NOTE: Only problems that have developed or become markedly worse since the head injury should be considered when completing the GOS-E Peds. That is, the child's premorbid status must be weighed when answering all questions.

1. CONSCIOUSNESS

1a) Is the head-injured person able to obey simple commands or say any words?

Or for younger patients: Can he or she act/react/interact beyond reflexes?

- ☐ Yes (Skip to 2.)
- ☐ No

⬇

Vegetative State (VS), Skip to end of form and record GOS- E**, Peds Score = 7.**

An individual who shows the ability to obey even simple commands or utter any word or communicate specifically in any other way is no longer considered to be in a vegetative state. Eye movements are not reliable evidence of meaningful responsiveness; corroborate with nursing staff and the child's parents when possible. Confirmation of VS requires full assessment as in the Royal College of Physician Guidelines. However, for infants, actively following the movement of a parent or people/object with eyes, grasping for objects, making faces, etc. are interactions; breast feeding and crying continuously can be reflexes.

2. INDEPENDENCE IN THE HOME

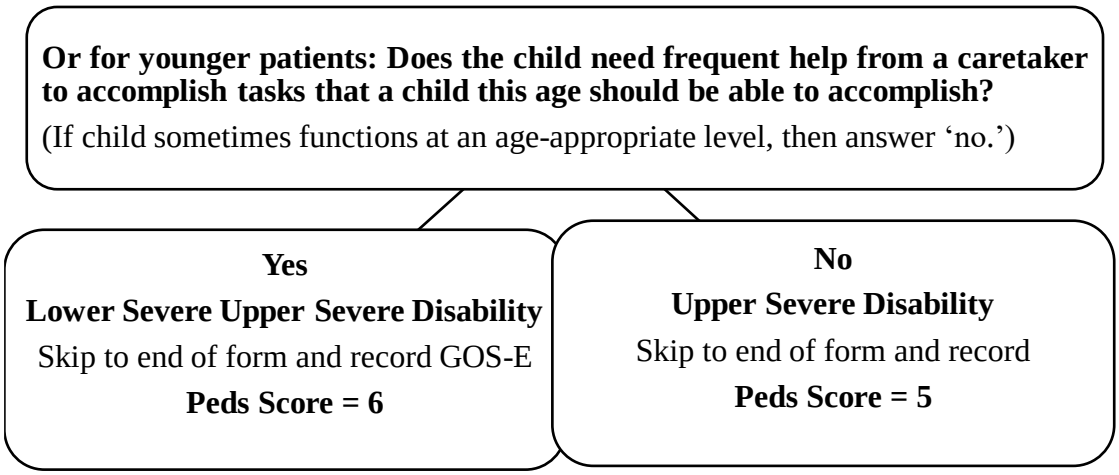
2a) Is the assistance of another person at home essential every day for some activities of daily living?

Or for younger patients: Is the child dependent upon a caretaker more so than is expected based on age?

- Yes (Go to 2b.)
- No (Skip to 3.)

For an older child, complete independence and a 'no' answer should mean that the person can get washed, put on clean clothes without prompting, prepare food for themselves, deal with callers, and handle minor domestic crises. The person should be able to carry out activities without needing prompting or reminding and should be capable of being left alone for an age-appropriate period. Young children should be able to accomplish age-appropriate developmental milestones without assistance (see Vineland Daily Living Skills). If a child compensates for physical disability to the point where developmental milestones are only mildly compromised, question parents to determine the level of independence (i.e., A child with a hemiparesis who is still able to complete tasks that other children of that age can be rated as independent).

2b) Does the child need frequent help or for someone to be around at home most of the time



3. INDEPENDENCE OUTSIDE THE HOME

3a) Is the child able to shop and travel without assistance?

Or for younger patients: Does the child behave age appropriately outside the home?

- Yes (Skip to 4.)
- No

Upper Severe Disability, Skip to end of form and record GOS- E, **Peds Score = 5**

This item considers activities such as shopping and traveling, always in the context of age-appropriate behaviors. This includes being able to plan what to buy, take care of money, and behave appropriately in public. The individual need not normally shop but must be able to do so. A younger child must behave age appropriately in public. An older child may drive or use public transit to get around. Ability to use a taxi is sufficient, provided the person can phone for it themselves and give instruction the driver. Older children who sometimes were allowed to travel independently before the injury should be able to walk toa neighbor's house, take a school bus, ride a bike, or take public transportation.

4. SCHOOL/WORK

4a) Can the child function at work or in school at his or her previous capacity?

- Yes (Skip to 5.)
- No (Go to 4b.)

If an adolescent was working before the injury, then his or her current capacity for work should be at the same level. If the individual was seeking work before, then the injury should not have adversely affected chances of obtaining work or the level of work for which he or she is eligible. If the patient was in preschool or a student before the injury, then capacity for schoolwork and school activities should not be adversely affected.

4b) Level of restriction

i) Able to work only in a sheltered workshop or non-competitive job, in a school setting for severely impaired children or tutored at home, or currently unable to work or go to school.
   - No (Go to 4b ii.)
   - Yes

Lower Moderate Disability, Skip to end of form and record, **GOS-E Peds Score = 4**

i) Reduced work or school capacity.

- ☐ Yes

Upper Moderate Disability, Skip to end of form and record GOS-E, **Peds Score = 3**

5. SOCIAL & LEISURE ACTIVITIES

5a) Is the child able to resume regular social and leisure activities?

- ☐ Yes (Skip to 6.)
- ☐ No (Go to 5b.)

The individual may not have resumed all previous leisure activities but should not be prevented from doing so by physical or mental impairment. If he or she has stopped the majority of activities because of loss of interest or motivation, then this is considered a disability. For younger children, social and leisure activities can include games and toys played with caretakers, siblings, or other children as well as the ability to interact in a playful manner with others.

5b) What is the extent of restrictions on social and leisure activities?

i) Unable to participate: Rarely, if ever, take part.

No (Go to 5b ii.)

Yes

Lower Moderate Disability, Skip to end of form and record, **GOS-E Peds Score = 4**

ii) Participate much less: Less than half as often.

- ☐ No (go to 5b iii.)
- ☐ Yes

Upper Moderate Disability, Skip to end of form and record, **GOS-E Peds Score = 3**

iii) Participate a bit less: At least half as often as before injury.

- ☐ No (Skip to 6.)
- ☐ Yes

Lower Good Recovery, Skip to end of form and record, **GOS-E Peds Score = 2**

6. FAMILY & FRIENDSHIPS

6a) Are there psychological problems that have resulted in ongoing disruption with respect to either family or friendships?

- ☐ Yes (Go to 6b.)
- ☐ No (Skip to 7.)

Typical post-traumatic personality changes: quick temper, irritability, anxiety, aggressive acts, insensitivity to others, mood swings, depression, and unreasonable or childish behavior that is not age appropriate.

6b) What is the extent of disruption or strain?

- ☐ Constant – daily and intolerable.

⬇

Lower Moderate Disability, Skip to end of form and record, **GOS-E Peds Score = 4.**

- ☐ Frequent – once a week or more, but tolerable

⬇

Upper Moderate Disability, Skip to end of form and record, **GOS-E Peds Score = 3**

- ☐ Occasional – less than weekly

⬇

Lower Good Recovery, Skip to end of form and record**, GOS-E Peds Score = 2**

7. RETURN TO NORMAL LIFE

7a) Are there any other problems relating to the injury that affect daily life?

- ☐ Yes

⬇

Lower Good Recovery, Skip to end of form and record**, GOS-E Peds Score = 2**

- ☐ No

⬇

Upper Good Recovery, Skip to end of form and record**, GOS-E Peds Score = 1**

Typical problems reported after head injury: headaches, dizziness, tiredness, sensitivity to noise or light, slowness, memory failures, concentration problems, or other problems.

RECORD GOS-E PEDS SCORE: _____

Scoring caveat: Remember to consider premorbid status when assigning category scores to an outcome of injury; problems in functioning should have deteriorated from premorbid level.

3.6 Statistical Analysis

Statistical analysis of the research data was performed with the help of David Zurakowski, PhD, the Director of Biostatistics at the Boston Children's Hospital and the associate professor of Anaesthesia at the Harvard Medical School.

Continuous variables are described using the median and interquartile range (IQR), eventually compared utilizing the nonparametric Mann-Whitney U-test. Ratios were correlated between groups by Fisher's exact test. Multivariable logistic regression analysis was used to distinguish independent risk factors of adverse neurodevelopmental sequelae (PSOM and GOS-E Peds) at 12 months of age or older based on covariates discovered to be significant by univariate analysis. Evaluation of the data was completed using Stata version 16 (StataCorp LLC, College Station, Texas). Two-tailed $P < 0.05$ were regarded as statistically significant.

4 Results

4.1 Characteristics of the Infants

Initially, fifty infants with CHD who had open-heart surgery without DHCA in the first 10 weeks of life and received a pre- and postoperative brain MRI were selected. Six patients diagnosed with congenital anomalies, or a syndrome related to cerebral or neurodevelopmental disorders were excluded from the study. Another two patients were excluded from the study cohort for prematurity (GA < 37 weeks). Ultimately, forty-two patients were enrolled in the study.

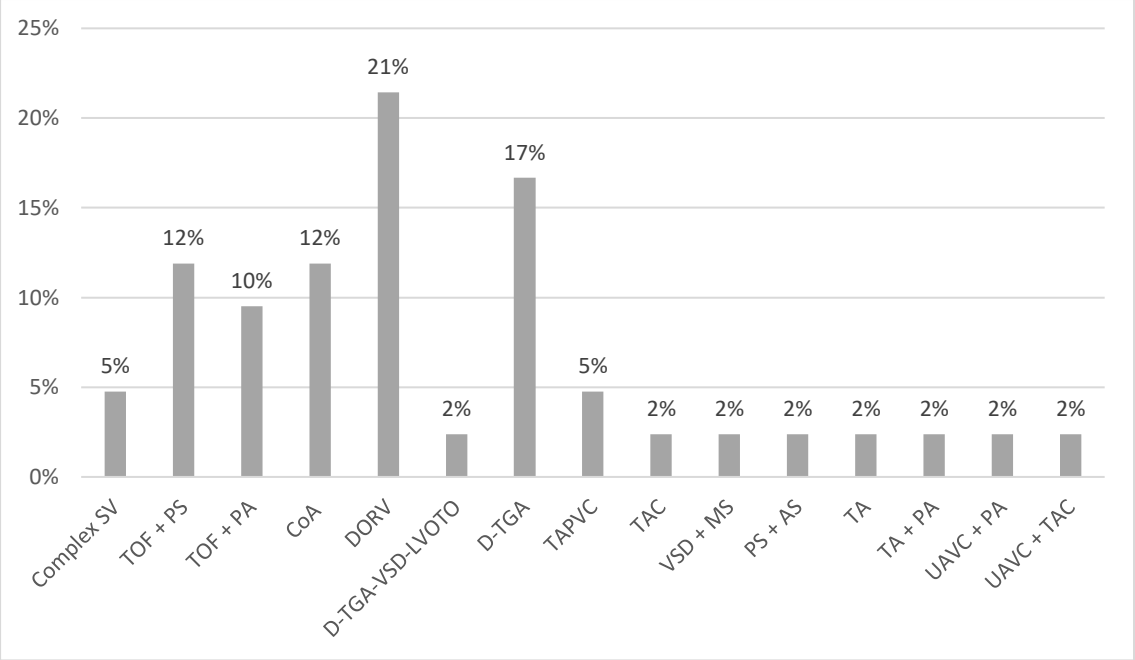
Patients' baseline characteristics and clinical data are demonstrated in Table 5. CHD was identified prenatally in 52% (n = 22) of patients, and median GA at birth was 39 (IQR 38-39) weeks. Head circumference at birth was normal (within 5th - 95th percentiles) in all patients. Consistent with prevalence-at-birth studies reporting that coarctation and other congenital heart defects such as tetralogy of Fallot (TOF), transposition complexes, or univentricular lesions are more prevalent in males, a strong male predominance was observed in my study (71%) (Marelli *et al.*, 2007).

In the cohort, the most frequent CHD lesions were transposition of the great arteries (TGA, n = 19%) as well as TOF, and double outlet right ventricle (DORV), the latter two were distributed equally (n = 9, 21%) (Figure 8). Mechanical ventilation was needed in more than half of the cohort (n = 23, 55%) prior to surgery, and the median duration of support was 7 (IQR 3-10) days. Infants underwent open-heart surgery at a median of 8 (IQR 5-14) days. Twenty-four (57%) surgeries were performed with CPB support. In most cases, a biventricular repair was undertaken (BV: n = 29, 69% vs SV: n = 13, 31%). MBT shunt was placed in twelve cases (29%). In twenty-two (52%) cases, at least one subsequent cardiovascular operation was required. The median ICU length of stay was 17 (IQR 12-32) days and the median hospital stay was 28 (IQR 18-60) days.

Table 5. Patients' baseline characteristics and clinical data adapted from (Kosiorek et al., 2021)

Variable	**Total cohort (n =42)**	**Patients with PSOM at ≥12 months (n = 29)**
Sex, n (%)		
Male	30 (71)	21 (72)
Female	12 (29)	8 (28)
Prenatal diagnosis, n (%)	22 (52)	17 (59)
Gestational age at birth, median weeks (IQR)	39 (38-39)	39 (38-40)
Birth weight, median kg (IQR)	3.3 (3.0-3.6)	3.3 (3.0-3.5)
Head circumference, median cm (IQR)	34 (33-35)	33.5 (32-34)
Mechanical ventilation prior to surgery, n (%)	23 (55)	14 (48)
Balloon atrial septostomy, n (%)	9 (21)	5 (17)
Age at cardiac surgery, median days (IQR)	8 (5-14)	7 (5-15)
Surgical repair type, n (%)		
Single Ventricle (SV)	13 (31)	10 (34)
Biventricular (BV)	29 (69)	19 (66)
Surgery with CPB, n (%)	24 (57)	15 (52)
Surgery without CPB, n (%)	18 (43)	14 (48)
Cardiac arrest postoperatively, n (%)	6 (14)	2 (7)
Seizures postoperatively, n (%)	3 (7)	3 (10)
ECMO postoperatively, n (%)	3 (7)	2 (7)
Duration of ICU stay, median days (IQR)	17 (13-32)	16 (12-38)
Duration of hospital stay, median days, (IQR)	28 (18-60)	25 (16-60)
Duration of mechanical ventilation, median days (IQR)	7 (3-10)	5 (3-9)
Duration from surgery to postoperative MRI, median days (IQR)	14 (8-29)	14 (9-32)
Subsequent cardiac surgery performed, n (%)	22 (52)	17 (59)
Surgery with CPB more than 1 time, n (%)	11 (26)	10 (34)
Age at neurological assessment, months median (IQR)	N/A	27.7 (17-50)

Figure 8. Distribution of heart defects in the study population (n=42)



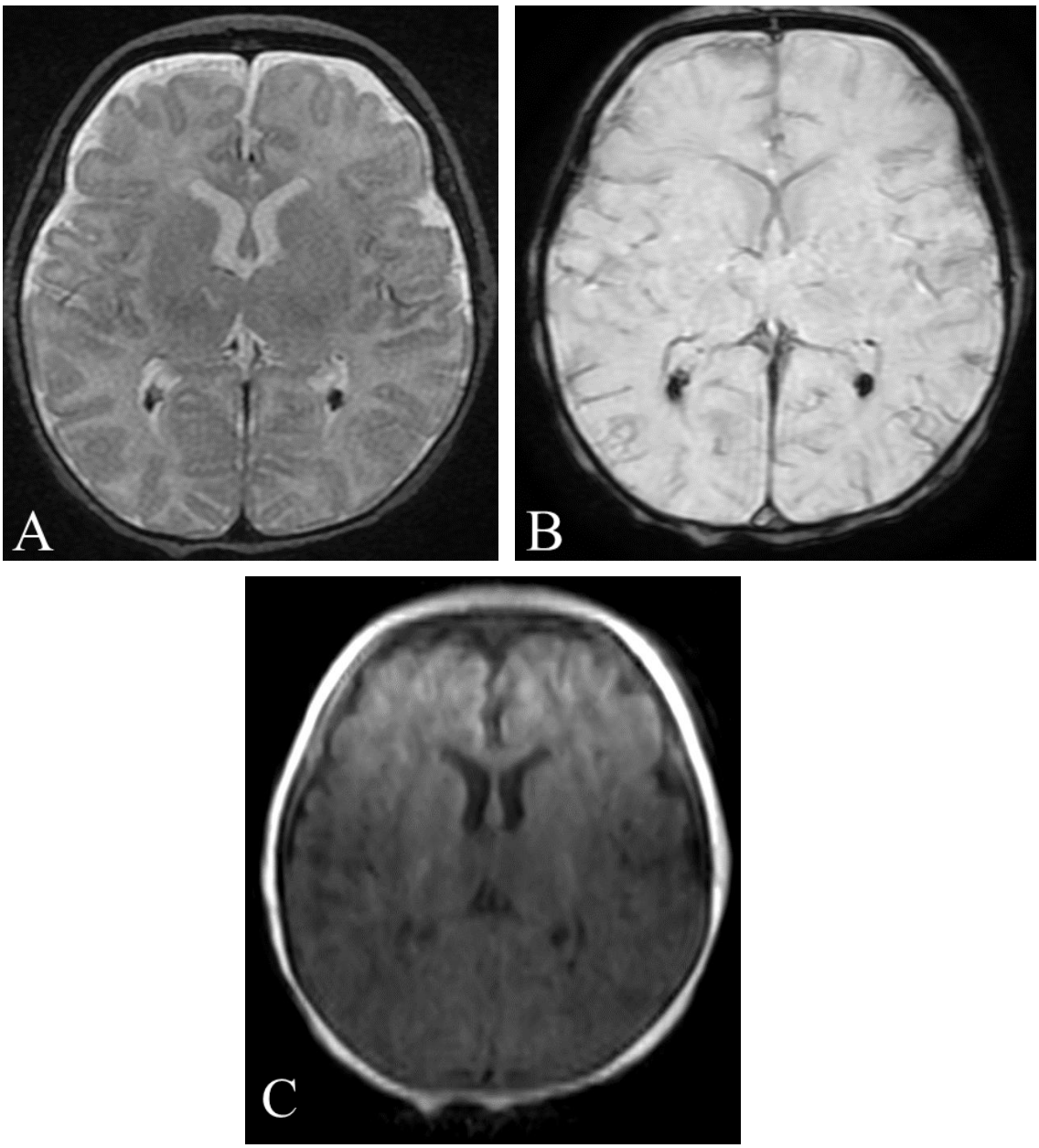
4.2 Radiographic data

The preoperative brain MRI scan was performed at the median age of 4 (IQR 3-5) days and the postoperative scan at 33 (IQR 18-50) days (Table 5). In most examinations sufficed a-feed and-swaddle technique. The feed-and-swaddle method is a sedation-free technique using feeding and swaddling to induce natural sleep in infants. In eleven preoperative and three postoperative scans, sedation with either fentanyl or morphine was required. Brain maturity was evaluated in 41 (98%) preoperative MRI scans with a mean TMS of 13 (IQR 12-14), comparable to brain maturity at around 40 weeks GA. The lowest TMS appreciated was 10.5, similar to brain maturity at around 35 weeks GA.

Half of the study cohort (n = 21) had a preoperative brain injury (Table 6). A new lesion was appreciated on 50% (n = 21) of postoperative brain MRIs with 67% (n = 28) of the cohort having an injury on a postoperative scan. Preoperatively, thirteen patients (31%) had more than one type of abnormality. On the postoperative scan, fourteen infants (34%) exhibited numerous types of injuries. SDH was the leading preoperative brain abnormality (n = 9, 21%), along with WMI (n = 8, 19 %) and ischemic infarction (n = 7,

17%). IVH (n = 4, 10%), and IPH (n = 2, 5%) were seen less frequent on the preoperative scans. Example of an intraventricular haemorrhage is illustrated in Figure 9.

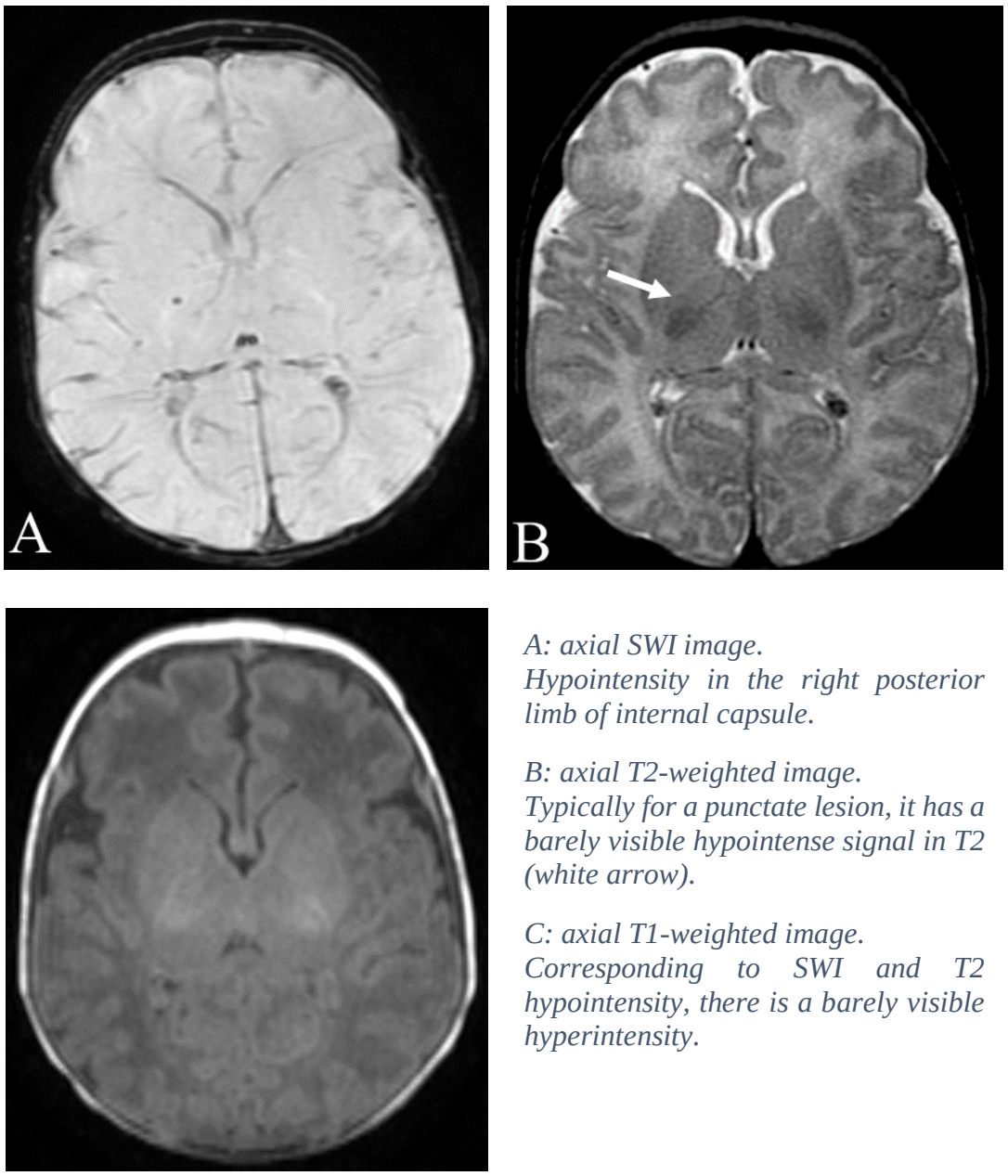
Figure 9. Intraventricular and choroid plexus hemorrhage



Hypointensities in T2 (A)- and T2 (C) as well as susceptibility (B: SWI) involving the lateral ventricular choroid plexus are consistent with sequela of hemorrhage. Small focus of susceptibility (B) in the occipital remainder of the right lateral ventricle is consistent with remote intraventricular hemorrhage.

On the postoperative scan, WMI was the most common abnormality type, making up to 26% (n = 11) of new lesions and found on 36% (n = 15) of postoperative cases total. The second leading injury type was PL (Figure 10) constituting 21% (n = 9) of new injuries and 21% (n = 21) of postoperative exams overall.

Figure 10. Punctate lesion in the right posterior limb of internal capsule



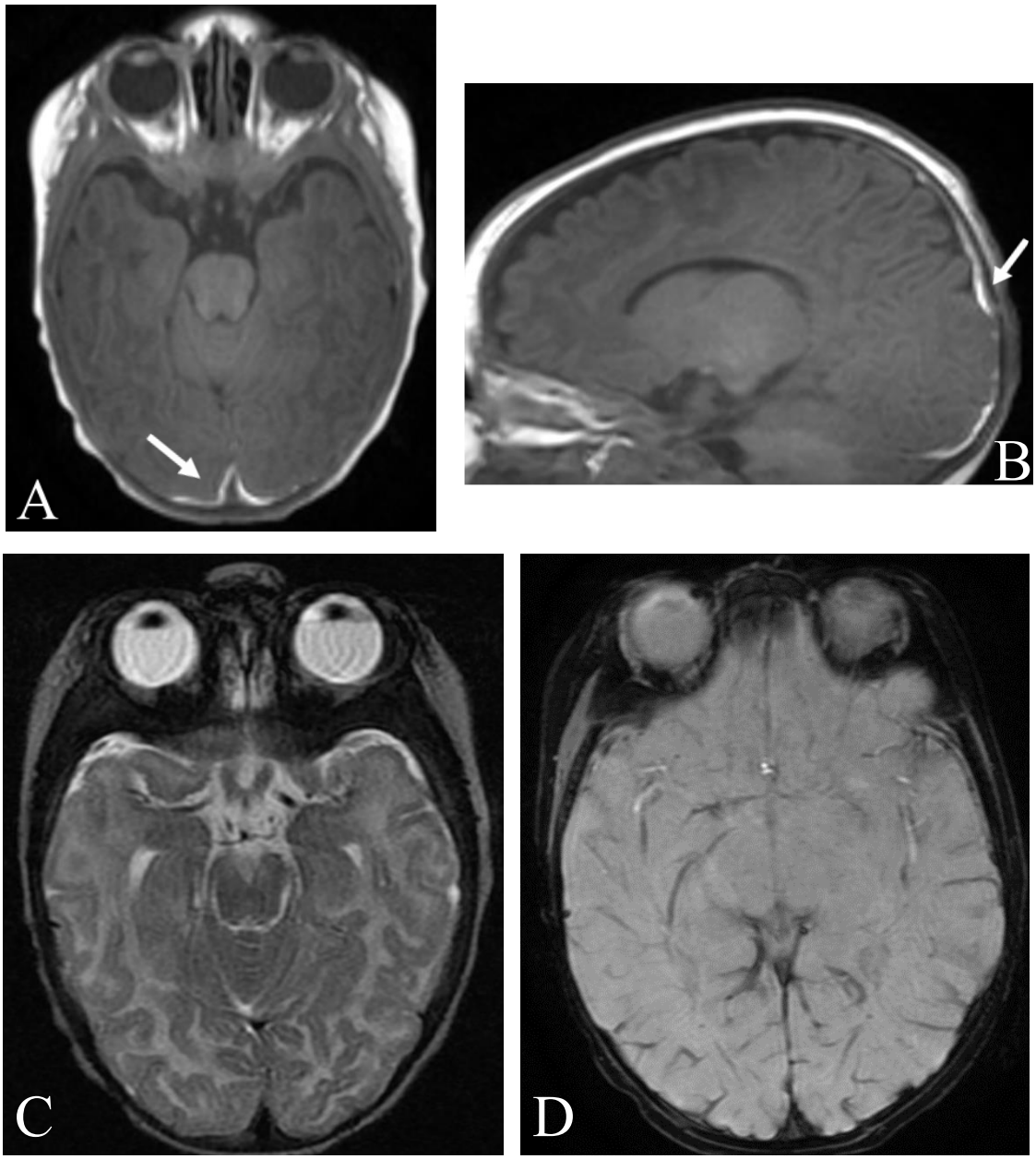
A: axial SWI image.
Hypointensity in the right posterior limb of internal capsule.

B: axial T2-weighted image.
Typically for a punctate lesion, it has a barely visible hypointense signal in T2 (white arrow).

C: axial T1-weighted image.
Corresponding to SWI and T2 hypointensity, there is a barely visible hyperintensity.

Nineteen percent (n = 8) of infants had SDH of which 12% (n = 5) were new. Figure 11 shows an exemplary postoperative subdural hemorrhage.

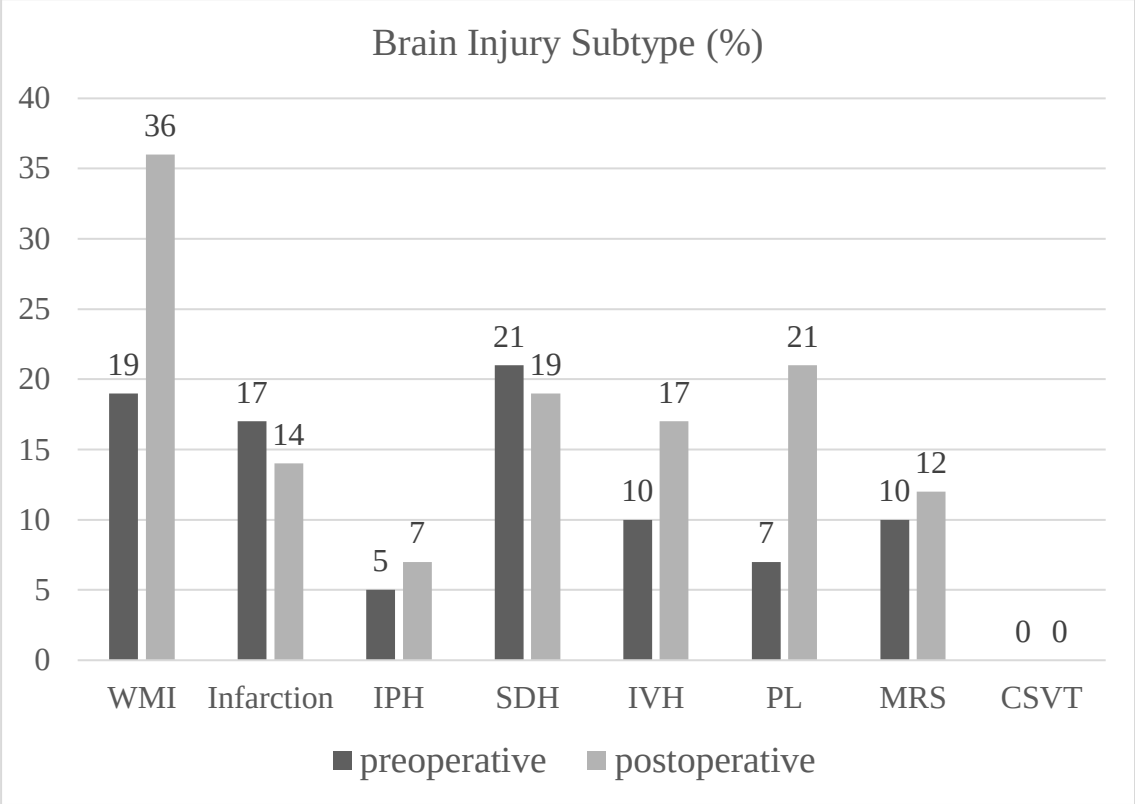
Figure 11. Postoperative epitentorial SDH



Epitentorial subdural hyperintersity (white arrows) in axial (A) and sagittal (B) T1-weighted images with corresponding hypointensity in T2 (C) and in SWI axial images (D).

IVH was observed in 17% (n = 7) of postoperative scans, of which 3 (7%) were not seen on the preoperative scan. Fourteen percent (n = 6) of patients suffered from ischemic preoperative findings. Neither pre- nor postoperative scans demonstrated CVST. In 10% (n = 4) pre- and 12 % (n = 5) of postoperative scans (new lesion: n = 4, 9%) elevated lactate on MRS was observed. Of those 8 cases with increased lactate, only 2 had no other injury types. Figure 12 compares pre- and postoperative brain injury types.

Figure 12. Pre- vs. postpostoperative brain injury



Postoperatively, twenty-seven of 42 (64%) patients had no lesion or only a mild TBIS (TBIS <6). 26% of the cases (n = 11) showed moderate injury (TBIS 6–10). Four (10%) patients suffered from severe injury (TBIS >10). The comparison between pre- and postoperative TBIS is depicted in Figure 13.

Figure 13. Pre- vs. postoperative TBIS

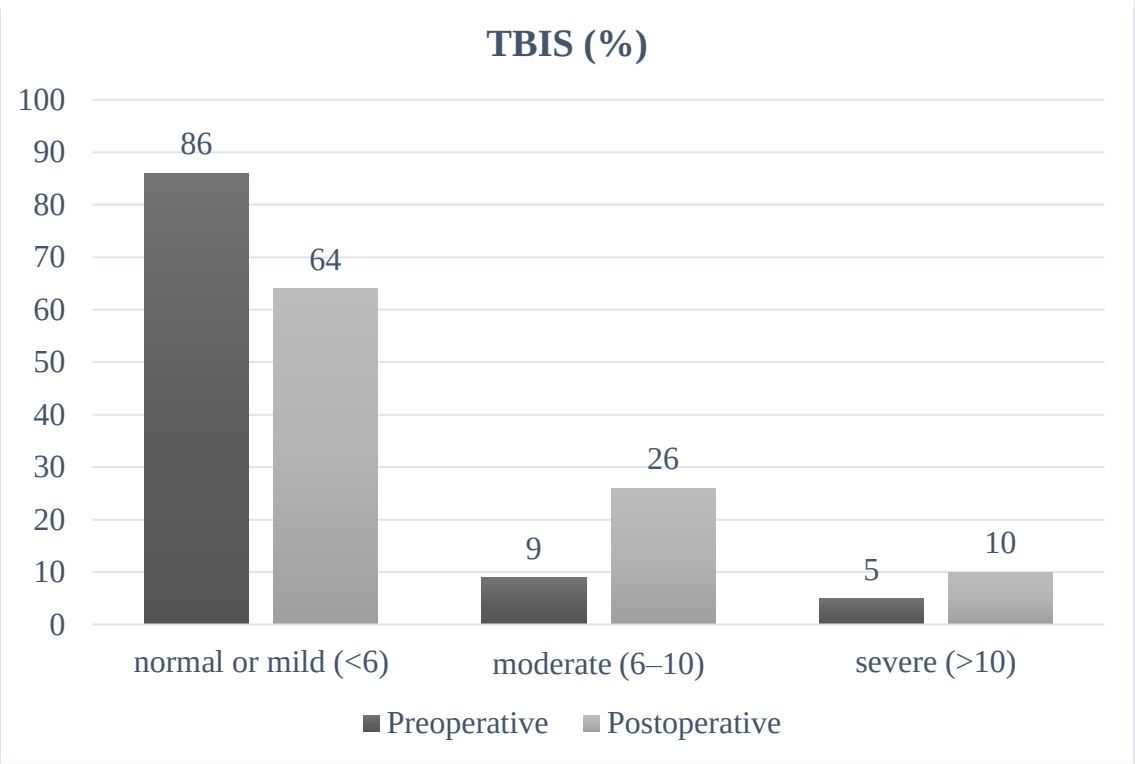


Table 6 and Table 7 summarize above mentioned radiographic data. Patients' cardiac diagnosis and surgery type, together with pre- and postoperative brain abnormalities, are listed in Table 8.

Table 6. Characteristics of pre- and postoperative brain MRIs adapted from (Kosiorek et al., 2021)

Variable	**Preoperative MRI** (n = 42)	**Postoperative MRI** (n = 42)	
Age (d) at time of MRI, median (IQR)	4 (3-5)	33 (18-50)	
TMS, median (IQR), n = 41	13 (12-14)	N/A	
TBIS, median (IQR)	1 (0-5)	4 (0-8)	
Brain Injury present, n (%)	21 (50)	28 (67)	
New Brain Injury, n (%)	N/A	21 (50)	
Brain Injury Subtype, n (%)		Total *	New Injury
WMI	8 (19)	15 (36)	11 (26)
Infarction	7 (17)	6 (14)	5 (12)
IPH	2 (5)	3 (7)	1 (2)
SDH	9 (21)	8 (19)	5 (12)
IVH	4 (10)	7 (17)	3 (7)
PL	3 (7)	9 (21)	9 (21)
MRS	4 (10)	5 (12)	4 (10)
CSVT	0 (0)	0 (0)	0 (0)

** Postoperative MRIs did not always demonstrate injury seen on pre-operative MRI.*

Table 7. Brain Injury Scores in patients with PSOM assessment at 12 months or grater (*Kosiorek et al.*, 2021)

Brain Injury Subtype, n (%)	**Preoperative MRI** (n = 29)	**Postoperative MRI** (n = 29)	
		Total	New Injury
WMI	6 (21)	11 (38)	7 (24)
Infarction*	4 (14)	4 (14)	4 (14)
IPH	2 (7)	3 (10)	1 (3)
SDH	8 (28)	7 (24)	4 (14)
IVH	3 (10)	4 (14)	1 (3)
PL	1 (3)	4 (14)	4 (14)
MRS	4 (14)	3 (10)	2 (7)
CSVT	0 (0)	0 (0)	0 (0)

** Infarctions noted on the preoperative MRI resolved or were reclassified as WMI on the postoperative scan.*

Table 8. Summary of cardiac defects, surgeries and brain injuries of the study population (Kosiorek et al., 2021)

Study ID	Diagnosis	Procedure	CPB	Pre-op WMI	Pre-op infarct/ IPH	New Post-op WMI	New Post-op infarct /IPH
Biventricular heart defects (n = 29):							
1	CoA	Left TT CoA Repair	2	2	2	3	2
2	CoA	Left TT CoA Repair	2	2	2	2	2
3	CoA	Left TT CoA Repair	2	1	2	2	2
4	CoA	Left TT CoA Repair	2	3	3	2	2
5	CoA	Left TT CoA Repair	2	2	1	1	2
6*	DORV	MBT Shunt	2	2	2	2	2
7	DORV	PAB + PDA Ligation	2	2	2	1	2
8	DORV	VSD Baffle	1	2	2	2	2
9	D-TGA	ASO	1	2	2	2	2
10	D-TGA	ASO	1	2	1	1	2
11	D-TGA	ASO + Tricuspid Annuloplasty	1	2	2	2	2
12	D-TGA	ASO	1	1	2	2	2
13	D-TGA	ASO	1	2	2	2	2
14	D-TGA	ASO	1	2	2	2	2
15	D-TGA	ASO	1	2	2	2	2
16	PS + AS	Pulmonary and Aortic Valvuloplasty	1	1	2	2	2
17	TAC	Repair of Truncus Arteriosus + VSD repair + Truncal Valve repair	1	2	1	1	1
18	TAPVC	TAPVC Repair	1	2	2	2	2
19	TAPVC	TAPVC Repair	1	1	1	2	2
20	TOF + PA	TOF Repair + RV-PA Conduit	1	2	1	2	1
21	TOF + PA	RV-PA Conduit	1	2	1	3	3

22	TOF + PA	TOF Repair + RV-PA Conduit	1	2	2	2	3
23	TOF + PA	TOF Repair	1	1	2	2	2
24	TOF + PS	TOF Repair	1	1	2	2	2
25	TOF + PS	TOF Repair	1	1	2	1	1
26	TOF + PS	TOF Repair	1	2	2	1	2
27	TOF + PS	TOF Repair + Supravalvar PAP	1	2	2	2	2
28	TOF + PS	TOF Repair	1	2	2	2	2
29	VSD + MS	VSD Repair	1	2	2	2	2
Single ventricle defects (n = 13):							
30	Complex SV	MBT Shunt	2	2	2	2	2
31	Complex SV	MBT Shunt	2	2	2	2	1
32	DORV	MBT Shunt	2	2	2	2	2
33	DORV	MBT Shunt	2	2	2	2	1
34	DORV	MBT Shunt	2	2	1	1	2
35	DORV	MBT Shunt	1	2	2	2	2
36	DORV	PAB + PDA Ligation	2	2	2	1	2
37*	DORV	MBT Shunt	2	2	1	1	2
38	D-TGA-VSD-LVOTO	MBT Shunt	2	2	2	2	2
39	TA	PAB + PDA Ligation	2	2	2	1	2
40	TA + PA	MBT Shunt	2	1	1	1	2
41*	UAVC + PA	MBT Shunt	2	2	2	3	1
42*	UAVC + TAC	MBT Shunt	1	2	2	2	1

*1 – yes, 2 – no, 3 – unable to perform, * deceased*

4.3 Neurological Outcome

Sixty-nine percent (n = 29) of the study cohort had a neurologic follow-up at or after 12 months of age (Table 5). The median age at neurologic assessment was 27.7 months. Based on the PSOM scoring system, 21% (6/29) of patients had a poor neurodevelopmental outcome (Table 9), including 4 deaths (age range within 12-90 months). 3 of the 4 deceased children had a neurologic evaluation after 12 months of age (i.e., before their death), all having a PSOM score > 1. The remaining child passed away at 9 months of age and consecutively did not receive a PSOM or GOS-E Peds evaluation. The median age at the neurologic evaluation of these 6 children with the adverse outcome by PSOM was 24 months (range: 12-80). In contrast, twenty-three children with the good outcome by PSOM had median age of 27 months (range: 14-77) at the assessment. Age difference at the evaluation between those with the adverse outcome versus those with the good outcome was not statistically significant (*P* = 0.477, Mann-Whitney U-test). By the GOS-E Peds assessment, 45% (13/29) had a poor outcome (Table 10)

Table 9. Impact of clinical and radiographic variables on PSOM outcome at 12 months or greater (Kosiorek *et al.*, 2021)

Variable	**Good Outcome (n = 23)**	**Poor Outcome (n = 6)**	***P* value**
Age at the time of assessment in months, median (range)	27 (14-77)	24 (12-80)	0.477
MBT shunt, n (%)	4 (18%)	5 (83%)	**0.005***
Surgery with CPB more than 1 time, n (%)	6 (26%)	4 (67%)	0.143
Days in ICU, median (IQR)	13 (10-22)	40 (34-200)	**0.003***
Total mechanical ventilation days, median (IQR)	4 (3-8)	13 (6-35)	**0.031***
Preoperative Injury, n (%)			
WMI	6 (26%)	0 (0%)	0.295
Infarct and/or IPH	5 (22%)	1 (17%)	0.999
Postoperative Injury, n (%)			
WMI	9 (39%)	2 (33%)	0.999
Infarct and/or IPH	3 (13%)	4 (67%)	**0.018***
Seizure postoperatively, n (%)	0 (0%)	3 (50%)	**0.005***

**Statistically significant univariate risk factor (P value < 0.05)*

Table 10. I*mpact* of c*linical and radiographic variables on GOS-E Peds at 12 months or greater* (Kosiorek *et al.*, 2021)

Variable	**Good Outcome (n = 16)**	**Poor Outcome (n = 13)**	***P* value**
Age at assessment in months, median (range)	26 (14-55)	27 (12-77)	0.559
MBT shunt, n (%)	3 (19%)	6 (46%)	0.226
Surgery with CPB more than 1 time, n (%)	4 (25%)	6 (46%)	0.271
Days in ICU, median (IQR)	14 (11-21)	38 (11-63)	0.124
Total mechanical ventilation days, median (IQR)	5 (3-8)	7 (3-21)	0.522
Preoperative Injury, n (%)			
WMI	5 (31%)	1 (8%)	0.183
Infarct and/or IPH	3 (19%)	3 (23%)	0.999
Postoperative Injury, n (%)			
WMI	7 (44%)	4 (31%)	0.702
Infarct and/or IPH	3 (19%)	4 (31%)	0.667
Seizure postoperatively, n (%)	0 (0%)	3 (23%)	0.078

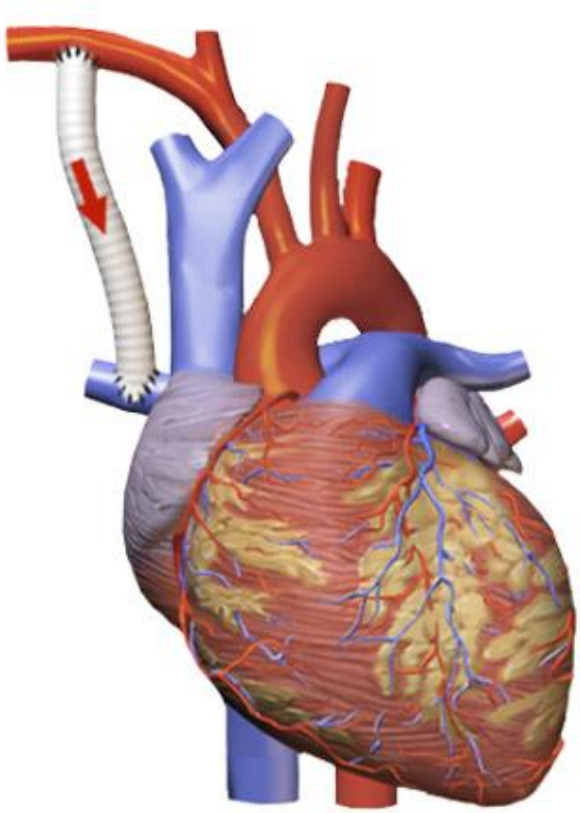
4.4 Seizure

On the whole, 31% (n = 13) of children had EEG monitoring during the hospital stay for their first heart surgery. Three of 13 (23%) monitored patients had an electrographic seizure, accounting for 10% (3/29) of the study population with a neurologic follow-up (Table 5). All seizures occurred outside of the immediate postoperative interval, in two cases during presumed sepsis and latter following a cardiac arrest. An ischemic lesion was reported on the postoperative brain scan in all three cases. Two patients had a border-zone infarction, and one patient had a global-hypoxic ischemic injury. All three patients had a poor neurologic outcome. 7 out of 10 remaining infants with EEG recording were monitored due to heightened risk for seizures after heart surgery with CPB support. Three patients had clinical events suspicious for seizure, however, continuous EEG monitoring did not prove electrographic seizures.

4.5 Predictors of Poor Neurological Outcome

In this study, the postoperative electrographic seizure was linked to the worse neurological outcome (PSOM: 50%, 3/6; P = 0.005). In addition, longer mechanical ventilation (P = 0.031) and prolonged ICU stay (P = 0.003) were also associated with the adverse outcome (by PSOM assessment). Analysis of surgical parameters showed that placing an MBT shunt (Figure 14) had a significant impact on neurological outcomes based on PSOM (P = 0.005) (Table 9) but not GOS-E Peds assessment (P = 0.226) (Table 10).

Figure 14. Diagram of modified Blalock Taussig Shunt, with a synthetic graft from the right subclavian artery to right pulmonary artery.

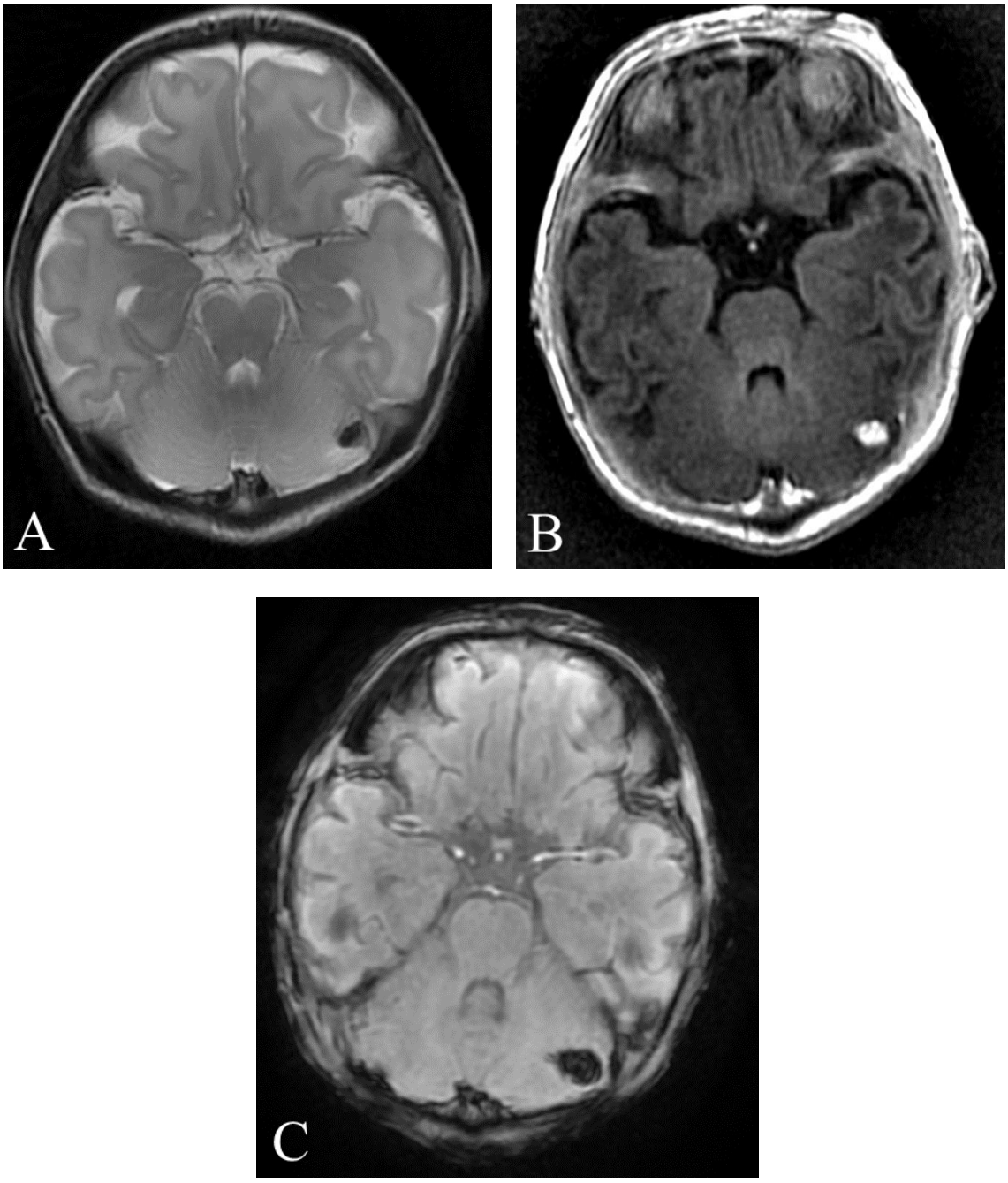


Original file: https://commons.wikimedia.org/wiki/File:Blalock_Taussig_Shunt_-_Aortic_to_Pulmonary.png. Modifications: Cropped and adjusted to page.

Particularly, 5 out of 9 (56%) patients with a history of MBT shunt had worse neurodevelopmental outcomes by PSOM evaluation. In contrast, only 1 out of 20 (5%) patients without a shunt had the poor outcome (odds ratio: 23.7, 95% confidence interval: 2.5-262). There was no significant difference in neurological sequelae between those undergoing a cardiac procedure with CPB once and more than once (PSOM: $P = 0.143$; GOS-E Peds: $P = 0.271$).

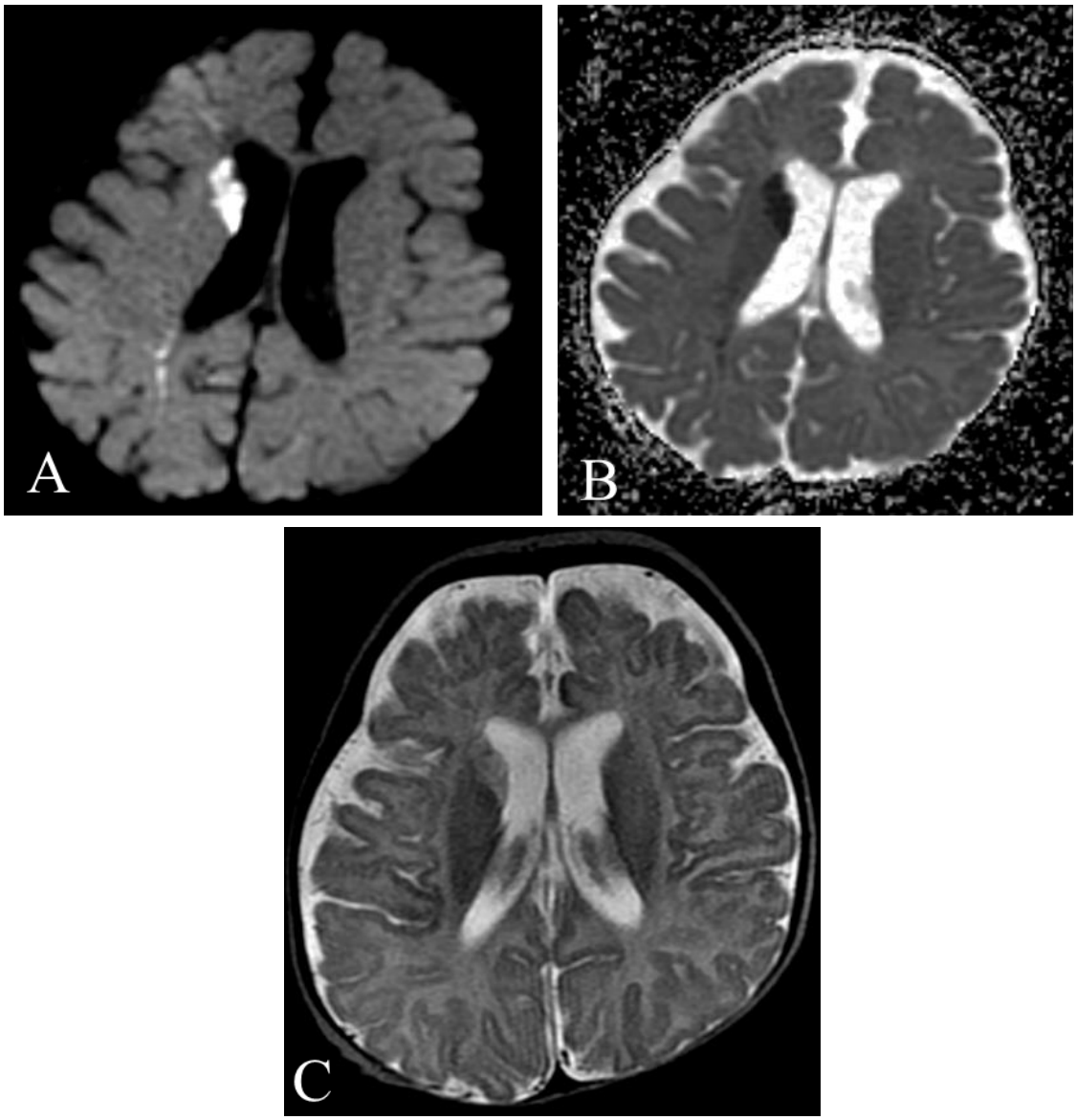
Assessment of preoperative brain injures demonstrated that both WMI and infarct/IPH had no significant influence on the outcome (Table 9 and Table 10). Furthermore, neither presence of postoperative WMI nor postoperative TBIS in the moderate or severe range (i.e., TBIS greater than 5) were linked to the poor outcome. In contrast, infarction and/or IPH postoperatively were proved to have a negative impact on the outcome (based on PSOM assessment) and found to be significant on multivariable analysis ($P = 0.018$) as well. This correlation was not observed with the GOS-E Peds evaluation, though ($P = 0.667$). Determinants of neurologic outcome (by univariate analysis) are demonstrated in Table 9 (PSOM) and Table 10 (GOS-E Peds). Examples of postoperative ischaemic infarction and IPH are presented in Figure 15 and Figure 16, respectively.

Figure 15. Postoperative left cerebellar hemorrhage



Left cerebellar hypointensity in T2 (A) and hyperintensity in T1(B)-weighted images with corresponding susceptibility in SWI (C).

Figure 16. Postoperative acute right caudate infarction



High DWI signal (A) and low ADC signal (B) with hyperintese signal in T2 (C) in the right caudate.

5 Discussion and Prospective

5.1 Introduction

To my knowledge, this is the first study that evaluates determinants of neurological outcome in CHD infants undergoing cardiac surgery exclusively without DHCA. Although this cohort has heterogeneous CHD diagnoses, the study intentionally excluded patients with features previously described to impact neurologic outcome (e.g., genetic condition and/or multiple congenital anomalies, prematurity).

5.2 Brain Injuries

In this population of CHD patients, pre- and postoperative cerebral abnormalities rates are consistent with findings from previous CHD studies. Preoperative brain injury was seen in 50% of MRI scans, similar to other studies, reporting that 23-57% of newborns with CHD have preoperative brain abnormality (Dent *et al.*, 2006; McQuillen *et al.*, 2007; Andropoulos *et al.*, 2010; Dimitropoulos *et al.*, 2013; Kelly *et al.*, 2019). Similarly, half of the cohort had a new postoperative brain lesion, which is at the high end of previous reports that documented new postoperative brain abnormalities in 35-48% of scans (Mahle *et al.*, 2002; McQuillen *et al.*, 2007; Chen *et al.*, 2009) (Table 11).

Contrary to what might have been anticipated, the removal of DHCA cases from the study group did not significantly decrease the frequency of brain injury postoperatively. Although this subpopulation of CHD infants was not emphasized in the past, an analysis of specific data from previous studies demonstrates that MRI findings in patients without DHCA exposure are similar to our cohort. For instance, in the study performed by Andropoulos et al., 88% of neonates who underwent neonatal heart surgery with two-ventricle repair (2V) were not exposed to DHCA (Andropoulos *et al.*, 2010). Neuroimaging in these neonates showed a similar prevalence of preoperative WMI (19%) and infarction (22%) to the CHD population examined here (19% and 17%, respectively). As far as new postoperative WMI is concerned, the rates were lower in the Andropoulos

et al. study, (6% vs. 26%). The incidence of new infarcts and/or IPH, on the other hand, was alike (18% vs. 14%).

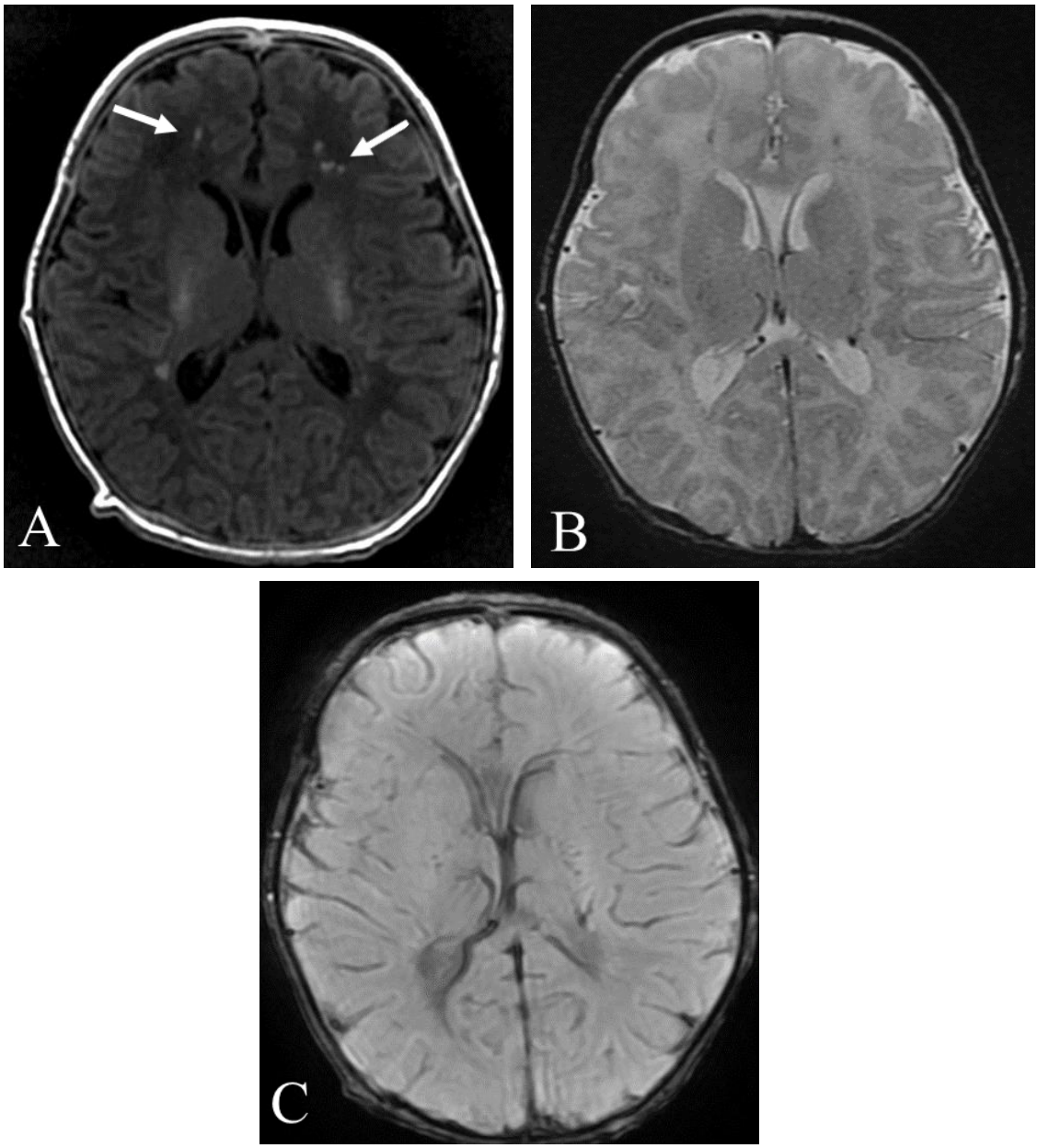
Even though numerous studies document a high incidence of brain injuries in pediatric patients with CHD undergoing heart surgery in infancy, the association between cerebral injury and neurological outcome has not been fully comprehended (Mebius *et al.*, 2017). This study showed that infarction and/or IPH postoperatively had a negative impact on the outcome. Similarly, in the Andropoulos et al. study, researchers describe an association between a new postoperative lesion and worse cognitive scores (Andropoulos *et al.*, 2010). Many questions concerning the influence of preoperative lesions on neurological outcomes remain unanswered. For instance, in the Beca et al. study, a preoperative lesion was not a predictor of worse outcome, similar to this cohort (Beca *et al.*, 2013).

Data from long-term neurodevelopmental outcome studies may shed light on this phenomenon.

In this study, WMI (pre- or postoperative) was not a predictor of poor neurodevelopmental outcome at 12 months or greater (Figure 17). This finding was also demonstrated in Beca's more extensive study of CHD neonates (n = 153) undergoing cardiac surgery with or without CPB support (Beca *et al.*, 2013). In the study, evidence of WMI had no influence on neurological outcome at 2 years of age. In contrary to these findings, there is growing evidence that WMI is associated with impairments in areas of higher cognitive function that might not be apparent in toddlers but first revealed in school-age children. This association, for instance, was reported in Claessens et al. study, where WMI was associated with lower Full-scale IQ at 6 years of age (Claessens *et al.*, 2018).

Further research on a larger study cohort is crucial to determine the long-term impact of neonatal WMI on neurodevelopment in CHD population.

Figure 17. Bilateral anterior and posterior WMI lesions

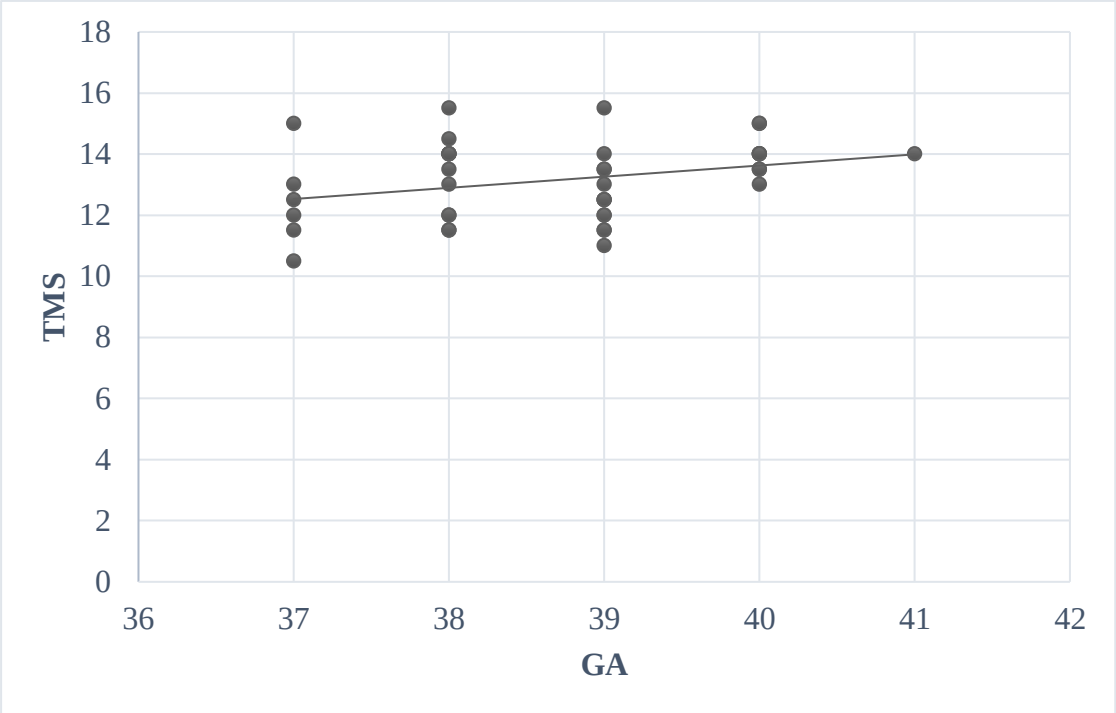


Hyperintensities (white arrows) in T2 (A) and hypointensities in T2 (B) without correlation in SWI (C), which is typical for this kind of lesions.

5.3 TMS

Brain maturation is delayed in term infants with complex CHD (Licht *et al.*, 2009). Licht et al. reported that mean TMS in CHD cohort are significantly lower, estimating a 1-month delay in structural brain development in comparison to healthy infants. Some neuroimaging studies associate delayed cerebral maturation in term CHD neonates with increased susceptibility to brain injury, especially WMI, and adverse neurodevelopmental outcome at 2 years of age and in adolescents (Licht et al., 2009; Andropoulos et al., 2010; Beca et al., 2013; Heinrichs et al., 2014). In my study, no assessment of impact or correlation between the TMS and cerebral injury or outcome could be made due to the low variability of preoperative TMS scores (Figure 18). On the other hand, this finding was an indication of the homogeneity of the study population.

Figure 18. Graph plot TMS vs GA



Each infant is represented by a single point, although some of points overlap.

5.4 PSOM vs. GOS-E Peds

In this series, two different neurological measures validated in pediatric patients were used to assess outcome: the PSOM and GOS-E Peds. The intention behind selecting these tools was their complementary nature, with the PSOM indicating the impairments observed during an exam and the GOS-E Peds quantifying functional deficits. The impact of investigated variables on outcome was not consistent among these two measurement tools.

Initially, the GOS-E Peds was created to assess pediatric TBI patients` outcomes from birth to 16 years old (Beers *et al.*, 2012). Outcome evaluations in this cohort were performed at a median age of around 28 months. The analysis of GOS-E Peds assessments showed no association between the selected variables and the outcome. One explanation may be that this measure is not sensitive enough to identify deficits in this age group. The gold standard for measuring developmental alterations in pediatric patients is the Bayley Scales of Infant and Toddler Development. Regrettably, no valuable analysis can be made using this standardized measure as it was not performed routinely throughout the study cohort.

Some studies have noticed a rise of psycho-cognitive dysfunction in school-age CHD children with history of surgery in infancy (Karl *et al.*, 2004; Liamlahi *et al.*, 2014). At 4 years of age, evaluations show deficits in expressive language, visual-motor integration and motor function (Bellinger *et al.*, 1999). Moreover, frequently reported maladjustments after open-heart surgery are behavioral deficits with internalized symptoms (e.g., anxiety) as well as externalizing symptoms (e.g., hyperactivity and inattention) (Shillingford *et al.*, 2008; Latal *et al.*, 2009; Liamlahi *et al.*, 2014). The neurologic evaluations performed in this series were primarily collected in children younger than 3 years of age, a developmental phase when it may be more challenging to delineate impairments in higher cognitive functions with the selected neurodevelopmental measures (i.e., PSOM and GOS-E Peds).

Further research is vital, as most developmental studies investigating both techniques focus on short-term outcomes exhibiting little predictive validity for long-term sequels.

5.5 Seizure

Seizures were an independent risk factor for poor outcomes in this cohort. Seizures can be observed in the postoperative period after heart surgery and are a hallmark of neurological dysfunction. Exposure to longer periods of DHCA, particular cardiac anatomy subtypes, and genetic conditions are all considered to be associated with an increased risk for postoperative seizures (Bellinger *et al.*, 1999; Clancy *et al.*, 2003, 2005; Marino *et al.*, 2012). In the immediate postoperative course (when monitored for 48 hours post-surgery), electrographic seizures are seen at a rate of 8% after neonatal heart surgery (Naim *et al.*, 2015). Seizures observed in this analysis developed outside the immediate post-surgery course and were related to subtle clinical change, leading to an ischemic cerebral injury. Ultimately, each seizure was a warning sign of an acute brain insult. Although the incidence rate of seizures in this study was low, these events were marked to influence the outcome. Comparably, Rappaport et al. disclosed that pediatric patients with clinical or electrographic seizures score lower on psychomotor and neurocognitive tests at 1 and 2.5 years of age and are at higher risk of brain injury (Rappaport *et al.*, 1998). Similarly, another study demonstrated that children with history of seizures in the perioperative period have lower mean IQ scores at 4 years of age (Bellinger *et al.*, 1999).

The rate of continuous EEG monitoring in this study cohort was low for two reasons. Firstly, patients enrolled in this study predate empiric EEG monitoring after cardiac surgery with CPB support at CNMC. Secondly, in this analysis, 43% of patients underwent surgery without CPB support and therefore would not qualify for routine monitoring at most institutions. All things considered, careful consideration should be given when interpreting the incidence of electrographic seizures and the influence on outcome in this series since continuous EEG monitoring was performed in minority of patients.

These findings strongly indicate that continuous EEG monitoring should be performed routinely in all infants undergoing open-heart surgery with or without CPB or DHCA.

5.6 MBT Shunt

An essential surgical predictor of adverse neurodevelopmental outcome examined in this analysis is the modified Blalock-Taussig shunt. MBT shunt is commonly performed in children with cyanotic heart defects to increase pulmonary arterial blood flow. Nevertheless, this palliative surgical procedure is reported to have high mortality (7%) and morbidity (13%), with an 11.8% incidence of acute thrombotic shunt occlusion (Gedicke *et al.*, 2010; Petrucci *et al.*, 2011; Gorla, Stumpf and Sandhu, 2018). Apart from the greater risk for hemodynamic instability associated with shunt thrombotic occlusion, MBT shunts may lead to diminished cerebral blood flow via innominate artery steal syndrome (IASS), resulting in a cerebral insufficiency with the retrograde flow on the right (Garabedian *et al.*, 1998). In this cohort, 29 % (n = 12) of patients underwent MBT, largely without CPB support (n = 10, 83%). MBT thrombosis was observed in 2 of out 12 patients (17 %). Placing MBT shunt was related to a longer stay in ICU (median 28 vs. 16 days) and mechanical ventilation duration (median 7 vs. 6 days). Overall, nine patients who underwent MBT participated in the neurological evaluation. Out of those 9 patients with a follow-up, more than half had an adverse outcome (PSOM, 5/9, 56%).

5.7 ICU Stay and Mechanical Ventilation

Last but not least, a protracted stay in ICU and longer mechanical ventilation were found to be independent predictors of adverse neurological sequelae in this cohort. These associations have been previously described in other studies (Wernovsky and Licht, 2016; Kuhn *et al.*, 2020). In addition to worse cognitive outcomes, higher incidence of repeated operations, as well as non-cardiac morbidity were linked to longer ICU stay (Newburger *et al.*, 2003; Sananes *et al.*, 2012; Tabbutt *et al.*, 2012; Andropoulos *et al.*, 2014; Wernovsky and Licht, 2016; Kuhn *et al.*, 2020).

The mechanisms behind worse outcomes after longer ICU length of stay have complex and multifactorial causation. In this analysis, neuroimaging was performed prior to discharge (median age of 34 days at the time of postoperative MRI), while Andropoulos et al. study reviewed MRIs within 7 days of surgery (Andropoulos *et al.*, 2010).

In the ICU setting, cerebral hypoperfusion and hypoxia are likely contributing factors for cerebral injuries in these patients. Nevertheless, further examination of these subtle correlations is needed. Another vital component to consider while reviewing the circumstances of an acquired cerebral insult and its potential impact on the neurodevelopmental outcome, is the time of postoperative MRI acquisition. While MRI performed in early stages enables detection of acute injuries after a specific high-risk incident (i.e., surgery), MRI performed in later stages allows assessment of lesions over a longer period of vulnerability (i.e., ICU stay). Table 11 portrays research studies and their key findings focusing on pre- and postoperative brain injury in CHD pediatric patients.

Further studies are essential to determine why injuries sustained postoperatively seem to have more adverse impact on outcome than preoperative injury.

Table 11. Comparison of studies investigating pre- and postoperative brain injury in CHD patients adapted from (Kosiorek et al., 2021)

Study	**Cohort:** Age (# of patients) Population	**Surgical conditions**	**MRI timing**	**Incidence of injury subtypes**	**Key findings**
(Mahle *et al.*, 2002) Institution: CHOP	Neonates (n = 24) CHD	DHCA in 88%	Preoperative	WMI 16% Stroke 8%	• High frequency of asymptomatic ischemic lesions on pre- and postoperative brain MRI in neonates with surgery for CHD
			Postoperative (up to 14 days, n = 21)	WMI 42% Stroke 19%	
(McQuillen *et al.*, 2007) Institution: UCSF	Neonates (n = 62) CHD	CPB in 91% DHCA in 23%	Preoperative	WMI 18% Stroke 21%	• BAS increases the risk for preoperative brain injury • Low mean BP on POD#1 increases the risk for postoperative WMI
			Postoperative (n = 53)	WMI 26% Stroke 9%	

					• Increased risk for postoperative brain injury in 1) SV with a Norwood and 2) CBP w/ RCP
(Chen *et al.*, 2009) Institution: CHOP	Infants < 6 m. (n = 122) CHD	All w/ CPB (DHCA in 62%)	Postoperative (3-14 days)	Stroke (10%) $^{\Sigma}$	• Increased stroke risk with lower BW, preop intubation, lower intraop HCT, higher SBP on CICU admission
(Andropoulos *et al.*, 2010) Institution: TCH	Neonates (n = 67) CHD	All w/ CPB DHCA in 50%	Preoperative	WMI 16% Stroke/IPH 20%	• Risk factors for postop WMI: low TMS & SV
			Postoperative (7-10 days)	WMI 15% Stroke/IPH 12%	
(Dimitropoulos *et al.*, 2013) Institution: UCSF/UCB	Infants <3 m. (n= 120) CHD	No data	Preoperative	WMI 21% Stroke 19%	• Higher SNAP-PE, lower preop O2 sat, lowest post op BP mean, and BAS (in TGA) predicted higher preoperative BIS • New postop BIS was assoc. with lower postop syst. & mean BP
			Postoperative (n = 104, median 10, 0-64 days)	WMI 18% Stroke 10%	
(Andropoulos *et al.*, 2014) Institution: TCH	Neonates (n=59) CHD	All w/ CPB (DHCA data not reported)	Preoperative	WMI 31% Stroke 23%	• New postop MRI injury, higher VAA exposure and inc ICU LOS each predicted lower cognitive scores
			Postoperative (within 7 days)	WMI 36% Stroke 26%	
(Kelly *et al.*, 2019) Institution: ELCH	Neonates (n=70) Critical or serious CHD	N/A	Preoperative	WMI 33% Stroke 4%	•Stroke only in TGA / BAS
(Beca *et al.*, 2013)		CPB in 84%	Preoperative	WMI 20%	

Institution: SCH/RCH	Infants < 8 wk. (n=153) CHD	(DHCA in 39%)		Stroke 21%	•New postop WMI predicted by longer CPB duration, postop lactate, brain maturity & preop WMI •Brain immaturity, but not brain injury predicted impaired neurodevelopment at 2 years
			Postoperative	WMI 44% Stroke 9%	
(Claessens *et al.*, 2018) Institution: UMCU	Neonates (n=34) CHD with aortic arch obstruction	All w/CPB	Preoperative	WMI 47%	•Mod-severe WMI was assoc. with lower cognitive scores at 2 yrs. and full-scale IQ at 6 years •Grey matter, focal infarctions did not impact outcome (n = 9, 26%) - pre vs. post not distinguished in the manuscript)
			Postoperative (< 10 days)	WMI 79%	
(Kuhn *et al.*, 2020) Institution: CNH	Neonates (n=53) TGA/HLHS	All w/ CPB, 94% w/DHCA	Preoperative	WMI 12% Stroke 11%	•BAS no assoc. with inc preop injury or stroke •HLHS inc risk for postop stroke in mod-severe range •ICU duration inc risk for postop injury in mod-severe range
			Postoperative (days 3-59)	WMI 35% Stroke 20%	

BAS Balloon septostomy, BW Birth weight, HLHS Hypoplastic left heart syndrome, inc increase, LOS Length of stay, POD Postoperative day, RCP Retrograde cerebral perfusion, (S)BP (Systolic) blood pressure, VAA Volatile Anesthetics,

CHOP Children's Hospital of Philadelphia, TCH Texas Children's Hospital, UMCU University Medical Center Utrecht, UCSF University of California San Francisco Beniof Children's Hospital, UCB British Columbia Children's Hospital, University of British Columbia, SCH Starship Children's Hospital, Auckland, New Zealand, RCH The Royal Children's Hospital, Melbourne, Australia, ELCH Evelina London Children's Hospital

**Postoperative injury—new lesions only presented*

$^{\Sigma}$*5% estimated to have occurred prior to surgery based on MRI appearance (subacute or remote)*

5.8 Limitations

Certain study limitations should be noted. This was a single-center study conducted on a small sample size with diverse heart defects and cardiac interventions. Although pre- and postoperative neuroimaging was advised for every pediatric patient undergoing cardiac corrective surgery in infancy, only a small number of infants had both scans. In addition, the inconsistent sampling might have led to sampling bias. For instance, an unstable medical condition of patients with complex CHD lesions might have prevented them from receiving preoperative neuroimaging. As a result, this population may be underrepresented in this series. On the other hand, MRI scans may not have been performed in patients with less severe heart defects at all. Variability in the timing of the postoperative scans may have affected brain injury assessment, as some lesions may resolve over time. Additionally, the small study cohort and, in particular, a small percent of infants with TBIS in the moderate/severe spectrum hindered the assessment concerning the influence of structural cerebral lesions on the outcome. As mentioned before, continuous EEG monitoring was performed in minority of patients. As a result, incidence of electrographic seizures and the influence on outcome in this series should be interpreted with consideration. Lastly, roughly one-third of patients did not return for a neurological evaluation, and hence their outcome is unnoted.

5.9 Conclusions

Considerable attention has been directed to cardiovascular surgical techniques that may lower the incidence of brain injury and boost neurological outcomes in CHD patients. This analysis, together with other studies mentioned above, emphasizes that cerebral injury and neurologic sequelae are affected mainly by the complexity of a cardiac defect and perioperative clinical course.

Pediatric patients with CHD undergoing infant cardiac surgery without DHCA are at risk of the adverse neurodevelopmental outcome. Longer ICU stay, prolonged mechanical ventilation, MBT shunt procedure, and presence of postoperative seizures are crucial determinants of the neurological outcome in this CHD subpopulation. Even though cerebral alterations in infants with CHD are frequently observed on MRI scans before and after open-heart surgery without DHCA, solely brain ischemic insults and/or IPH were related to worse neurological outcomes among this select population.

6 Summary

Introduction: Numerous studies identified potential risk factors for adverse neurodevelopmental outcome in infants with congenital heart disease (CHD). Nevertheless, little is known about neurologic sequelae within CHD subpopulations. The aim of the study was to illustrate perioperative variables and abnormal brain MRI findings in a specific CHD subpopulation of infants who were not exposed to deep hypothermic circulatory arrest (DHCA) during their first heart surgery. A secondary aim was to determine the impact of clinical characteristics, perioperative course and neuroimaging abnormalities on neurological outcome in this subpopulation of CHD patients.

Methods: Infants with CHD who underwent open heart surgery without DHCA between 2009 and 2017 were identified from a cardiac surgery database. Full term infants < 10 weeks of age at the time of surgery who received both a pre- and post-operative brain MRI were included. Patients with genetic neurodevelopmental disorders were excluded. Brain Injury Scores (BIS) were assigned to pre- and postoperative brain MRIs. Variables were examined for association with neurological outcome of the patients at ≥ 12 months of age using the Pediatric Stroke Outcome Measure and Glasgow Outcome Scale-Extended.

Results: In the study, 42 infants were enrolled and evaluated, of which 69 % (n = 29) participated in a neurological follow-up at ≥ 12 months of age. Prolonged stay in the intensive care unit (ICU, $P = 0.003$), extended mechanical ventilation ($P = 0.031$), modified Blalock-Taussig (MBT) shunt procedure ($P = 0.005$) and presence of seizures in the postoperative period ($P = 0.005$) were associated with worse neurological outcome. In the multivariable analysis postoperative cerebral infarction and/or intraparenchymal hemorrhage (IPH) were linked to adverse outcome ($P = 0.018$). Total BIS scores did not predict the outcome.

Conclusion: Adverse neurologic outcome in infants with CHD after infant cardiac surgery without DHCA was associated with prolonged ICU stay, extended mechanical ventilation, MBT shunt, presence of postoperative seizures as well as postoperative stroke and/or IPH.

7 Zusammenfassung

Einleitung: Zahlreiche Studien haben bereits potenzielle Risikofaktoren für ein negatives neurologisches Outcome bei Säuglingen mit kongenitalen Herzfehlern (CHD) identifiziert. Derzeit ist jedoch wenig zu den Subpopulationen mit CHD bekannt. Ziel dieser Studie war es, perioperative Variablen und abnormale MRI-Befunde des Gehirns innerhalb einer Subpopulation mit CHD, die während ihrer ersten Herzoperation keinen tiefen hypothermischen Kreislaufstillstand (DHCA) ausgesetzt waren, darzustellen. Als sekundäres Ziel sollte der Einfluss klinischer Merkmale, des perioperativen Verlaufs und von Hirnschäden auf die neurologische Entwicklung dieser Subpopulation evaluiert werden.

Methoden: Säuglinge mit CHD, bei denen zwischen 2009 und 2017 eine Operation am offenen Herzen ohne DHCA durchgeführt wurde, wurden über eine herzchirurgische Datenbank identifiziert. Alle termingeborene Säuglinge, die bei der Operation < 10 Wochen waren sowie eine prä- und postoperative MRI des Gehirns hatten, wurden eingeschlossen. Brain Injury Scores (BIS) wurden den Hirn-MRIs zugeordnet. Der Zusammenhang zwischen den Variablen und dem neurologischen Outcome aller Patienten mit neurologischer Folgeuntersuchung im Alter von ≥12 Monaten wurde mit dem *Pediatric Stroke Outcome Measure* und *Glasgow Outcome Scale-Extended* untersucht.

Ergebnisse: In die Studie wurden 42 Säuglinge eingeschlossen und charakterisiert, von denen 69% (n = 29) an der neurologischen Folgeuntersuchung im Alter ≥ 12 Monaten teilnahmen. Längere Aufenthalte auf der Intensivstation (ICU, P = 0,003), längere mechanische Beatmung (P = 0,031), modifizierte Blalock-Taussig (MBT) Shunt-Verfahren (P = 0,005) und postoperative epileptische Anfälle (P = 0,005) wurden mit einem schlechteren neurologischen Outcome assoziiert. Ein postoperativer Hirninfarkt und/oder eine intraparenchymatöse Blutung (IPH) waren in der multivariablen Analyse mit einem schlechteren Outcome verbunden (P = 0,018), dagegen sagten die Gesamt-BIS-Scores die neurologischen Folgen nicht voraus.

Schlussfolgerungen: Als negativen Einfluss auf die neurologische Entwicklung von Säuglingen mit CHD nach einer Herzoperation ohne DHCA konnten verlängerte ICU-Aufenthalte, verlängerte mechanische Beatmung, ein MBT-Shunt und postoperative epileptische Anfälle sowie postoperative Hirninfarkte und/oder IPH identifiziert werden.

8 Abbreviations

AS	Aortic stenosis
ASO	Arterial switch operation
B	Bands of migrating glial cells
BAS	Balloon septostomy
BW	Birth weight
CANDO	Cardiac Neurodevelopmental Outcome Program
CHD	Congenital heart disease
CHOP	Children’s Hospital of Philadelphia
CNMC	Children's National Medical Center
C	Cortical and insular infolding
CoA	Coarctation of aorta
CPB	Cardiopulmonary bypass
CSVT	Dural sinovenous thrombosis
DHCA	Deep hypothermic circulatory arrest
DORV	Double outlet right ventricle
D-TGA	D-transposition of great arteries
ECMO	Extracorporeal membrane oxygenation
ELCH	Evelina London Children’s Hospital
GA	Gestational age
GM	Germinal matrix
GOS-E Peds	The Pediatric version of Glasgow Outcome Scale-Extended
HLHS	Hypoplastic left heart syndrome
IASS	Innominate artery steal syndrome
ICU	Intensive care unit

Inc	increase
IPH	Intraparenchymal hemorrhage
IVH	Intraventricular hemorrhage
Left TT	Left thoracotomy
LOS	Length of stay
LVOTO	Left ventricular outflow tract obstruction
M	Myelination
MBT	Modified Blalock-Taussig
MRI	Magnetic resonance imaging
MRS	Elevated lactate on MR spectroscopy
MS	Mitral stenosis
OL	Oligodendrocytes
PA	Pulmonary atresia
PAB	Pulmonary artery band
PAP	Pulmonary artery plasty
PDA	Patent ductus arteriosus
PL	Punctate lesions
POD	Postoperative day
PS	Pulmonary stenosis
PSOM	The Pediatric Stroke Outcome Measure
PVL	Periventricular leukomalacia
RCH	The Royal Children's Hospital, Melbourne, Australia
RCP	Retrograde cerebral perfusion
RV-PA	Right ventricle to pulmonary artery
SCH	Starship Children's Hospital, Auckland, New Zealand
SDH	Subdural hemorrhage

SV	Complex single ventricle
(S)BP	(Systolic) blood pressure
TA	Tricuspid atresia
TAC	Truncus arteriosus
TAPVC	Total anomalous pulmonary venous connection
(T)BIS	(Total) Brain Injury Score
TCH	Texas Children's Hospital
TGA	Transposition of the great arteries
TMS	The total maturation score
TOF	Tetralogy of Fallot
UAVC	Unbalanced atrioventricular canal defect
UCB	British Columbia Children's Hospital, University of British Columbia
UCSF	University of California San Francisco Benioff Children's Hospital
UMCU	University Medical Center Utrecht
VAA	Volatile Anesthetics
VSD	Ventricular septal defect
WM	White matter
WMI	White matter injury

9 List of Tables

10 List of Figures

11 Bibliography

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12 Publications

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13 Ehrenwörtliche Erklärung

„Hiermit erkläre ich, dass ich die vorliegende Arbeit selbständig und ohne unzulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Alle Textstellen, die wörtlich oder sinngemäß aus veröffentlichten oder nichtveröffentlichten Schriften entnommen sind, und alle Angaben, die auf mündlichen Auskünften beruhen, sind als solche kenntlich gemacht. Bei den von mir durchgeführten und in der Dissertation erwähnten Untersuchungen habe ich die Grundsätze guter wissenschaftlicher Praxis, wie sie in der „Satzung der Justus-Liebig-Universität Gießen zur Sicherung guter wissenschaftlicher Praxis“ niedergelegt sind, eingehalten sowie ethische, datenschutzrechtliche und tierschutzrechtliche Grundsätze befolgt. Ich versichere, dass Dritte von mir weder unmittelbar noch mittelbar geldwerte Leistungen für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen, oder habe diese nachstehend spezifiziert. Die vorgelegte Arbeit wurde weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde zum Zweck einer Promotion oder eines anderen Prüfungsverfahrens vorgelegt. Alles aus anderen Quellen und von anderen Personen übernommene Material, das in der Arbeit verwendet wurde oder auf das direkt Bezug genommen wird, wurde als solches kenntlich gemacht. Insbesondere wurden alle Personen genannt, die direkt und indirekt an der Entstehung der vorliegenden Arbeit beteiligt waren.

Mit der Überprüfung meiner Arbeit durch eine Plagiatserkennungssoftware bzw. ein internetbasiertes Softwareprogramm erkläre ich mich einverstanden.“

Datum: 01.02.2022

Agnieszka Kosiorek

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15 Curriculum Vitae