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Short communication

Smaller brain volumes at two years of age in patients with hypoplastic left heart syndrome - Impact of surgical approach

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ABSTRACT

Background: Brain growth in hypoplastic left heart syndrome (HLHS) is reduced before and after birth. Little is known about further brain growth until two years of age before Fontan procedure and the potential impact of type of surgery.
Methods: In a prospective, two-center study 29 patients with HLHS and variants were treated by Norwood (n = 5) or Hybrid procedure (n = 24). At two years of age a cerebral MRI was performed and brain volumes (total gray, deep gray, white matter) and cerebrospinal fluid volume were calculated using FreeSurfer image analysis suite and compared to a healthy control group (n = 8).
Results: The total brain volumes in patients with HLHS were smaller compared to controls (HLHS: 893 ± 76 ml vs. controls: 1015 ± 148 ml, p = 0.005). This difference was found in all three brain compartments after Norwood procedure, whereas patients after Hybrid procedure had total and deep gray volumes comparable to controls. When comparing Norwood to Hybrid patients, deep gray matter volume reduction was more pronounced (Norwood: 38.4 ± 4.1 ml vs. Hybrid: 44.4 ± 3.9 ml, p = 0.005) than white matter reduction (Norwood: 255 ± 19 ml vs. Hybrid: 285 ± 31 ml, p = 0.032).
Conclusions: Smaller total and regional brain volumes were found two years after Norwood or Hybrid procedure in children with HLHS. The brain volume reduction was more distinct after Norwood than after Hybrid procedure. Longitudinal studies are needed to identify impact of early staged-surgeries on brain development and may become part of the decision-making process in individual patients.
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1. Introduction

Impaired brain growth and brain development has been described for fetuses before [1] and neonates after birth [2] in hypoplastic left heart syndrome (HLHS), one of the most complex types of congenital heart disease (CHD). Little is known about brain volumes at two years of age before Fontan procedure. The treatment of HLHS includes a staged surgical approach with Norwood stage I after birth and stage II at 4 months of age with bidirectional cavo-pulmonary anastomosis. The Hybrid procedure with stenting of the patent arterial duct, balloon dilatation of the atrial septum defect, and bilateral pulmonary artery banding has been established as an alternative to the conventional HLHS treatment by Norwood procedure with high survival rates [3,4] and comparable long-term results [5]. The Hybrid procedure postpones the cardiopulmonary bypass for the comprehensive stage II surgery to an older age of 4 months, and therefore may be neuroprotective.

Brain development of neonates with HLHS is delayed by approximately 5 weeks at birth [6]. Immature brain structures are more vulnerable towards various risk factors [7,8], and postponing of cardiac surgery to a later time point might be potentially neuroprotective, but this could not be shown so far on a clinical outcome purpose at 4 years of age without data on brain volume before Fontan procedure [9]. However, retrograde cerebral perfusion remains until stage II and the number of catheter-based re-interventions are higher for the Hybrid procedure between stage I and stage II, which may neutralize the potentially beneficial effect of delayed surgery [5,10].

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Therefore, the aim of this study was to compare brain volumes in infants with HLHS treated either by Norwood or by Hybrid procedure determined at two years of age before stage III Fontan procedure, which finalizes parallel (i.e. systemic and pulmonary) circulation in HLHS.

2. Methods

This prospective, two-center study was performed at two Pediatric Heart Centers at the University Children's Hospital, Zurich, Switzerland and Giessen, Germany between 2012 and 2015 in a larger cohort of children with univentricular heart defects [10]. For this secondary analysis of brain volumes, we studied a subgroup of 29 patients with either HLHS (n = 25) or variants of HLHS (n = 4). HLHS included mitral atresia (MA)/aortic atresia (AA) (n = 10), mitral stenosis (MS)/AA (n = 7), MA/aortic stenosis (AS) (n = 5), and MS/AS (n = 3). Variants of HLHS included patients with hypoplastic left heart complex (HLHC) with severe aortic arch hypoplasia with borderline left ventricle (n = 3), and unbalanced atrio-ventricular septal defect (n = 1). Perioperative intensive care data, surgical and catheter-interventional details, and outcome are described in prior publications [10,11]. Both centers are experienced with Norwood and Hybrid procedures since more than one decade, both with a preference for the Hybrid procedure. Indications for Norwood procedure are a diminutive diameter of the ascending aorta (<2 mm) and technical problems of duct stenting.

Cerebral MRI was performed before Fontan procedure at an age (mean ± SD) of 27.3 ± 4.1 months under sedation, combined with routine diagnostic cardiac catheterization. Furthermore, a control group of healthy age-matched children (n = 8) was enrolled, scanned at a comparable age (29.7 ± 9.5 months) for headache (n = 3), afebrile epileptic seizure (n = 3), suspected elevated intracranial pressure (n = 1), and dermatologic lesion (n = 1). All of them had a normal cerebral MRI and showed a normal neurodevelopment. For brain volumetric measurements, high-resolution 3D T1-weighted images (Giessen: magnetization prepared rapid acquisition gradient echo, MP-RAGE; Zürich: spoiled gradient echo, SPGR) were used, as previously described [10]. Volumes were calculated with the Freesurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/) on a Linux workstation, which has been validated for this age group [10]. The brain volumes were anatomically segmented into total gray, deep gray, white matter (with the sum of all three tissue compartments defined as total brain volume) and cerebrospinal fluid (CSF) (with the sum of all four compartments as total intracranial volume). For the evaluation of focal and diffuse brain injury pattern on cerebral MRI we used this segmenting technique, as previously described for different age groups [12,13], different brain compartments [14] and during brain development at different time points starting at fetal life [15]. Statistical analyses were performed with IBM SPSS Statistics for Macintosh, version 24 (IBM Corp., Armonk, N.Y.). To calculate group differences, we used the *t*-test or the Mann-Whitney-*U* test based on the dispersion of the data. A significance level of 0.05 was applied.

The study was approved by the local ethical committees and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki [16].

Norwood procedure was performed in five patients, Hybrid procedure without heart-lung machine was performed in 22 patients. In two patients, a short heart-lung machine surgery became necessary at Stage I for atrial septectomy due to a restrictive foramen ovale. However, this procedure was done without cardioplegia, under normal body temperature 36 °C, and with sustained cerebral perfusion. Therefore, we included these two patients to the Hybrid group (n = 24).

3. Results

Total brain volumes of two-year-old single-ventricle infants were smaller before Fontan procedure compared to healthy age-matched controls (HLHS: 893 ± 76 ml vs. controls: 1015 ± 148 ml, p = 0.005, Table 1). Smaller regional brain volumes were also found within the three calculated tissue compartments including total gray matter (HLHS: 615 ± 60 ml vs. controls: 685 ± 86 ml, p = 0.011), deep gray matter (HLHS: 43.4 ± 4.5 ml vs. controls: 49.6 ± 6.7 ml, p = 0.004), and white matter (HLHS: 280 ± 23 ml vs. controls: 331 ± 64 ml, p = 0.003) (Table 1). The CSF volume was larger in infants with HLHS compared to controls (HLHS: 17.7 ml [IQR 13.3 to 22.2] vs. controls: 11.9 ml [IQR 9.5 to 13.8]; p = 0.004) (Table 1). The relative differences (%) between HLHS compared with controls were calculated for total brain volume with 12.0%, for total gray matter with 10.2%, deep gray matter with 12.5%, and for white matter with 15.4%.

When comparing the surgical approaches, we found smaller regional brain volumes in the deep gray (Norwood: 38.4 ± 4.1 ml vs. Hybrid: 44.4 ± 3.9 ml; p = 0.005) and white matter (Norwood: 255 ± 19 ml vs. Hybrid: 285 ± 31 ml; p = 0.032) (Fig. 1). The average relative difference for deep gray matter and white matter volumes was 12.5% and 10.5%, respectively.

4. Discussion

In this study, we found smaller total brain matter and greater CSF volumes in infants treated for HLHS compared to healthy controls at two to three years of age (Table 1). This finding was more pronounced for Norwood patients compared to patients followed by the Hybrid approach, which had comparable total gray matter and deep gray matter volumes to controls (Fig. 1).

Impairment of global and regional brain growth and development has been described for fetuses [1], neonates [13], small infants [2], and adolescents with different types of CHD [12]. After birth, before cardiac surgery a reduction of global brain volume of 21% and of regional brain volumes ranging between 8% and 28% has been reported [13]. Ortinau et al. recently showed ongoing longitudinal brain growth trajectories from fetal life until 4 months of age in complex CHD patients [2]. In children with complex CHD multiple innate [17] and external factors affect brain development and impact short and long-term outcome [18]. Various patho-mechanisms are relevant for brain development during fetal life when oxygen and energy supply is reduced in cases of hypoplastic aortic arch morphologies [19]. After birth, multiple events impairing brain development can occur due to the need for early neonatal cardiopulmonary bypass surgery associated with long perioperative intensive care courses (including hospital stay, mechanical ventilation, anaesthetic drugs, malnutrition, and infection/inflammation), recently reviewed by Peyvandi et al. [20]. Hence, the reduction of brain matter in 2 year-old single-ventricle CHD patients that was more pronounced in the Norwood group might depict a potential benefit of the Hybrid procedure. However, other therapy-related factors, such as a higher number of catheter-based reinterventions in the Hybrid procedure between stage I and II, prolonged retrograde perfusion of the aortic arch and coronary arteries, especially in cases with aortic atresia and extreme hypoplastic ascending aorta should lead to consideration which type of surgery might be beneficial for the individual patient [5]. So far, little is known about the impact of the described regional brain volume reduction in patients treated for HLHS on long-term outcome until adulthood [14]. On the other hand, at the age of 2 to 3 years significant differences of neurodevelopmental outcome using by the Bayley-III scores between

Table 1
Intracranial volumes in HLHS children after Hybrid or Norwood approach at two to three years of age compared among each other and compared to healthy controls.

	HLHS (n = 29)	HLHS Hybrid (n = 24)	HLHS Norwood (n = 5)	Controls (n = 8)	p-Value HLHS vs. controls	p-Value Norwood vs. controls	p-Value Hybrid vs. controls	p-Value Hybrid vs. Norwood
Age at MRI	27.3 ± 4.1	27.6 ± 4.3	26.4 ± 3.3	29.7 ± 9.5	*0.520*	*0.280*	*0.450*	*0.629*
Total intracranial volume (ml)	918 ± 83	932 ± 82	851 ± 59	1028 ± 148	*0.078*	***0.029***	*0.117*	*0.051*
Total brain matter (ml)	893 ± 76	907 ± 87	831 ± 61	1015 ± 148	***0.005***	***0.025***	***0.016***	*0.089*
Total gray matter (ml)	614.8 ± 59.8	622.6 ± 60.7	577.6 ± 42.1	685.2 ± 86.2	***0.011***	***0.030***	*0.051*	*0.101*
Deep gray matter (ml)	43.4 ± 4.5	44.4 ± 3.9	38.4 ± 4.1	49.6 ± 6.7	***0.004***	***0.019***	*0.051*	***0.005***
White matter (ml)	279.8 ± 23.1	284.9 ± 30.8	255.2 ± 18.6	331.1 ± 64.3	***0.003***	***0.045***	***0.041***	***0.032***
Cerebrospinal fluid volume (ml)	17.7 (13.2, 22.2)	17.6 (13.1, 22.5)	17.9 (13.1, 23.6)	11.9 (9.5, 13.8)	***0.004***	***0.030***	***0.008***	*0.933*

Data are given as mean and SD or median and interquartile-range (Q1, Q3). p-Values by *t*-test or Mann-Whitney *U* test.
Boldfaced italic numbers indicate significance, p < 0.05.

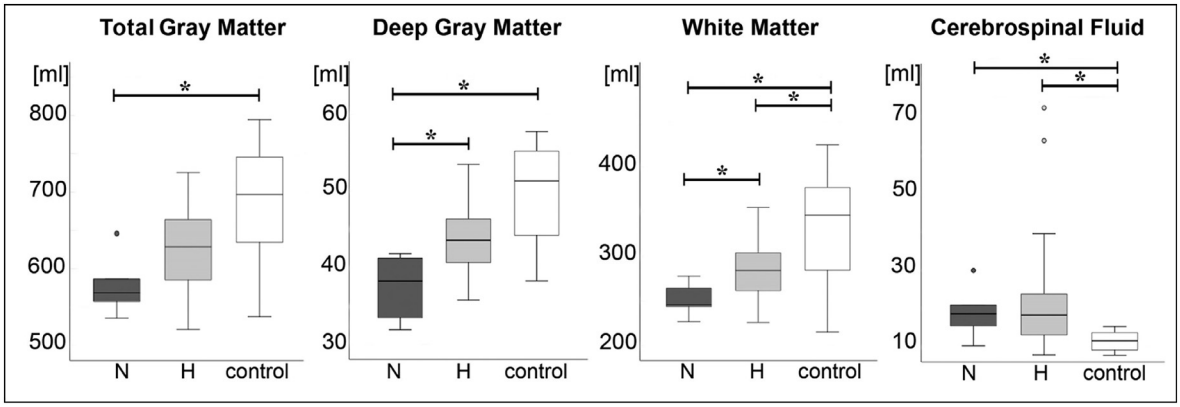

Fig. 1. The graphs show brain volumes of HLHS patients at two to three years of age, with median and interquartile range. Patients received either Hybrid (H, n = 24, light gray bars), Norwood operation (N, n = 5, dark gray bars), or were healthy toddlers (n = 8, control, white bars). Circles represent outliers. Significant differences between patients in deep gray matter volumes, white matter volumes, and cerebrospinal fluid (CSF) are displayed (*<0.05). p-Values by Student's *t*-test or Mann-Whitney *U* test.

Norwood and Hybrid procedure, HLHS versus non-HLHS have not been determined [11]. Longitudinal studies are needed to follow those children until older age, when more differentiating neurodevelopmental tests are available.

Limitations to the study are the small number of patients, particularly with regard to surgical procedures, and the enrollment from two different participating centers including their preference and performance for Norwood or Hybrid, which significantly limits statistical adjustment for potential confounders such as repeated re-interventions or patient-specific factors.

In future, larger longitudinal multi-center studies are needed for a better understanding of brain development by serial cerebral MRI and the correlation of neurodevelopmental outcome during long-term follow up.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.03.055.

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