# Neurodevelopmental outcome in hypoplastic left heart syndrome after hybrid procedure

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**Background:** Little is known about the mid-term outcome and brain development in patients following the hybrid approach for hypoplastic left heart syndrome (HLHS). This study investigates neurodevelopmental outcome, quality of life (QoL) and brain MRI findings in HLHS preschoolers treated with the hybrid approach.

**Methods:** Twenty HLHS patients (60% males) have been examined after neonatal hybrid Stage I and comprehensive stage II operation at the Pediatric Heart Center Giessen, Germany, between 2012 and 2016. Patients were evaluated with the Bayley Scales of Infant and Toddler Development III (Bayley-III), neurological examination, the Preschool Children Quality of Life Questionnaire (TAPQOL) at age 26.5±3.6 months, and again at 39.7±3.9 months with the Pediatric Cardiac Quality of Life Inventory (PCQLI). Furthermore, brain volumetric measurements and conventional brain MRI findings (27.3±4.5 months) were analyzed and compared with six healthy controls (29.2±11.1 months, P=0.53). Children with verified genetic comorbidities were excluded.

**Results:** Mean cognitive, language, and motor composite scores on the Bayley-III were not different from healthy norms (100±15), and were 101±9.3 (P=0.48), 100±13 (P=0.93), and 98±11.7 (P=0.45), respectively. Status post stroke was the most common brain MRI abnormality, and was found in 3/19 (16%) patients, most common affecting the middle cerebral artery territory. In comparison to controls, total white matter volumes were reduced (P=0.014), and cerebrospinal fluid (CSF) volumes were increased (P=0.042) in patients. Overall health-related QoL in 2 to 3 years aged children HLHS was good, but inferior scores in the motor subscale were noted compared to healthy norms (P=0.007). However, at 3 to 4 years, parents reported comparable QoL for their children in the PCQLI to children with biventricular heart lesion.

**Conclusions:** HLHS patients followed by hybrid approach without major complications show a favorable neurodevelopment at 2–3 years of age. Despite extensive health-related burden, the vast majority of Fontan preschoolers with HLHS showed a good health-related QoL. Nevertheless, comprehensive care and establishing routine follow-up examinations are important to recognize long-term challenges and further improve neurodevelopmental outcome of this high-risk patient population.

**Keywords:** Congenital heart disease (CHD); hypoplastic left heart syndrome (HLHS); brain development; neurodevelopmental outcome; hybrid procedure

## Introduction

Improvements in prenatal diagnosis, birth, perinatal, and perioperative management in specialized pediatric heart centers have raised survival rates up to 86% even for the most complex forms of congenital heart disease (CHD), like the hypoplastic left heart syndrome (HLHS) (1). However, this is paralleled by only slight improvement of neurodevelopmental outcome (2). Neurological impairments and intellectual problems remain recognized challenges among long-term survivors with HLHS (3). Endeavor in the care of this growing high-risk population has shifted from reduction of mortality to prevention of long-term morbidity, improvement of health-related quality of life (HRQoL) and neurodevelopmental sequelae (4).

Antenatal brain maturational delay has been described to play an important role in this altered cerebral development (5). In fetuses with HLHS, abnormal brain growth, especially of the white matter structures, becomes detectable as early as the second trimester and reduced retrograde blood flow via the hypoplastic aortic arch has been hypothesized to be a culprit factor (6,7). It is well described that term infants with HLHS show disproportionately reduced head circumferences at birth (7-9) and a delay of approximately one month in structural brain development (10), constituting a risk factor for consequent brain injury and developmental delay (11,12). It has been postulated that prevalence and severity of developmental disabilities further increase, if open-heart surgery is required during the neonatal period, since hypoxic/ischemic conditions, coagulation imbalances, inflammatory processes, and anesthetic drugs related to surgeries may further delay brain maturation and increase the risk of secondary acquired structural brain injury (13).

After nearly two decades of experience with the Hybrid procedure (surgical bilateral pulmonary banding and catheter-guided stenting of patent arterial duct, as well as interventional atrial septum manipulation on demand) as an alternative option to the conventional strategy to treat neonates with HLHS (14,15), the aim was to examine midterm outcome, pathological cerebral MRI findings, brain volumes and HRQoL of HLHS hybrid patients. We hypothesized that children with HLHS undergoing the hybrid procedure and receiving their cardiac staged surgeries and intervention within the last 6 years, where neuroprotective strategies were in focus, will have better outcome and a higher HRQoL.
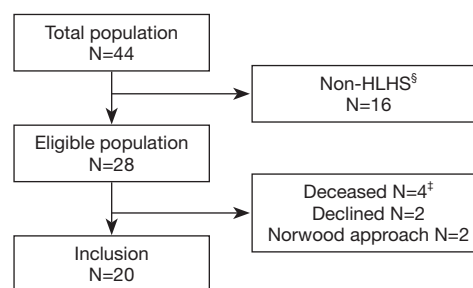


**Figure 1** Flow chart of patients included in the final analysis. Of 44 patients with left sided heart lesions, 16 patients with HLHC were excluded. Eight of the 28 eligible patients were excluded, leaving 20 patients with HLHS for final analysis. [§], 16 patients with HLHC: n=11 biventricular repair, n=3 univentricular palliation, n=2 deceased (one case with cardiac failure and multi organ failure on second run on ECMO, one patient undiagnosed prenatally suffered cardiogenic shock). [‡], 4 deceased HLHS patients. Palliative care in n=2; one case with obstructive TAPVR, one prenatally undiagnosed individual and parental decision of palliative treatment. One case with cardiogenic shock due to high-grade Re-ISTA after stage I, one case s/p reanimation after apnea/seizure at home after stage II. HLHC, hypoplastic left heart complex; ECMO, extracorporal membrane oxygenation; TAPVR, total anomalous pulmonary venous return; ISTA, aortic isthmus stenosis.

## Methods

### Study design

Twenty patients with HLHS and hybrid approach were prospectively enrolled at the University pediatric heart center of Giessen, Germany and examined prior Fontan surgery between October 2012 and July 2016. Patients were enrolled out of a cohort of 44 HLHS/HLHC (hypoplastic left heart complex) patients without known chromosomal abnormalities, born between April 2010 and May 2014 (*Figure 1*). Sixteen had HLHC morphology and were excluded for subsequent analysis. Of the 28 HLHS patients, 2 patients received a Norwood Stage I operation, in 2 patients, the parents decided for palliative care, and 2 parents rejected participation. The remaining 20 HLHS patients followed the hybrid approach and were all included into the study. The demographic data and clinical parameters were prospectively collected at admission and during the hospital stay for each operation or intervention. Perinatal data were retrospectively extracted from patients file. Growth data were transformed into z-scores based on WHO

Child Growth Standards (Anthro Software, Version 3.2.2 from www.who.int/childgrowth/). Small-for-gestational age was defined as standardized weight (z-score weight; WTZ) and/or standardized height (z-score height, HTZ) <10th percentile. As measure of disproportionate head growth, the difference between standardized measures of HC (z-score HC; HCZ) and WTZ as well as HTZ was calculated, and relative head growth as HC change in cm by weight gain in kg (HC/weight change) and by height growth in cm (HC/height change) was analyzed. Socioeconomic status was evaluated with a demographic questionnaire (16). The control cases included children admitted to the pediatric neurology department and who received a cerebral MRI for headache [2], afebrile, generalized epileptic seizures [2], suspected epilepsy, not confirmed in follow-up [1], and recurrent vomiting [1]. All control patients had a cerebral MRI scan without pathological findings and a normal neurocognitive development. There were no significant differences of birth history between HLHS patients and the control patients. The study protocol concurred to the ethical guidelines of the 1975 declaration of Helsinki as reflected in a prior approval by the local ethics committee and written consent provided by parents or caregivers.

### Surgical approach and standard care

The 20 patients were palliated with the Hybrid approach as stage I procedure, which includes surgical bilateral pulmonary banding and catheter-guided stenting of patent arterial duct, with interventional atrial septum manipulation on demand, without use of cardiopulmonary bypass (CPB). After stage I we aim to admit the neonate to a normal neonatal unit as soon as possible, where it has close contact to its parents in a less stressful ambience and where often (partial) breastfeeding is possible. After discharge, the patients are seen weekly at our outpatient clinic to estimate the right date for comprehensive stage II operation. All patients received comprehensive stage II, which combines the Norwood stage I and II in one step: removal of the bilateral pulmonary bands, removal of the PDA stent and PDA closure, aortic arch reconstruction, and anastomosis of the superior vena cava to the right pulmonary artery (Glenn procedure) (14). All CPB surgeries were performed under moderate hypothermia, and "beating-heart" condition, with selective head perfusion (n=20, 100%). During comprehensive stage II operation selective antegrade head perfusion has a flow rate of 35–50 mL/KG/BW), MAP (right arm) is kept ≥40 mmHg, cerebral $SO_2$ is kept >65% and hemoglobin is kept >10 g/dL. After disconnection of

the CPB hemoglobine is strived between 12–15 g/dL by hemofiltration, milrinone (0.5 µg/KG/min) is started, nitrite oxide given on 20 ppm, and noradrenaline is administrated on 0.1–0.3 µg/KG/min. Continuous perioperative brain monitoring with near infrared spectroscopy monitoring as well as modified ultrafiltration at the end of CPB was performed in all patients. We also target to extubate 2 to 6 hours after comprehensive stage II surgery on the pediatric cardiac ICU.

### Neurodevelopmental assessments

All HLHS patients were assessed with the Bayley-III by a trained developmental pediatrician. The Bayley-III measures cognition (Cognitive Composite Score, CCS), language (Language Composite Score, LCS) and motor function (Motor Composite Score, MCS). Normative composite scores were calculated by age for each scale and compared to American test norms: mean 100±15 points, cut-off points for moderate and severe developmental delay of <85 points (1 SD below normative mean) and <70 points (2 SD below normative mean) (17). All study patients received a detailed examination by a pediatric neurologist or a developmental pediatrician. Depending on severity they were divided into different groups: normal, milder reflex or tone abnormality, distinct reflex and tone abnormality or cerebral palsy (18).

### Brain MRI and brain volumetry

Brain MRI scans were performed on a 3.0 Tesla Magnetom Verio B17 scanner (Siemens Medical Systems, Erlangen, Germany) under sedation and were rated by a single pediatric neuroradiologist. The volumes of each tissue compartment were calculated with the Freesurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/) from high resolution 3D T1-weighted images acquired with a magnetization prepared rapid acquisition gradient echo (MP-RAGE) scan (TR, 1,900 ms; TI, 900 ms; FOV, 35.0 mm × 26.3 mm; matrix 256×256; flip angle 9; sagittal plane; slice thickness 1.2 mm; 112 slices) (19). Total brain volume was defined as sum of gray, deep gray and white matter, and total intracranial volume included total brain volume and CSF.

### QoL questionnaires

QoL by proxy report at the time of Bayley examination was

assessed with the TNO-AZL Preschool Children Quality of Life (TAPQOL). The questionnaire contains 43 items divided over 12 multi-item scales that contain physical, social, cognitive and emotional functioning domains (20).

At 3 to 4 years of life, the parents' perception of HRQoL was assessed with the German version of the Preschool Pediatric Cardiac Quality of Life (P-PCQLI) questionnaire (21). This 51-item questionnaire measures the frequency of disease related problems and severity of negative emotions about these on five scales (physical, emotional, social, therapeutic impact, functional development). The total score (range, 51 to 255) is calculated as the average score of the five scales.

### Statistical analyses

Statistical analyses were carried out with IBM SPSS Statistics for Macintosh, version 24 (IBM Corp., Armonk, NY, USA) and R (Vienna, Austria; http://www.R-project.org/). With the respective measures of dispersion, descriptive statistics are presented as mean, SD or median, IQR for continuous variables, and as frequency and percentage for categorical variables. A Shapiro-Wilk test was used to test normality. ANOVA or Kruskal Wallis and post hoc students $t$-test or Mann-Whitney-U test were

used to calculate differences between groups. Correlations of brain volume ratios with growth data and neurologic outcome were calculated with Pearson's correlation for normally distributed variables and Spearman's rho for non-normally distributed data. Linear regression was used to assess for impact of growth on outcome. A significance level of 0.05 was applied.

## Results

### Patient data and cardiac diagnoses

Characteristics of the 20 HLHS patients and control children are listed in *Table 1*. Cardiac subtypes of HLHS are shown in *Table 1*. All patients received the hybrid procedure at stage I without use of cardiopulmonary bypass (median age of 4 days), and the subsequent comprehensive stage II operation at 4.1±0.5 months. The average length of intensive care unit stay and discharge time at stage I and stage II was 8.4±5.3 days (range, 1.0 to 24.0), and 16.5±14.0 days (range, 7.0 to 49.0), respectively. The median discharge time after stage I and II was after 17.5 days (range, 8 to 32) and 27.5 days (range, 17 to 116), respectively. Two patients who were not discharged between the two surgeries had a total hospital stay of 145 and

**Table 1** Patient characteristics

| Characteristic | HLHS (n=20) | Controls (n=6) | $P_{WHO}$ |
|---|---|---|---|
| Cardiac diagnosis HLHS | 20 (100.0) | – | – |
| MA/AA | 11 (55.0) | – | – |
| MS/AA | 5 (25.0) | – | – |
| MA/AS | 1 (5.0) | – | – |
| MS/AS | 3 (15.0) | – | – |
| Male Gender | 12 (60.0) | 4 (66.7) | – |
| Prenatal diagnosis | 13 (65.0) | – | – |
| Socioeconomic status | 8.0±2.53 | – | – |
| High | 4 (20.0) | – | – |
| Intermediate | 10 (50.0) | – | – |
| Low | 6 (30.0) | – | – |
| Family status, separated | 0 | – | – |
| Gestational age at birth, weeks | 39.2±1.4 | 40.17±0.34 | – |
| Apgar at 5 minutes | 9 [9, 10] | 10 [9.25, 10] | – |

**Table 1** (continued)

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**Table 1** *(continued)*

| Characteristic | HLHS (n=20) | Controls (n=6) | $P_{WHO}$ |
|---|---|---|---|
| Umbilical cord pH | 7.33±0.08 | 7.32±0.03 | – |
| Weight at birth, z-score | −0.46±1.07 | 0.14±0.33 | 0.071 |
| Length at birth, z-score | −0.55±1.27 | 1.01±0.49 | 0.068 |
| SGA (length or weight <10P) | 8 (40.0) | 0 | – |
| Head circumference at birth, z-score | −0.24±1.10 | 0.18±0.19 | 0.355 |
| z-score <10P | 3 (15.0) | 0 | – |
| Microcephaly (z-score <3P) | 2 (10.0) | 0 | – |
| Weight at stage II, z-score | −2.20±1.15 | – | <0.001*** |
| Length at stage II, z-score | −1.04±1.81 | – | 0.018* |
| Head circumference at Stage II, z-score | −1.20±1.60 | – | 0.033* |
| Weight at MRI, z-score | −0.44±0.88 | 0.26±0.99 | 0.036* |
| Length at MRI, z-score | −0.77±1.15 | 0.66±1.03 | 0.007** |
| Head circumference at MRI, z-score | 0.09±1.03 | 0.31±0.68 | 0.701 |
| Age at stage I, days | 4 [2, 4] | – | – |
| Age at stage II, months | 4.12 (0.52) | – | – |
| Age at stage III, months | 35.4 (6.04) | – | – |
| Severe complication (ECMO/reanimation) | 3 (15) | – | – |
| Total hospital-stay, days | 61 [42, 94] | – | – |
| Hospital stay stage I, days | 18 [14, 20] | – | – |
| Hospital stay stage II, days | 28 [23, 55] | – | – |
| Total Intensive care unit stay, days | 21 [18, 38] | – | – |
| Intensive care unit stay stage I, days | 7 [5, 11] | – | – |
| Intensive care unit stay stage II, days | 10 [8, 15] | – | – |
| Cumulated time of mechanical ventilation, days | 2.0 [1.50, 3.50] | – | – |
| Mechanical ventilation stage I, days | 1.0 [0.5, 1] | – | – |
| Mechanical ventilation stage II, days | 1.0 [0.5, 2.6] | – | – |
| Cumulated aortic clamp time, min (mean ± SD) | 69 [62, 81] | – | – |
| Cumulated time on HLM, min | 260 [238, 272] | – | – |
| Use of DH stage I | 0 | – | – |
| Use of DH stage II | 1 (5.0) | – | – |
| Selective Cerebral Perfusion stage II | 20 (100.0) | – | – |

Numbers are given in n (%), mean ± SD or median [Q1, Q3], group comparison with Students *t*-test for normally distributed data and with Wilcoxon test for non-normally distributed or ordinal data. *, P<0.05; **, P<0.01; ***, P<0.001. HLHS, hypoplastic left heart syndrome; MRI, magnetic resonance imaging; SGA, small-for-gestational age; DH, deep hypothermia.

**Table 2** Surgical and catheter reinterventions

| Surgical or catheter reintervention | N=20 |
|---|---|
| Surgical reintervention, any | 8 (40.0) |
| Surgical reintervention post stage I, any | 2 (10.0) |
| Secondary closure of thorax | 1 |
| Second look without intervention | 1 |
| Surgical reintervention post stage II, any[†] | 6 (30.0) |
| Secondary closure of thorax | 3 |
| Revisions[‡] | 2 |
| Diaphragm plastic | 1 |
| ECMO takedown | 1 |
| Pacemaker/defibrillator[§] | 3 |
| Cardiac catheterization/reintervention, any | 13 (65.0) |
| Cardiac catheterisation/reintervention post stage I[¶] | 7 (35.0) |
| Stenting atrial septal defect | 3 |
| Dilation IAS | 2 |
| Secondary PDA stent | 2 |
| Dilation PDA stent | 4 |
| Dilation LPA/RPA banding | 1 |
| Dilation vena verticalis | 1 |
| Cardiac catheterisation/reintervention post stage II[°] | 8 (40.0) |
| Dilatation of RPA/LPA/MPA | 6 |
| Stent RPA/LPA/MPA | 5 |
| MAPCA closure | 1 |

Numbers are given in n (%) or count. [†], total 10 procedures, multiple procedures in n=2 patients; [‡], revisions for postoperative bleeding with pericardial tamponade, n=1; and for tricuspid valve plastic, n=1; [§], pacemaker/defibrillator 3 procedures in n=1 patient; [¶], total 13 catheterizations; multiple procedures in n=4 patients. Stenting atrial septal defect (n=3), dilation IAS (n=2), secondary PDA stent (n=2), dilation PDA stent (n=4), dilation Vena verticalis (n=1), dilation LPA/RPA banding (n=1). [°], total 12 catheterizations, multiple procedures in n=5 patients. IAS, Interatrial Septum; PDA, Persistent Ductus Arteriosus; LPA, left pulmonary artery; RPA, right pulmonary artery; MPA, main pulmonary artery.

228 days. Eight (40%) patients after Hybrid stage I and 13 (65%) after stage II had a complicated course with need for reintervention. Surgical reinterventions and cardiac catheterizations were needed in 2 and 7 patients after stage I, and in 6 and 8 patients after stage II, respectively (*Table 2*).

*Growth*

Growth parameters were in the lower normal range at birth with mean values for weight, length and head circumference at $32^{th}$ percentile (P=0.07), $29^{th}$ percentile (P=0.06) and $40^{th}$ percentile, respectively (P=0.35) (*Figure 2*). One patient was microcephalic (head circumference below $3^{rd}$ percentile) and two patients (10%) had head circumferences below the $10^{th}$ percentile. The rate of small-for-gestational age newborns was 40%. After a significant drop in all growth parameters until stage II (average weight: $2^{nd}$ percentile; average height: $15^{th}$ percentile; average head circumference: $12^{th}$ percentile), we found catch-up growth in head circumference ($53^{th}$ percentile, P=0.701) until follow-up at 2–3 years of age prior to Fontan surgery. However, both weight ($32^{th}$ percentile, P=0.036) and height ($22^{nd}$ percentile, P=0.007) remained below normative values before Fontan surgery, with a slight increase in stunting (HC to weight: P=0.24, HC to length: P=0.19) (*Figure 2*).

*Neurodevelopmental outcome*

Mean age at follow-up was 26.5±3.6 months. The CCS, LCS, and MCS average scores were 101.5±9.3 (range, 80 to 120, P=0.48), 100.3±13.0 (range, 74 to 124), and 98±11.7 (range, 70 to 121); and thus were comparable to normative data (*Table 3*). Mild/moderate developmental delay (score <85) was noted in 2/20 patients (10%) in each the CCS and LCS, and in 1/20 of the patients (5%) in the MCS: no subject scored <70 in these scales (*Figure 3*). Stunting (relative head circumference to weight and height) was not associated with any of the Bayley-III scales (all P>0.05). Neurological assessment showed mild abnormalities such as muscular hypotonia or motor coordination deficits in 2/20 participants (10%). No major neurological handicap like cerebral palsy, deafness or blindness was noted.

*MRI findings*

Out of 19 patients undergoing brain MRI scans, 4 (21%) had at least one abnormality, with two patients presenting with multiple findings (*Table 3*, *Figure 4*). In one patient cerebral MRI could not be performed due to a MR-incompatible pacemaker. Most common findings were late sequelae of old strokes present in 3 patients (16%), all smaller than one third of the cerebral artery supply territory.
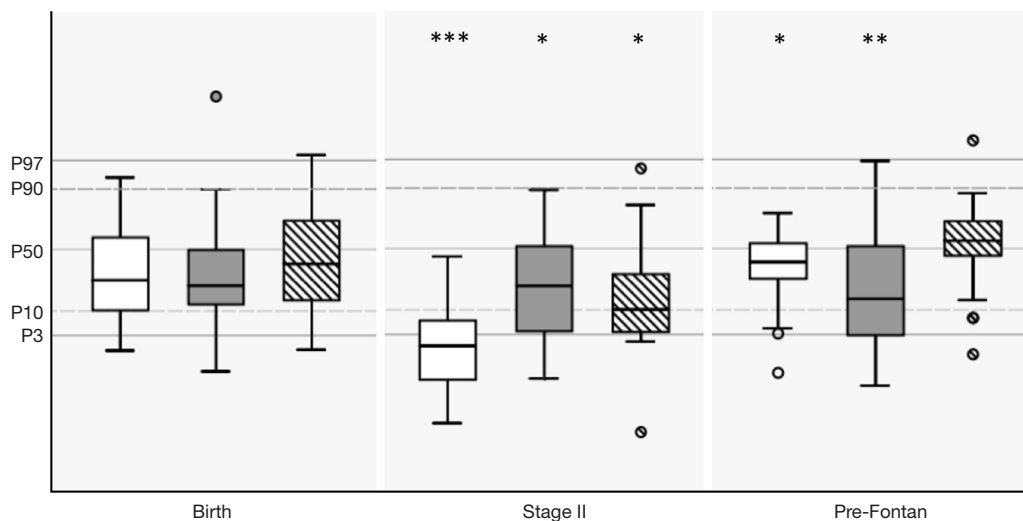
**Figure 2** Median growth indices (weight, height, and head circumference) at birth, before stage II, and at the time of follow-up pre-Fontan of 20 children with HLHS following the hybrid approach. Horizontal lines depict 50th percentile and lower and upper boundary of 3rd and 97th percentile, dashed horizontal lines depict lower and upper boundary of 10th and 90th percentile; dots represent outliers. *, P<0.05; **, P<0.01; ***, P<0.001. HLHS, hypoplastic left heart syndrome.

**Table 3** Cerebral MRI findings

| Cerebral MRI findings | N=19 |
| --- | --- |
| Any abnormality in cMRI scan, any[†] | 4 (21.1) |
| Status post stroke[‡] | 3 (15.8) |
|   Right Middle Cerebral Artery | 1 (5.3) |
|   Right and left Middle Cerebral Artery | 1 (5.3) |
|   Right Middle Cerebral Artery and right Posterior Cerebral Artery | 1 (5.3) |
| CSF space enlargement[§] | 1 (5.3) |
| Minimal focal white matter Injury | 2 (10.5) |

[†], multiple findings in 2 patients. [‡], infarctions were smaller than one third of the cerebral artery supply territories. [§], enlargement of supratentorial outer CSF space was focal and associated with status post right MCA stroke in one patient. MRI, magnetic resonance imaging; CSF, cerebrospinal fluid.

In one of these patients associated focal enlargement of supratentorial outer liquor spaces was visible. Patients with focal lesions did not show poorer outcome compared to patients with normal MRI scans (data not shown).

Compared to controls, white matter volume was lower (WM/ICV ratio P=0.014), and CSF volumes (CSF/ICV ratio P=0.042) were higher in HLHS patients (*Table 4*). HCZ at birth (r: 0.47; P=0.044), at stage II (r: 0.69; P=0.009) and at

the time of the brain MRI scan (r: 0.61; P=0.005) correlated with total brain matter volume. Interestingly, HCZ change from birth to stage II was related to WM volume (r: 0.58, P=0.009) and explained 30% of its variability, whereas head growth between stage II and pre Fontan was not. Brain volumes were not associated with neurodevelopmental outcome (all P>0.05).

### *Quality of life questionnaires (TAPQOL/PCQLI)*

The average TAPQOL total score in our cohort was 88±5.7, which was comparable to the median total score for normal controls (86±9.5, P=0.67), showing an overall well discernible QoL evaluated by parent as proxy report (*Table 5*). The median physical items were lower compared to healthy controls (P=0.007). However, HRQoL by proxy report assessed at 39.7±3.9 months with the PCQLI was comparable to the reference data of patients with biventricular CHD in all subscales (*Figure 3B*, *Table 6*).

### Discussion

An increase in survival rate of children with HLHS over the past decade and recognition of neurodevelopmental disabilities in this growing population has set the focus on innovations for protecting the brain. This study investigated
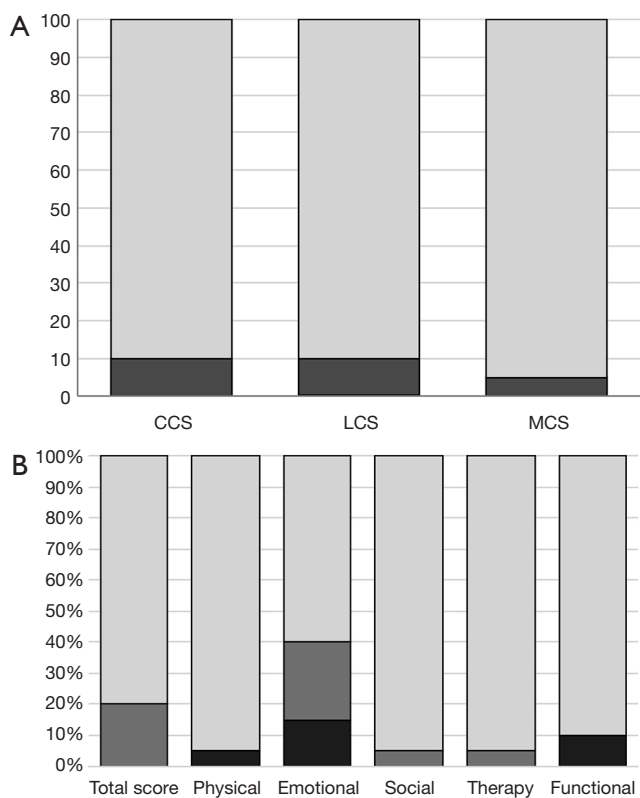
**Figure 3** Percentage of development within the normal range and of moderate developmental delay and of good, intermediate and poor health-related quality of life. (A) Distribution of CCS, LCS and MCS Bayley-III scores of 2- to 3-year-old study patients. Y-axis shows percentage of scores below 85, that equates to 1 SD below the norm (dark gray bar). Light gray bars represent percentage of patients within the normal range (above 85); (B) frequency of total score and sub-scores of all patients evaluated at 3–4 years of age with the PCQLI, divided into three categories; good (light gray bar), intermediate (dark gray bar), and poor (black bar). CCS, cognitive composite score; LCS, language composite score; MCS, motor composite score.

outcome of HLHS hybrid patients before Fontan surgery, receiving their palliative correction between 2010 and 2014, where potential neuroprotective interventions like moderate hypothermia, selective head perfusion, "beating-heart" operation and brain monitoring constitute the perioperative standard protocol at the Pediatric Heart Center Giessen, Germany. Measurements of the Bayley-III Scales and HRQoL were favorable for the majority of patients, with median outcome scales comparable to the norm. Notably, only 10% (2/20) of the patients showed mild developmental delay in at least one domain at 2 to 3 years of age.

These findings are encouraging compared to significantly lower motor and cognitive outcome scores for children receiving heart surgeries and interventions between 1996 and 2011 (2,22-24); although one has to keep in mind that some of these studies used the Bayley-II, which in comparison to the Bayley-III reports lower developmental scores (25,26).

It has been postulated that the Hybrid procedure might be beneficial in terms of protecting the premature brain (27). Nevertheless, the type of first stage procedure in respect to timing of the CBP surgery might be a discriminating factor. Brain immaturity has been identified as a risk factor for consequent brain injury and developmental delay (11). Therefore, one possible reason could be the impact of early use of heart-lung machine and the inevitable invasive intra- and postoperative management during an immature developmental stage when the brain is more vulnerable. A short postoperative care after hybrid approach, early extubation after placement of the pulmonary artery bandings and fast transfer to a normal ward, where the neonate can be close to its parents, and less feeding problems seem to be not so invasive and immobilizing for the neonate. In fact, adequate caloric intake during either pre- and post-surgical period, was suggested to improve outcome of CHD patients (28). In contrast, failure to thrive and poor head growth in childhood have been related to mid-term and long-term cognitive delay (e.g., attention deficit disorders, aggressive behavior and poor social and emotional development) (7,29-31). We found a decline in all growth parameters before stage II in our cohort, with a complete catch-up only for HCZ pre-Fontan, and thus increased stunting at follow-up compared to birth. Neither HC growth, nor stunting was associated with neurodevelopmental outcome. Lack of association between asymmetric head growth and neurodevelopmental outcome was previously described by Miller *et al.*, and it has been suggested that the brain-sparing mechanism is not applicable to SV CHD. Multiple contributors to abnormal head growth in HLHS, such as cerebral ischemia and reperfusion injury, combined with impaired autoregulation of the brain vessels, infection/inflammatory processes and analgesic/sedative drugs increase the complexity of neonatal brain injury in HLHS (32,33). These insults may lead to oxidative stress and apoptotic cell death of immature brain cells, especially immature white matter and subplate neurons (34,35). Delay in brain maturation of approximately 1 month at term (10) and propensity for the critically ill neonate to exhibit a pressure-passive circulation related to a disturbance of
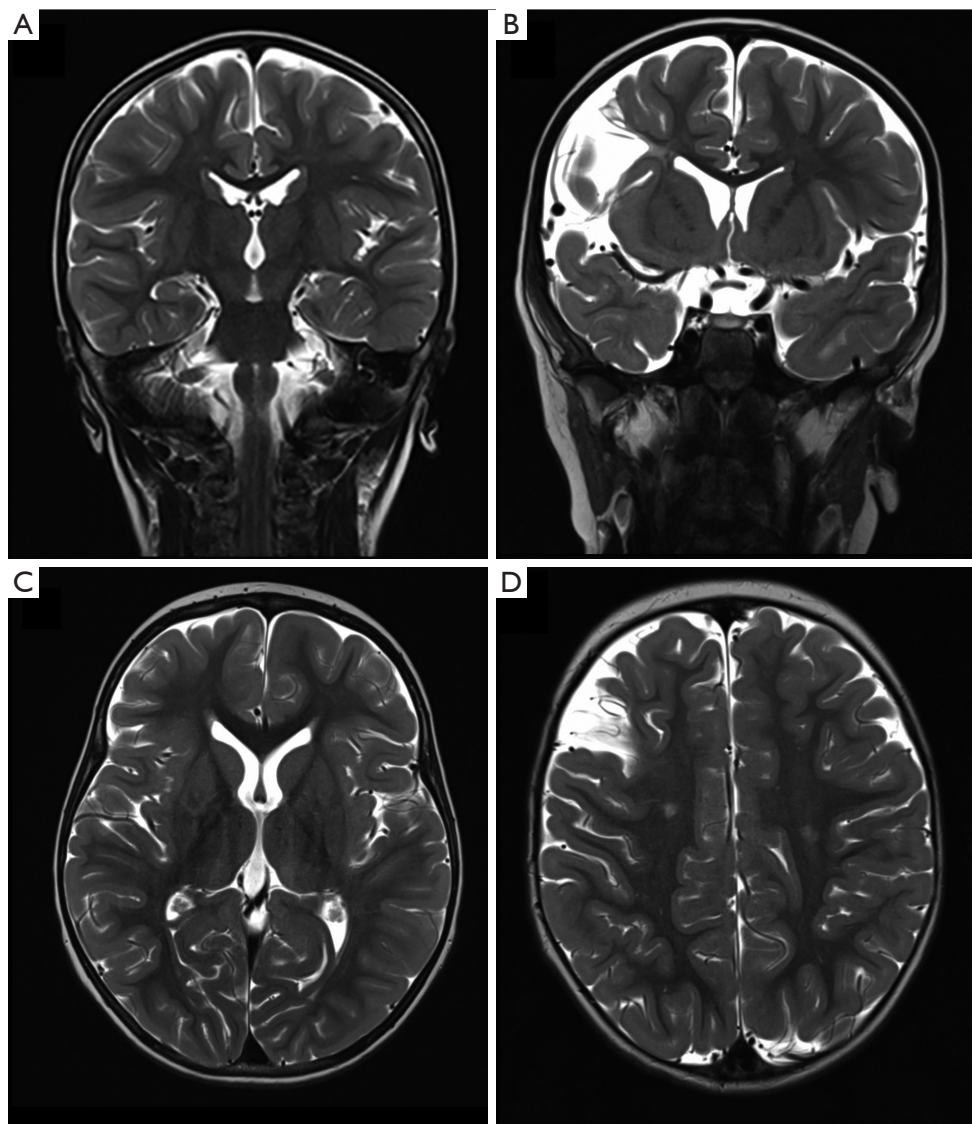
**Figure 4** Cerebral MRI scans of two HLHS patients before Fontan procedure. Coronar (A,B) and corresponding axial scans (C,D) of two HLHS patients. A and C, no detected abnormalities. B and D, residual ischemic stroke in the gray matter (right A. cerebri media, <1/3) and focal white matter injuries in the central white matter. MRI, magnetic resonance imaging; HLHS, hypoplastic left heart syndrome.

cerebral auto-regulation (36) underscore the importance for early postnatal brain-protection. Postponement of the time of cardiopulmonary bypass surgery from the more susceptible neonatal time period towards 4 to 6 months of age may lead to higher brain maturity and may contribute to a reduced vulnerability of these structures towards perioperative cerebral damage.

In fact, head growth and in particular extent of head growth restriction before stage II was predictive of WM volume at 2–3 years of age, pointing to early vulnerability of the maturing brain. WM volumes were reduced and CSF volumes were increased in patients compared to norms, as previously described (6,37). Still, need for staged palliation puts these children at risk for repeated chronic hypoxic conditions, intracerebral hemorrhages, strokes and inflammatory episodes (38). Detection of old brain lesions indicating previous insults in 16% (3/19) of our patients, and association with poorer language development highlights the importance of neuroimaging for risk stratification in this high-risk population.

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Table 4 Intracranial volumes in HLHS patients compared to healthy toddlers

| Age at MRI and intracranial volumes | HLHS (n=19)§, mean ± SD | Control (n=6), mean ± SD | P |
|---|---|---|---|
| Age at MRI | 27.3±4.5 | 29.2±11.1 | 0.531 |
| Total intracranial volume | 935±106 | 1,009±158 | 0.188 |
| Gray Matter volume | 630±67 | 668±87 | 0.276 |
| Subcortical Gray Matter volume | 44.4±4.4 | 48.3±7.0 | 0.136 |
| White Matter volume | 286±35 | 329±71 | 0.058 |
| Ventricular cerebrospinal fluid volume | 14.5 [12.8, 18.0] | 11.9 [10.9, 13.5] | 0.098 |
| Total cerebrospinal fluid volume | 15.0 [13.8, 19.0] | 12.6 [11.8, 14.1] | 0.086 |
| Volumes in relation to TIV (Ratio) | | | |
| Gray Matter/TIV | 0.67 (0.01) | 0.66 (0.02) | 0.156 |
| Subcortical Gray Matter/TIV | 0.05 (0.00) | 0.05 (0.00) | 0.899 |
| White Matter/TIV | 0.31 (0.01) | 0.32 (0.02) | 0.014* |
| Ventricular CSF/TIV | 0.02 [0.01, 0.02] | 0.01 [0.01, 0.01] | 0.049* |
| Total CSF/TIV | 0.02 [0.01, 0.02] | 0.01 [0.01, 0.02] | 0.042* |

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 numbers indicate significance, P<0.05. §, one patient had a MR-incompatible pacemaker; *, P<0.05. HLHS, hypoplastic left heart syndrome; CSF, cerebrospinal fluid; TIV, total intracranial volume.

Table 5 Bayley-III Scores, Neuroscore and Quality of Life Questionnaire Scores (TAPQOL)

| Bayley-III and TAPQOL scores | HLHS patients (N=20), mean ± SD | Normal reference, mean ± SD | P$_{norm}$ |
|---|---|---|---|
| Bayley-III scales | | | |
| Age at examination, months | 26.5±3.6 | | |
| Cognitive composite score | 101±9.3 | 100±15 | 1.00 |
| Language composite score | 100±13.0 | 100±15 | 0.79 |
| Motor composite score | 99±11.7 | 100±15 | 0.22 |
| TAPQOL | | N=121 | |
| Age at TAPQOL, months | 26.5±3.6 | 26.4±5.2 | 0.87 |
| Total score | 88±5.7 | 86±9.5 | 0.67 |
| Physical Score, median [Q1, Q3] | 88 [86, 91] | 91±6.9 | 0.007** |
| Social Score | 84±9.0 | 77±13.9 | 0.067 |
| Emotional Score, median [Q1, Q3] | 92 [83, 100] | 92±7.2 | 0.46 |

**, P<0.01.

While the favorable outcome data from our participants seem to be emboldening, caretakers of these patients have to keep in mind that children with HLHS who performed well within the norm in early childhood, might show impairments in more complex functions such as language, memory function (39), and also in fine motor and visuomotor skills when they reach school age (40). In early childhood, motor development is more affected than cognition, with lower motor scores than cognitive scores (41). Hence, these patients need to be re-assessed

**Table 6** Preschool Pediatric Cardiac Quality of Life (P-PCQLI) proxy report questionnaire

| P-PCQLI scores | HLHS (N=20), mean ± SD | Biventricular CHD (N=26), mean ± SD | P |
|---|---|---|---|
| Age at PCQLI, months | 39.68±3.87 | 41.38±7.53 | 0.13 |
| Total score | 193.90±19.21 | 203.75±36.40 | 0.24 |
| Physical score | 60.25±7.33 | 63.44±14.74 | 0.34 |
| Emotional score | 39.55±6.44 | 41.38±7.53 | 0.33 |
| Social score | 37.60±4.02 | 37.73±6.19 | 0.93 |
| Therapy score | 24.60±2.68 | 24.04±3.73 | 0.56 |
| Functional score, median [Q1, Q3] | 31.00 [28.75, 34.75] | 31.64±7.40 | 0.58 |

HLHS, hypoplastic left heart syndrome; CHD, congenital heart disease.

longitudinally when they reach school age, which is part of an ongoing clinical study.

Assessment of HRQoL using the TAPQOL, a generic questionnaire and the PCQLI, a tool for disease related problems showed an overall good QoL of HLHS hybrid patients reported by parents. However, the median physical items of patients were lower compared to healthy controls (P=0.007). This is consistent with the finding of a study examining HRQoL in 1-year-old infants with CHD and open-heart surgery, that also found a significant reduction of parental-reported physical functioning. When these children were examined at four years, parents reported poorer communication but better social functioning and similar physical functioning compared to healthy controls (42). In contrast to our expectations, children showed an overall comparable HRQoL to a normative cohort of biventricular CHD. This good QoL can be explained by the disability paradox (43), as perceived QoL is a function of overall burden and parents may overlook difficulties, because parents are relieved that their children have survived the critical first months of life. It might also be due to the finding that behavior problems occur more frequently in older children, being confronted with more difficulties when interacting with older peers (44).

Our study is limited by the small size of our patient cohort. Therefore, some significant correlations might have occurred by chance. We used a cross-sectional study model, which impeded a longitudinal assessment of volumetric changes over time. Consequently, the effects of reduction of brain volumes on neurodevelopment, executive functioning and behavior later in life remain unclear. Therefore, a multicenter follow-up study with a longitudinal design is already running.

In conclusion, we found that HLHS patients following the Hybrid approach show favorable Bayley-III Scales and good QoL for the majority of patients, with median outcome scales that were not significantly different from the norm. Approximately, one quarter showed disease related pathological findings at cerebral MRI and, compared to controls, white matter volumes were reduced and CSF volumes were increased in HLHS patients. Extended neuroprotective strategies during perioperative management, improvement of nutrition and growth are important tools to further improve outcome. Routine neurodevelopmental follow-up assessments of performance at school age will elucidate the long-term clinical impact of these early imaging findings.

## Footnote

*Conflicts of Interest*: The authors have no conflicts of interest to declare.

*Ethical Statement*: The study was approved by the institutional ethics committee (Justus-Liebig University, Faculty of Medicine) (No. 42/12) and informed consent was taken from all the patients.

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