Neurodevelopmental Burden at Age 5 Years in Patients With Univentricular Heart

WHAT'S KNOWN ON THIS SUBJECT: With increasing survival rates, there is growing interest in long-term quality of life among patients with univentricular heart defects, and neurodevelopmental deficits play a major role in adverse outcome.

WHAT THIS STUDY ADDS: Although median cognitive performance was within normal limits, major neurodevelopmental impairment was found in one-fourth, and minor neurologic dysfunction in almost half of patients. Brain MRI showed mostly ischemic findings of different degrees in the majority of patients.

abstract

BACKGROUND: Despite increasing survival, patients with hypoplastic left heart syndrome (HLHS) and other forms of functionally univentricular heart defects (UVHs) remain at increased risk of long-term neurodevelopmental deficits.

METHODS: A nationwide sample of 23 patients with HLHS, 13 with UVH, and 40 controls were followed prospectively until the age of 5 years, when neurologic, neuropsychological, and motor examinations and brain MRI were performed.

RESULTS: The median full-scale IQ was significantly lower in patients with HLHS (97, P < .001) and patients with UVH (112, P = .024) compared with controls (121). Major neurodevelopmental impairment was found in 26% of the patients with HLHS and 23% of those with UVH, and minor neurologic dysfunction was found in 43% and 46%, respectively. MRI revealed abnormalities, mostly ischemic changes of different degrees, in 82% of the patients with HLHS and in 56% of those with UVH. Prominent changes were significantly associated with neurodevelopmental findings and parental reports of adaptive behavior. In linear regression, significant risk factors for a worse outcome were a history of clinical seizures in connection with the primary operation, a lower diameter of the neonatal ascending aorta, and several pre-, peri-, and postoperative factors related to the primary and bidirectional Glenn operations.

CONCLUSIONS: Although median cognitive performance was within the normal range, neurodevelopmental and brain MRI abnormalities were found in the majority of the patients with UVH, and especially in those with HLHS, at preschool age. Both a narrowed ascending aorta and operation-related factors contributed to these findings. Pediatrics 2012;130:e1636–e1646

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KEY WORDS congenital heart defects, Fontan procedure, brain, MRI, risk factors

ABBREVIATIONS

AV—atrophic ventricular
BDG—bidirectional Glenn
CHD—congenital heart defect
DHCA—deep hypothermic cardiac arrest
FIQ—full-scale IQ
HLHS—hypoplastic left heart syndrome
MDI—Mental Developmental Index
MND—minor neurologic dysfunction
Movement ABC—Movement Assessment Battery for Children
RLFP—regional low-flow perfusion
TCPC—total cavopulmonary connection
UVH—functionally univentricular heart defect
VABS—Vineland Adaptive Behavior Scales
VIQ—verbal IQ
VMI—Beery-Buktenica Developmental Test of Visual-Motor Integration
WPPSI-R—Wechsler Preschool and Primary Scale of Intelligence–Revised

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The surgical and perioperative treatments of congenital heart defects (CHDs) have greatly developed during the past few decades, but, despite improved survival rates, the neurodevelopmental complications remain a major concern. In particular, patients with hypoplastic left heart syndrome (HLHS) or other forms of functionally univentricular heart defects (UVHs) have a high risk of long-term neurologic sequelae after staged palliative surgery according to the Norwood strategy presented in 1983.\textsuperscript{1–5} The latest reports on patients who underwent the Norwood operation at the beginning of this century present early developmental results with mean Bayley Mental Developmental Indices (MDIs) at the lower end of normal limits, and unequivocally lower psychomotor developmental indexes at the lower end of mildly delayed performance.\textsuperscript{6–10} Recently, a mean full-scale IQ (FIQ) of 95 was reported at the age of 4 years among patients with HLHS, being significantly lower than in patients with other forms of severe CHD.\textsuperscript{11}

In considering whether further prevention of brain injury among patients with CHD is possible, it is necessary to recognize that the causes are multifactorial. Which operative support strategy poses a bigger risk to the developing brain remains controversial,\textsuperscript{8,9,12} and patient-related factors have in fact emerged alongside operative factors as major contributors.\textsuperscript{6} Nevertheless, MRI studies indicate that perioperative

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.pdf}
\caption{Patient course during the 5-year follow-up. HTX, heart transplantation.}
\end{figure}
brain injury in the form of white matter injury or infarct is common,\textsuperscript{13,14} although its impact on later neurodevelopment remains uncertain.

We performed a prospective multiprofessional neurodevelopmental follow-up study on a population-based sample of patients with HLHS or UVH with healthy age- and gender-matched controls. The neurodevelopmental outcome results at the age of 5 years were correlated with brain MRI results, and a wide range of risk factors were analyzed to further evaluate the risk points for brain damage in this high-risk patient group.

**METHODS**

All pediatric cardiac surgery in Finland is performed at the Department of Gynecology and Pediatrics of Helsinki University Central Hospital. Between August 2002 and February 2005, all patients with HLHS or UVH were offered the possibility to take part in a 5-year prospective neurodevelopmental follow-up study.\textsuperscript{15,16}

Forty-six healthy age- and gender-matched control children from low-risk deliveries at the Kätilöopisto Maternity Hospital of Helsinki University Central Hospital were recruited as newborns. At the median age of 5.1 (range, 5.0–5.4) years, 23 patients with HLHS, 13 with UVH, and 40 healthy controls were examined (Fig 1). The cardiac diagnoses and operations performed before the study point are presented in Table 1.

**Surgical and Perfusion Strategies**

The aortic reconstruction during Norwood-type operations and possible additional aortic reconstructions were performed during either regional low-flow perfusion (RLFP) alone or in combination with short periods (<10 minutes) of deep hypothermic cardiac arrest (DHCA). During all operations involving aortic arch reconstruction, the hematocrit was kept at 30%, and cooling was aimed at 18°C. During the bidirectional Glenn (BDG) operation, as well as the total cavopulmonary connection (TCPC), the hematocrit was also aimed at 30%, but the body temperature was kept between 30 and 34°C.

**Outcome Measures**

The neurologic examination was performed according to a test modified from Touwen,\textsuperscript{17} with a few items added to more accurately assess gross and fine motor skills. The findings were classified according to Hadders-Algra\textsuperscript{18} (Table 2). Height, weight, and head circumference were measured and compared with Finnish national standards.\textsuperscript{19,20}

Cognitive testing was performed according to the Finnish version of the Wechsler Preschool and Primary Scale of Intelligence—Revised (WPPSI-R), which provides an FIQ, comprising verbal IQ (VIQ) and performance IQ (PIQ).\textsuperscript{21} Visual-motor integration was tested according to the Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI).\textsuperscript{22} For logistic reasons, 5 patients living further away were examined at their local hospitals. Two patients with HLHS could not be assessed with WPPSI-R because of their severe intellectual disability, and their MDI was instead determined according to the Bayley Scales of Infant Development\textsuperscript{23} by dividing their developmental age by their calendar age. These scores were used instead of FIQ in the risk factor analysis as the best available estimate of their developmental level, but their neuropsychological results were not included in the comparison between the groups. The parents were interviewed according to the Vineland Adaptive Behavior Scales (VABS) to obtain reports on the adaptive behavior of the children in their daily environment.\textsuperscript{24} A physiotherapist assessed gross and

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>HLHS and UVH Patients Examined at a Median Age of 5.1 Years (n = 36): Diagnoses and Operations Performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>----------</td>
<td>-----------</td>
</tr>
<tr>
<td>Primary operation</td>
<td></td>
</tr>
<tr>
<td>Norwood</td>
<td>HLHS</td>
</tr>
<tr>
<td>Norwood/DKS</td>
<td>UVH</td>
</tr>
<tr>
<td>Other</td>
<td>UVH</td>
</tr>
<tr>
<td>No operation</td>
<td>UVH</td>
</tr>
<tr>
<td>BDG operation</td>
<td></td>
</tr>
<tr>
<td>TCPC operation</td>
<td></td>
</tr>
<tr>
<td>Additional operation</td>
<td></td>
</tr>
<tr>
<td>HLHS</td>
<td>5</td>
</tr>
<tr>
<td>UVH</td>
<td>4</td>
</tr>
<tr>
<td>2 additional operations</td>
<td>HLHS</td>
</tr>
<tr>
<td>3 additional operations</td>
<td>HLHS</td>
</tr>
</tbody>
</table>

Medians (ranges) are presented for age and the support times. CPB, cardiopulmonary bypass; DKS, Damus-Kaye-Stansel. —, not used.
fine motor skills according to the Movement Assessment Battery for Children (Movement ABC) test. This standardized test for gross and fine motor functions yields a total impairment score and impairment scores for 3 subtests (Table 3). An EEG recording and a brain MRI scan (Philips Intera 1.5 T; T1-weighted sagittal, T2-weighted axial and coronal, fluid-attenuated inversion recovery and diffusion-weighted axial images) were performed on the patients when clinically indicated and at the age of 5 years. Extensive collection of possible risk factors was performed as described earlier concerning patient-related data, operations, and clinical follow-up until the study visit at age 5 years. In addition, ultrasound data were collected on the lowest diameter of the ascending aortic arch in the pre-operative neonatal period. Parental reports on their socioeconomic status (level of education and occupation) were updated. All these data (Table 4) were tested for associations with the primary outcome variable FIQ/MDI.

Statistics

SPSS version 17.0 software (SPSS Inc, Chicago, IL) was used for statistical analysis. Kruskal-Wallis and Dunn tests were used for comparison of the continuous outcome variables between the subgroups (patients with HLHS, patients with UVH, and controls). The Fisher exact test with Bonferroni correction for multiple comparisons was used for binary data. The Pearson correlation coefficient was used for normally distributed continuous factors, and the Spearman correlation coefficient was used for nonnormally distributed continuous and categorical factors to assess their correlation with FIQ/MDI. For nonnormally distributed continuous factors, logarithmic transformation was used if it produced a normal distribution and correlated significantly with FIQ/MDI.

All factors significantly (P < .05) associated with FIQ/MDI were included in a linear regression model adjusted for diagnosis (HLHS/UVH), gender, and maternal level of education. For this purpose, categorical factors were transformed into binary variables. Of those factors that measured closely related parameters, the one that correlated more significantly with FIQ/MDI was selected.

RESULTS

Neurologic Outcome

Abnormalities in the neurologic examination were present in the majority of the patients, and they were most prevalent in gross and fine motor domains (Tables 2 and 5). The results of the neurologic examination were considered normal in...
Neuropsychological Results

There were no significant differences in WPPSI-R and VMI results between the patients with HLHS and UVH, although the patients with HLHS performed more significantly below the controls (Table 3, Table 6, and Fig 2). Three patients, all with HLHS, had intellectual disability (defined as FIO/MDI <70 and significant limitations in adaptive behavior). All 3 had an eventful recovery from the Norwood I operation with clinical seizures. Two of them showed global ischemic brain damage in early MRI and were later diagnosed with severe intellectual disability.

Motor Function

Four patients with HLHS (21%), 3 with UVH (25%), and 3 control children (8%) performed in gross and fine motor function according to the Movement ABC test in the borderline range, and 6 (32%), 3 (25%), and 1 (3%), respectively, in the clearly abnormal range (Table 3). These results were highly congruent with the findings in the neurologic examination, those children with abnormal gross motor function (Table 2) had significantly higher (ie, worse) total scores in the Movement ABC (16.8 vs 4.1, P < .001), and, similarly, those with abnormal fine motor function had significantly higher scores in the manual dexterity subdomain (6.5 vs 2.1, P < .001).

Adaptive Behavior

Three patients with HLHS had adaptive behavior composite scores below the normative −2 SD level of 70 (Table 3). The VABS scores correlated significantly with the corresponding professional assessments (VABS composite scores with FIO/MDI, r = 0.632, P < .001; verbal communication subdomain with VIQ, r = 0.550, P < .001; motor skills subdomain with Movement ABC, r = −0.627, P < .001). In addition, the motor skill subdomain scores were associated with abnormal gross motor function (84.4 vs 104.0, P < .001) and fine motor function (82.6 vs 103.5, P < .001) in the neurologic examination.

MRI and EEG

MRI was performed on 26 patients (17 with HLHS and 9 with UVH). The abnormalities observed in MRI (Table 5, Fig 3) predominantly comprised ischemic changes of different degrees. The patients with prominent MRI lesions (more severe than 1 or 2 minimal ischemic lesions) had significantly lower cognitive performance (median FIO/MDI 89.0 vs 107.0, P = .048) and worse Movement ABC results (20.5 vs 8.0, P = .015) and VABS composite scores (85.0 vs 98.5, P = .002) than the other patients. They all had either major neurodevelopmental impairment (8/13) or minor neurologic dysfunction (MND; 5/13, P = .039 for the difference compared with the others, of which 8/13 had MND). No patient with normal results on the neurologic examination had any prominent MRI findings.

Twenty-nine patients (16 with HLHS and 13 with UVH) underwent EEG recording. The EEG abnormalities (Table 5) included diffuse background abnormality in 1, asymmetry in 1, and epileptiform activity (either spiking or spike-wave discharges) in 7 patients. Of the patients with major neurodevelopmental impairment, 71%...
(5/7) had abnormal EEG results, compared with 18% (4/22, \(P = .016\)) of those with either MND or a normal neurologic examination results.

**Risk Factor Analysis**

Because the maternal level of education (median 5.0 vs 6.0, \(P = .035\)) and occupation (median 4.0 vs 3.0, \(P = .041\)) were significantly lower among patients with HLHS compared with controls, 2-way univariate analysis of variance was used to adjust for socioeconomic status. There was no interaction between maternal skill level and patient group (\(P = .484\)). The main effect for patient group was statistically significant (\(P < .001\)), but the effect for maternal occupational skill level was not (\(P = .112\)).

In the linear regression model (Table 7), 5 factors related to the primary and BDG operations, and the preoperative cardiac status correlated significantly with FIQ/MDI, with an explanation rate of 76%. The most important correlate was a history of clinical seizures in connection with the primary operation. These were most often clonic or tonic convulsions that appeared between postoperative days 4 and 12. Routine EEG recording performed on the same or following day revealed spikes or discharges. These seizures were also related to a significantly smaller relative head circumference at the age of 5 years (median \(-1.185\) vs \(-0.30\ SD, P = .003\)). Prominent MRI abnormalities were seen in 7 of 9 of those with seizures during the follow-up compared with 6 of 17 of those without (\(P = .048\)). Of the significant predictors of cognitive outcome, the highest hematocrit after the BDG operation was also higher in those with prominent MRI abnormalities (48.4 vs 43.4, \(P = .002\)).

After excluding the 2 outliers, a history of clinical seizures in connection with the primary operation (\(P < .001\)), significant preoperative atrioventricular (AV) valve regurgitation (\(P = .047\)), and reduced cardiac function after the BDG operation (\(P = .031\)) remained, and the neonatal diameter of the aortic arch (\(P = .016\)) emerged as a risk factor, with an overall explanation rate of 64%.

**Longitudinal Comparison of the Follow-up Results**

After the previous neurodevelopmental evaluation at the age of 30 months, 2 patients experienced a cerebral infarct leading to hemiplegia: on the seventh postoperative day after the TCPC operation in one, and 58 months after TCPC in the other. The FIQ results correlated significantly with MDI at the age of
30 months ($r = 0.731, P < .001$), and the Griffiths general development at the age of 12 months ($r = 0.436, P < .001$). The Movement ABC results correlated significantly with earlier motor development (psychomotor developmental indexes, $r = -0.490, P < .001$; Alberta Infant Motor Scale, $r = -0.500, P < .001$; Griffiths motor subdomain, $r = -0.527, P < .001$).

**TABLE 5** Neurologic and Neuroradiological Findings and Growth at a Median Age of 5.1 (Range, 5.0–5.4) Years

<table>
<thead>
<tr>
<th>Ischemic changes</th>
<th>HLHS, n (%)</th>
<th>UVH, n (%)</th>
<th>Control, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>2/17 (12)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Infarct</td>
<td>4/17 (24)</td>
<td>2/9 (22)</td>
<td></td>
</tr>
<tr>
<td>Diffuse</td>
<td>0</td>
<td>1/9 (11)</td>
<td></td>
</tr>
<tr>
<td>Minimala</td>
<td>5/17 (29)</td>
<td>1/9 (11)</td>
<td></td>
</tr>
<tr>
<td>Volume loss</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical</td>
<td>1/17 (6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Central</td>
<td>1/17 (6)b</td>
<td>1/9 (11)c</td>
<td></td>
</tr>
<tr>
<td>Microhemorrhages</td>
<td>1/17 (6)</td>
<td>1/9 (11)c</td>
<td></td>
</tr>
<tr>
<td>Receiving any therapy</td>
<td>13/23 (57)</td>
<td>6/13 (46)</td>
<td>7/40 (18)</td>
</tr>
<tr>
<td>Physiotherapy</td>
<td>7/23 (30)</td>
<td>5/13 (39)</td>
<td>2/40 (5)</td>
</tr>
<tr>
<td>Speech therapy</td>
<td>10/23 (44)</td>
<td>2/13 (15)</td>
<td>5/40 (13)</td>
</tr>
<tr>
<td>Occupational therapy</td>
<td>7/23 (30)</td>
<td>2/13 (15)</td>
<td>0</td>
</tr>
<tr>
<td>Head circumference $&lt; -2$ SD</td>
<td>4/23 (17)</td>
<td>1/13 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Height $&lt; -2$ SD</td>
<td>2/23 (9)</td>
<td>1/13 (8)</td>
<td>0</td>
</tr>
</tbody>
</table>

Intelectual disability was defined as significant limitations in intellectual functioning (FIQ/MDI <70) and in adaptive behavior (VABS composite score <70).

a Indicating 1 or 2 minimal focal ischemic lesions, located most often in the centrum semiovale.

b This patient also had atrophy of vermis.

c One patient had both central volume loss and microhemorrhages.

**DISCUSSION**

Our prospective follow-up results from a nationwide sample of patients with HLHS or UVH revealed a significantly lower cognitive outcome at preschool age among each patient group in comparison with the controls. Despite improved surgical treatment, the implementation of RLFP to replace DHCA, and high survival rates, different degrees of neurodevelopmental deficits were still found in the majority of patients. In comparison with our earlier cohort of patients born between 1995 and 1999,28 which included most of the earliest Norwood survivors in Finland and were operated on before the application of RLFP, a similar percentage of patients presented with major neurodevelopmental impairment: 26% in the present and 29% in the earlier cohort of the patients with HLHS, and 23% and 20% in the cohorts of the patients with UVH, respectively. Other recent studies on the early development of patients with HLHS operated on at the beginning of this century also support the paucity of improvement in the neurodevelopmental outcome of these patients.6–11

There is growing evidence that the cerebral circulation in patients with HLHS is already diminished during fetal life because of impaired antegrade blood flow in the aortic arch.29,30 This leads to impaired brain growth and maturation30–33 and increases the risk of white matter injury atypical for term infants.13,14,33 Therefore, we added the diameter of the ascending aortic arch to our risk factor analysis, and it correlated significantly with FIQ in multiple linear regression analysis after excluding 2 outliers with global ischemic brain damage. This finding suggests that impaired fetal cerebral circulation may contribute to later neurodevelopmental deficits.

Our risk factor analysis revealed no significant associations with support times or support-related techniques, but several correlates of cognitive outcome related to the primary and BDG operations with a high explanation rate, suggesting a multifactorial etiology of cognitive deficits. A history of clinical seizures in connection with the primary operation was the strongest correlate, clearly indicating brain injury, especially because seizures were also related to microcephaly and MRI abnormalities.
Other studies on children with CHD have also associated clinical or electrographic seizures with a worse cognitive outcome. In the early postoperative period after the Norwood operation, regional cerebral oxygenation decreases and is significantly influenced by the systemic hemodynamics. In our patients, a clinically significant neonatal AV valve regurgitation and impaired cardiac function after the BDG operation increased the risk of brain damage, most likely because of impaired hemodynamics. A high hematocrit level after the BDG operation, leading to higher blood viscosity, correlated with both worse motor development at the age of 30 months and lower cognitive development at the age of 5 years. These values, ranging from 40% to 59%, may have led to a decreased microcirculatory blood flow or increased risk of thrombosis and thus impaired cerebral oxygen supply. The hematocrit level as well as a history of seizures during the follow-up were also significantly associated with prominent abnormalities in MRI findings. As a potentially modifiable factor, the hematocrit level presents 1 possibility to optimize the postoperative care of these patients.

In addition to the postoperative hematocrit level, the reduced cardiac systolic function after the BDG operation also emerged as a significant risk factor at the age of 30 months. The stay in the respirator after stage I correlated significantly with both MDI and FIQ, but it is also strongly related with the duration of inotrope use, which had an even more significant correlation with FIQ and was therefore chosen for linear regression. The maternal level of education correlated significantly with MDI, and its correlation with FIQ also approached significance ($P = .072$). Height was a significant predictor of MDI, but growth parameters were only significant predictors of FIQ in the univariate, not in the

FIGURE 2
FIQ scores among patients with HLHS ($n = 21$), patients with UVH ($n = 13$), and control children ($n = 40$) at a median age of 5.1 (range, 5.0–5.4) years.
multivariate analysis. Surprisingly, the history of seizures was not a significant factor in the risk factor analysis at the age of 30 months, but in the less comprehensive analysis at the age of 1 year it was. In multivariate models with several risk factors and a rather small number of patients, some factors may emerge as significant by chance, which may explain the differences between results at different ages. However, it is clear that these patients may experience brain damage with multiple interacting mechanisms at different phases of treatment and even before treatment. Most of the significant factors in our analysis represent factors that are physiologically plausible and have potential clinical relevance. Thus, these results may help in optimizing treatment and in recognizing patients with the highest risk of neurodevelopmental sequelae.

The impact on later neurodevelopment of the often transitory pre- and postoperative white matter injury reported in neonates with HLHS or other forms of CHD remains unknown. Few neuroradiological studies have been conducted at a later age on Fontan survivors. MRI abnormalities, mostly previous ischemia or infarction, were found in half of these patients at the age of 34 to 96 months, but did not correlate with the cognitive outcome. In our earlier cohort, 4 of 6 of patients with HLHS and 2 of 13 of those with UVH had abnormalities in brain computed tomography scans or MRI at the age of 5 to 7 years. In the current study, we observed different degrees of ischemic MRI changes or volume loss in the majority of the patients who underwent imaging. Prominent changes were significantly associated with cognition, motor scores, abnormalities in the neurologic examination, and also adaptive behavior reported by the parents. Of those 8 patients with either infarct or global ischemic damage on MRI, in 5 the occurrence of clear neurologic symptoms could date the insult to the I or II postoperative stage. Three others experienced a brain infarct between the ages of 1 and 5 years, 2 of them without a connection to any operation. Thus, these patients remain at risk for major brain injury outside the stages of palliative surgery.
The cognitive and motor development assessments at the age of 5 years correlated significantly with the earlier longitudinal follow-up results at the age of 12 and 30 months. Thus, neurodevelopmental impairments could often be recognized in early infancy. Multiprofessional assessments of different developmental domains at the age of 5 years yielded similar results compared with each other and with parental reports. Probably owing to a more accurate assessment at this older age, and to the age-related increase in the complexity of brain function, neurologic abnormalities were found more often than earlier. They mainly included difficulties in gross and fine motor functions and balance, which are known to be the most disturbed areas of functioning among patients with CHD. A recent volumetric study on infants with different forms of CHD several months after cardiac surgery revealed that the frontal gray matter volume was reduced, especially in those patients with preoperative hypoxia or a diagnosis of HLHS. This reduction correlated weakly with impaired psychomotor development, attributable to the motor cortex located in this area. Methods of neuromonitoring such as near-infrared spectroscopy, transcranial Doppler, and continuous EEG recording, which were not yet in use at our clinic during this study, may help in detecting vulnerable peri- and postoperative periods, which may relate to the neurodevelopmental outcome. Whether an improved neurodevelopmental outcome is achievable needs to be further evaluated with prospective studies. The prevention of brain injury alongside improvement in survival rates among patients with complex CHD remains the main future challenge in pediatric heart surgery.

CONCLUSIONS

At the age of 5 years, neurodevelopmental deficits were frequently found in patients with UVH, and especially in those with HLHS, and were associated with ischemic findings on brain MRI. Despite declining mortality rates, improvement in the neurodevelopmental outcome during recent decades thus remains limited. Risk factors identified were the narrowness of the ascending aortic arch leading to impaired fetal cerebral circulation and hemodynamic factors related to the first operative stages performed in infancy. Nevertheless, neurologic injury can occur at any phase, and clinical seizures are indicators of brain damage.

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REFERENCES

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