Prospective follow-up study of children with univentricular heart: Neurodevelopmental outcome at age 12 months

Anne Sarajuuri, MD,^a Tuula Lönnqvist, MD, PhD,^a Leena Mildh, MD, PhD,^b Irmeli Rajantie, PT,^a Marianne Eronen, MD, PhD,^c Ilkka Mattila, MD, PhD,^d and Eero Jokinen, MD, PhD^c

Objectives: Despite recent advances in the treatment of children with univentricular heart, their neurodevelopmental outcome remains a major concern.

Methods: This prospective follow-up study evaluated the neurodevelopmental outcome of 23 patients with hypoplastic left heart syndrome, 14 with other forms of univentricular heart, and 46 healthy control subjects at a median age of 12.2 months. The Griffiths Developmental Scale and Alberta Infant Motor Scale served for developmental evaluation.

Results: The mean Griffiths developmental quotient of children with hypoplastic left heart syndrome was significantly less (91.6) than that of control children (106.8, $P < .001$). Patients with univentricular heart scored significantly lower than control subjects only in the gross motor domain ($P = .001$) but not in overall development (100.6). Alberta Infant Motor Scale scores were significantly lower in children with hypoplastic left heart syndrome (37.5, $P < .001$) and univentricular heart (43.5, $P = .011$) than in control subjects (53.3). In linear regression a diagnosis of hypoplastic left heart syndrome ($P = .016$), a clinical history of seizure ($P = .002$), and the highest plasma lactate level after the bidirectional Glenn operation ($P = .045$) were significantly associated with the developmental quotient.

Conclusions: At age 1 year, the level of development of children with univentricular heart was significantly lower than for control subjects only in motor skills, whereas children with hypoplastic left heart syndrome had a more widespread developmental delay. The diagnosis, a clinical seizure history, and increased plasma lactate levels after the bidirectional Glenn operation emerged as risk factors.

Supplemental material is available online.

With progress in surgical and perioperative care, the survival rate of children with hypoplastic left heart syndrome (HLHS) and other forms of univentricular heart (UVH) has increased.¹ Consequently, the survivors' neurodevelopment has become a focus of interest. Recent surgical advances include right ventricle–pulmonary artery (RV–PA) shunt in the Norwood operation² and the implementation of regional low-flow perfusion (RLFP) to replace deep hypothermic cardiac arrest (DHCA).³ The risk for cerebral damage increases significantly if the duration of DHCA exceeds 40 to 45 minutes,⁴ which was often the case in the Norwood operation earlier. The Boston Circulatory Arrest

Study, evaluating children with transposition of the great arteries, showed that compared with the use of RLFP, DHCA was associated with worse neurologic outcome, especially in the motor area.⁴ On the other hand, such an association has not been found in 2 recent studies comparing DHCA and RLFP among patients who underwent the Norwood operation.^{5,6} Use of an RV–PA shunt has been associated with faster recovery after the Norwood operation,⁷ although no significant difference in mortality has been found.⁸ Studies comparing neurodevelopmental outcome are lacking. In addition to these intraoperative factors, several preoperative and postoperative factors increase the neurologic risks to patients: structural brain anomalies, low preoperative cerebral blood flow, postoperative hemodynamic instability, chronic hypoxemia, and cerebrovascular accidents.

In most studies of children with HLHS operated on in the 1990's, mean intelligence has remained in the low average range.^{9–12} Only a minority of patients has more serious neurologic sequelae, such as cerebral palsy or mental retardation, but specific learning difficulties are common. To assess more carefully the neuropsychologic profile to determine the risk for learning difficulties requires comparison with healthy control children, which has not been done in most previous studies.

MATERIALS AND METHODS

Patient Population

Children with HLHS or other forms of UVH born between August 2002 and February 2005 and operated on at the Department of Paediatric and Adolescent Medicine of the Helsinki University Central Hospital were offered

From the Divisions of Neurology^a Anesthesiology and Intensive Care Medicine^b Paediatric Cardiology,^c and Surgery^d Department of Paediatric and Adolescent Medicine, Helsinki University Central Hospital, Helsinki, Finland.

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Address for reprints: Anne Sarajuuri, MD, Department of Child Neurology, Department of Paediatric and Adolescent Medicine, Helsinki University Central Hospital, Lastenlinnantie 2, 00029 HUS, Finland (E-mail: Anne.Sarajuuri@hus.fi).

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Abbreviations and Acronyms

AIMS	= Alberta Infant Motor Scale
BDG	= bidirectional Glenn operation
BT	= Blalock–Taussig
DHCA	= deep hypothermic cardiac arrest
DQ	= developmental quotient
EEG	= electroencephalography
HLHS	= hypoplastic left heart syndrome
RLFP	= regional low-flow perfusion
RV–PA	= right ventricle–pulmonary artery
SD	= standard deviation
UVH	= univentricular heart

the possibility to participate in a prospective neurodevelopmental follow-up study. All pediatric cardiac surgery in the Finnish population of 5.3 million is performed at this hospital. During this time period, 2 patients with HLHS were not actively treated. The number of eligible children with HLHS/UVH, after the exclusion of 1 patient because of Cantrell's pentology and 2 because of a chromosomal defect, was 52. Nine patients were not recruited because of a lack of parental consent. This meant 28 children with HLHS and 15 children with other forms of UVH were recruited. Control children numbered 46, with a similar age and sex distribution (64.9% boys among the patients and 65.2% among the control subjects). The control children were recruited from low-risk deliveries at the Department of Obstetrics and Gynecology of Helsinki University Central Hospital after a pediatric check-up with normal findings. Their normal cardiac anatomy was confirmed with ultrasonographic analysis. The study was approved by the Ethics Committee of the Department of Paediatric and Adolescent Medicine at the Helsinki University Central Hospital. Written informed consent of all parents was obtained.

Neurodevelopmental Assessment

A routine neurologic examination of all subjects was performed at a median age of 12.2 months, with assessment of muscle tone (level and symmetry), deep tendon reflexes, functions of the cranial nerves (pupillary reactions, possible strabismus, eye movements, symmetry of mimics and pharynx, localization of sound, and head turning), side and back protection reflexes from a sitting position, and parachute reaction. The findings were classified as either normal or abnormal, except for muscle tone, which was graded as either normal, mild hypotonia, severe hypotonia, or hypertonia. The neurologic findings were classified as mildly abnormal if aberrant findings existed in 1 or 2 compartments and clearly abnormal for aberrant findings in more than 2 compartments. As a common finding, mild muscle hypotonia was not included in this grading of neurologic abnormality. Head circumference, weight, and length were recorded and compared with Finnish national standards.^{13,14} Microcephaly was diagnosed if head circumference was more than 2 standard deviations (SDs) below the mean for the age- and sex-specific population standard. The Griffiths developmental scale¹⁵ served for developmental assessment, and the Alberta Infant Motor Scale (AIMS)¹⁶ served for a more detailed motor evaluation. A Griffiths developmental quotient (DQ) was determined according to the test manual if all 5 subdomains (gross motor, social, verbal, and visuomotor development and performance) could be adequately evaluated. The motor assessments were recorded on videotape and were analyzed according to the AIMS manual by 2 physiotherapists well experienced in child developmental assessment.

Surgical and Perfusion Strategies

The aortic reconstructions during Norwood-type operations and possible additional aortic reconstructions caused by aortic recoarctations were

performed during either RLFP alone or in combination with short periods of DHCA (maximum of 9 minutes), and 1 patient underwent a correction of the superior vena cava with a DHCA of 20 minutes. During surgical corrections, the perfusion strategies were as follows. With the Norwood I procedure and all other operations involving aortic arch reconstruction, (1) the hematocrit value was kept at 0.30%, (2) cooling was aimed at 18°C, and (3) α -stat pH management was used, and during RLFP, the pump flow was kept between 15 and 20 mL · kg⁻¹ · min⁻¹. With the bidirectional Glenn operation (BDG), hematocrit values were also aimed at 0.30%, but the body temperature was kept between 30°C and 32°C. Toward the end of perfusion, ultrafiltration was performed, if needed, to increase the hematocrit value. During BDG, the superior vena cava was cannulated distally, almost at the junction of the jugular and anonymous veins. Another cannula was placed to the right atrial appendix except when intracardial procedures were performed; then it was placed to the inferior vena cava.

Clinical Data Collection

The medical records were analyzed concerning the operations performed and the durations of cardiopulmonary bypass, DHCA, RLFP, aortic crossclamping, cooling, and rewarming and the level and duration of hypothermia. The levels of diuresis (in milliliters per kilogram per hour) during the first 3 postoperative days and the highest plasma concentration of lactate (in millimoles per liter) during the postoperative time intervals of 0 to 6, 6 to 24, 24 to 48, and 48 to 72 hours were recorded. Possible clinical seizures and resuscitations were documented. Electroencephalography (EEG) was performed on clinical indication for those with suspected convulsions. Of the EEG findings, focal abnormality was considered significant (either focal spikes/discharges or asymmetry). Perinatal data concerning Apgar scores at 1, 5, and 10 minutes and weight, height, and head circumference at birth were collected. Maternal and paternal occupation,¹⁷ as well as level of education,¹⁸ were recorded and classified according to the Finnish versions of these classifications. All these data were analyzed for association with the primary outcome measure, Griffiths DQ, in the univariate analysis.

Statistical Analysis

SPSS version 13.0 software (SPSS, Inc, Chicago, Ill) was used for statistical analysis. The Mann–Whitney test served for comparison of continuous variables between patients and control subjects. Kruskal–Wallis and Dunn tests were used for continuous data, and the Fisher's exact test was used for binary data to compare the results between the subgroups (children with HLHS, children with UVH, and control subjects). The Bonferroni correction was made for Fisher's *P* values to correct for multiple comparisons. Pearson correlation coefficients were computed as a measurement of association with DQ for normally distributed continuous factors, and Spearman correlation coefficients were computed for categorical and nonnormally distributed continuous factors. Natural logarithm and exponential transformations were performed for those nonnormally distributed continuous factors that approached significance. All factors significantly associated with DQ were added into the linear regression model.

RESULTS

Patient Characteristics

Five of the recruited patients (4 with HLHS and 1 with UVH) died before the age of 12 months. One patient was unable to participate in the follow-up visit at 12 months because of a tracheostomy caused by bilateral recurrent nerve paralysis and inability to travel long distances. At a median age of 12.2 months, 37 surviving patients and 46 healthy control children were examined. The diagnoses

and operations performed are presented in Table E1. During our study, both the modified Blalock–Taussig (BT) shunt (13 patients) and the RV–PA shunt (15 patients) were used. Before the study visit, all children but 1 had undergone the BDG operation at a median age of 5.7 months, 8 patients needed a reconstruction of the aortic arch in connection with the BDG operation, and 6 children had experienced 1 and 2 patients had experienced 2 additional operations. The median support times are presented in Table 1. Extracardiac malformations were found in 3 study patients: diaphragmal hernia and asplenia related to heterotaxy, scoliosis, and vertebral anomalies, as well as a sensorineural hearing deficit.

Developmental Assessment

The mean Griffiths DQ could be adequately evaluated for 32 patients and 46 control children. The DQ was 95.0 in all patients with congenital heart defects compared with 106.8 in control subjects ($P < .001$). The difference from control subjects was significant for children with HLHS but not for children with UVH (Table 2). Of the developmental domains, those with UVH were scored at a significantly lower level than control subjects only in the gross motor domain (29.5 vs 34.7, $P = .004$), whereas the children with HLHS were scored at a significantly lower level than control children in the gross motor (27.0 vs 34.7, $P < .001$), social (30.1 vs 33.7, $P < .001$), visuomotor (28.5 vs 32.0, $P = .015$), and performance domains (29.2 vs 32.9, $P < .001$; Figure 1).

The mean results in the AIMS motor developmental assessment were significantly better for the control subjects (53.3 points; SD, 4.5) than for either children with HLHS (37.5 points; SD, 14.5; $P < .001$) or children with UVH

(43.5 points; SD, 13.1; $P = .011$; Figure 2). The AIMS results correlated significantly with Griffiths DQ results ($P < .001$) and with Griffiths gross motor ($P < .001$), social ($P = .005$), and performance ($P = .011$) domains.

Neurologic Outcome

Muscle hypotonia was a common finding among the children with HLHS/UVH (70.3% compared with 19.6% in healthy control subjects, $P < .001$). It was mild in all control children, whereas 4 patients had severe muscle hypotonia, and 1 had muscle hypertonia. Asymmetric muscle tone was found in 17.4% of the children with HLHS (widespread in 1 and mild and local in 3) but in none of the control subjects or the children with UVH. The results of the neurologic examination when muscle hypotonia was excluded were abnormal in 10 patients with HLHS (43.5%), 3 patients with UVH (21.4%, not significant), and 1 control child (2.2%, $P < .001$ for the difference from HLHS). The abnormality was mild in all but 3 patients with HLHS (13.0%). Cerebral palsy resulting from a perioperative cerebral infarct was found: the form of hemiplegia in 1 (4.3%) of the children with HLHS, and in the form of a hemiparesis in 1 (7.1%) of the children with UVH. Ten (27.0%) patients had received physiotherapy and 1 received speech therapy because of eating problems before the age of 12 months; 1 control child received physiotherapy because of a mildly delayed motor development.

Growth Data

The means of birth weight (3520 vs 3510 g), height (50.4 cm in both groups), and head circumference (35.4 vs 35.3

TABLE 1. Median support times in the operations

	CPB (min)			RLFP time (min)			DHCA time (min)			Duration of cooling (min)			Duration of rewarming (min)		
	Median	Range	n	Median	Range	n	Median	Range	n	Median	Range	n	Median	Range	n
Primary operation															
HLHS	190.0	137–252	23	71.5	40–106	22*	5.0	2–9	10	30.0	10–60	23	35.0	20–95	23
UVH	175.0	116–181	5	61.0	42–81	5	8.0	8	1	20.0	15–35	5	35.0	30–50	5
BDG operation															
HLHS	88.0	48–232	23	22.0	8–50	6				30.0	5–85	9	50.0	30–80	9
UVH	85.0	65–176	12	17.0	16–32	3				25.0	15–50	5	30.0	25–40	5
Additional operation															
HLHS	97.5	34–132	4												
UVH	93.0	81–139	3												
Second additional operation															
HLHS	120.0	92–148	2	29.0	29	1	20.0	20	1						
Cumulative times															
HLHS	277.0	221–485	23	72.0	18–151	23	5.0	2–20	11						
UVH	211.0	65–351	12	77.0	55–102	5	8.0	8	1						

CPB, Cardiopulmonary bypass; RLFP, regional low-flow perfusion; DHCA, deep hypothermic cardiac arrest; HLHS, hypoplastic left heart syndrome; UVH, univentricular heart; BDG, bidirectional Glenn operation. *One patient with HLHS was managed during the Norwood operation with a perfusion in which the right upper body, carotid artery, base of the ascending aorta, and lower body through the aorta were perfused.

TABLE 2. Griffiths developmental quotient results in children with hypoplastic left heart syndrome, children with other forms of univentricular heart, and control subjects

	HLHS (n = 20)	UVH (n = 12)	Control subjects (n = 46)
Mean Griffiths developmental quotient	91.6	100.6	106.8
<i>P</i> value for difference from control subjects	<.001	NS	
<i>P</i> value for difference between children with HLHS and children with UVH	NS		
Proportion of children with a developmental quotient >1 SD lower than the mean of the control subjects	15/20 (75.0%)	4/12 (33.3%)	10/46 (21.7%)
<i>P</i> value for difference from control subjects	.002	NS	
<i>P</i> value for difference between children with HLHS and children with UVH	NS		
Proportion of children with a developmental quotient >2 SDs lower than the mean of the control subjects	7/20 (35.0%)	2/12 (16.7%)	0/46 (0%)
<i>P</i> value for difference from control subjects	.003	NS	
<i>P</i> value for difference between children with HLHS and children with UVH	NS		

Kruskal–Wallis and Dunn tests were used to compare the differences between the mean values in the groups. The Fisher's exact test was used for proportional data with the Bonferroni correction. NS, Not significant; SD, standard deviation.

cm; 35.5 cm in children with HLHS and 34.8 cm in children with UVH) did not differ significantly between patients and control subjects. One (7.1%) patient with UVH and 2 (8.7%) patients with HLHS had congenital microcephaly. Those 2 patients with HLHS and microcephaly at birth had a head circumference within normal limits at 12 months of age, whereas 2 other patients with HLHS had become and 1 patient with UVH remained microcephalic. As a group, the patients with HLHS/UVH had a significantly smaller mean head circumference than did the control children at the study visit (age- and sex-adjusted head circumference, -0.776 vs -0.111 [SD], $P = .001$), with no significant difference between those with HLHS and those with UVH. By contrast, mean height and weight did not differ significantly between the patients and control subjects.

Occurrence of Seizures

Eight (21.1%) of the surviving patients (5 with HLHS and 3 with UVH) had clinical seizures with focal EEG abnormality during follow-up. Six patients had seizures during the postoperative period after the Norwood operation, 3 of them also with neuroradiologic evidence of cerebral injury. In 2 patients brain magnetic resonance imaging showed wide cerebral atrophy at the age of 2 months. They both presented with global developmental delay and abnormal eye movements with strabismus in the study assessment. The third child had ischemic changes in the watershed area on magnetic resonance imaging at age 17 months; she also has a bilateral sensorineural hearing deficit and vertebral anomalies. The 3 other patients with seizures during their recovery from the Norwood operation showed no other evidence of neurologic injury. In addition, after the Norwood operation, 1 patient with HLHS had a suspected mild facial palsy without any detectable convulsions. Her EEG showed widespread spike-wave discharges, and computed tomographic analysis revealed a suspected small infarct in the median cerebral artery region contralateral to the facial palsy.

Of the 8 patients with epileptic seizures, 2 had their convulsions during recovery from the BDG operation. They each had a cerebral infarct, with convulsions and hemiplegia as presenting symptoms. Neither the type of a shunt in the Norwood operation (23.1% in the BT group and 20.0% in the right ventricle group) nor the support times were associated with the occurrence of seizures.

Predictors of Neurodevelopmental Outcome

In the risk factor analysis with DQ as the primary outcome measure, those patients who had postoperative seizures and a focal EEG abnormality ($n = 7$) had significantly lower mean DQ results than the others (77.3 vs 99.9 , $P = .006$; Figure E1). Five (71.4%) of them had a DQ more than 2 SDs below the mean of the control subjects compared with 4 (16.0%) of 25 of all other patients ($P = .010$). These patients with epileptic seizures also had a significantly smaller age- and sex-adjusted head circumference than those without seizures (-1.8 vs -0.5 [SD], $P = .004$). Factors that did not significantly affect DQ included prenatal diagnosis (available for 5 patients with HLHS and 3 patients with UVH), history of a Norwood-type operation, use of an RV–PA versus BT shunt in the Norwood operation, and an additional correction of the aortic arch afterward. Those 3 patients with circulatory collapse during the neonatal period caused by delayed diagnosis, as well as those 2 who had been resuscitated, did not have lower results than the others. None of the growth values at birth but the age- and sex-adjusted head circumference at 1 year of age correlated significantly with DQ among the patients (Pearson = 0.536, $P = .002$).

Factors related to support times and hypothermia and postoperative levels of diuresis did not correlate significantly with DQ. Apgar scores at 1 and 5 minutes correlated significantly with DQ among the patients (Spearman = 0.432, $P = .014$, and Spearman = 0.512, $P = .007$, respectively) but not among the control subjects. After BDG, those patients whose plasma lactate levels reached 2.5 mmol/L or

FIGURE 1. Griffiths developmental subscale results in patients with hypoplastic left heart syndrome (HLHS), patients with univentricular heart (UVH), and healthy control subjects.

higher during the first 3 postoperative days had a significantly lower mean DQ than those with a lower lactate level (81.8 vs 98.0, $P = .030$). The DQ correlated negatively with the natural logarithm transformation of the highest plasma lactate levels 0 to 6 hours (Pearson = -0.375 , $P = .034$), 6 to 24 hours (Pearson = -0.438 , $P = .012$), and 0 to 72 hours (Pearson = -0.464 , $P = .007$) after BDG (Figure 3). Neither maternal or paternal occupational nor educational level correlated significantly with DQ among either the patients or the control subjects, but because paternal educational level approached significance for the overall group (Spearman = 0.209 , $P = .068$), it was used in the linear regression model to adjust for socioeconomic status.

In the multiple linear regression analysis adjusted for sex and level of paternal education, the HLHS diagnosis ($P = .016$), clinical seizure history with abnormal EEG results ($P = .002$), and natural logarithm transformation of the highest plasma lactate level in the first 3 postoperative days after BDG ($P = .045$) were significantly associated with the primary outcome of DQ, with an explanation rate of 54.2%.

DISCUSSION

Our follow-up study showed that the development of children with HLHS and UVH at age 12 months was most disturbed in the motor area, but the children with HLHS had significantly lower results than control subjects in many other fields of development as well. The results from this population undergoing surgical intervention after the implementation of RLFP are comparable with earlier results, where the mean full-scale intelligence quotient has ranged from 84 to 94 in patients with HLHS and from 89 to 107 in patients with other forms of UVH.^{9-12,19,20} These earlier reports are cross-sectional retrospective studies of patients who were operated on at the time when DHCA was the support method in reconstructing the aortic arch. Our findings, compared with our earlier report on neurodevelopmental outcome of children with HLHS or UVH at age 5 to 7 years,¹¹ suggest some improvement in the neurodevelopmental outcomes of these patients. This might apply especially to patients with UVH, even if the Griffiths DQ at

FIGURE 2. Alberta Infant Motor Scale (AIMS) results in patients with hypoplastic left heart syndrome (HLHS), patients with other forms of univentricular heart (UVH) undergoing the Norwood operation, other patients with UVH, and control children at a median age of 12.2 months (range, 11.0–14.7 months). DKS, Damus–Kaye–Stansel.

age 1 year and full-scale intelligence quotient results at age 5 to 7 years cannot be directly compared. In addition to the use of RLFP instead of longer periods of DHCA, this improvement might be due to several other factors in the development of the preoperative, perioperative, and postoperative care of these patients.

We found that the development of these children is particularly impaired in the area of gross motor function at age 1 year. A similar trend toward lower motor performance compared with mental development among patients undergoing the Norwood operation at age 1 to 2 years has been shown by other investigators as well.^{5,6,21,22} Among older children with HLHS⁹ and in other forms of congenital heart disease,^{23,24} motor deficits are also common. This might be a consequence of the vulnerability of certain brain areas, but at age 1 year, the delay in gross motor function might in part be explained by the immobilization related to the 1 to 2 operations performed during the first year of life and by muscle hypotonia.

An increased frequency of microcephaly occurs among patients with HLHS^{9,12} or other forms of congenital heart disease.²⁴ Head circumference at birth correlates with

FIGURE 3. Highest plasma lactate level (in millimoles per liter) during the first 72 postoperative hours after the bidirectional Glenn operation and Griffiths developmental quotient (DQ) at a median age of 12.2 months in 32 patients. Outer lines represent the 95% confidence interval.

ascending aortic diameter in children with HLHS, signifying diminished brain growth caused by their abnormal circulation.²⁵ In our study population microcephaly was not as common as in some earlier reports, and mean head circumference at birth did not differ from that of control subjects. By contrast, at 1 year of age, the incidence of microcephaly remained the same, but mean head circumference was significantly lower in patients than in control subjects, which is in contrast to weight and height. Among patients, but not among control subjects, age- and sex-adjusted head circumference correlated significantly with DQ and was also strongly associated with any seizures experienced. Correlation of head size with DQ can be explained by diminished brain growth as a result of ischemic brain damage. This is confirmed by the fact that after exclusion of the 2 patients with HLHS with global ischemic damage, the correlation was no longer significant.

Of the risk factors examined, diagnosis of HLHS, clinical seizures with abnormal EEG activity, and increased postoperative plasma lactate levels after BDG surgery were significantly associated with outcome. Patients with HLHS have been shown to be at higher risk for neurodevelopmental sequelae than those with other forms of UVH.^{19,21} This difference can arise from several factors, such as impaired fetal and preoperative cerebral blood flow, possible structural brain anomalies, and the demanding Norwood operation, which is performed in only some patients with UVH. One limitation of our study is that the small number of patients with UVH might affect their results. In a few earlier retrospective reports, the occurrence of clinical preoperative⁹ or perioperative¹⁹ seizures has emerged among these patients as a predictor of worse outcome. The Boston Circulatory

Arrest Study found, among patients with transposition of the great arteries, a significant correlation between both clinical and electroencephalographic postoperative seizures and worse psychomotor development at 1 year of age, although not with mental development.²⁶ Meanwhile, other investigators have found no significant correlation between electroencephalographic seizures and early neurodevelopmental outcome; however, in this case the EEG seizures were treated on the basis of clinical discretion, which might have reduced their detrimental effect on development.²⁷ Whether the seizures lead to brain damage as such or reflect underlying brain damage remains debatable. Among many of our patients, clinical seizures were one sign of more profound neurologic damage, a fact also neuroradiologically evident.

High serum lactate levels were associated with mortality in several reports.²⁸ As an indicator of tissue hypoxia, lactate could be assumed to associate with neurodevelopmental outcome as well, but reports of such an association among survivors of congenital heart surgery are few. In one study the time needed for the plasma lactate levels to decrease to 2 mmol/L was longer among those with adverse neurodevelopmental outcome than among intact survivors, although not significantly so (16 vs 11 hours, $P = .07$).²⁹ Among 34 patients after correction of total anomalous pulmonary venous return, the highest plasma lactate level correlated significantly with psychomotor, but not with mental, development at age 18 to 24 months.³⁰ We found a significant correlation between plasma lactate concentration during the first 3 postoperative days after the BDG operation and global development at age 1 year. The correlation existed even though the lactate levels were only mildly increased. Why this was not true for the relatively higher lactate levels after the Norwood operation remains unknown.

We conclude that at 1 year of age, children with HLHS had significantly lower developmental results in most areas examined, whereas the development of children with UVH was significantly inferior to that of their control subjects in the motor area only. The neurologic abnormalities were usually mild but significantly more frequent among patients with HLHS than among control subjects. In addition to the HLHS diagnosis, a history of postoperative clinical seizures and the highest plasma lactate levels during the first 3 postoperative days after the BDG operation were significant predictors of outcome.

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FIGURE E1. Griffiths developmental quotient (DQ) values in patients with hypoplastic left heart syndrome/univentricular heart with ($n = 7$) and without ($n = 25$) epileptic seizures. *Thick lines* represent medians. The *upper end of the box* represents 75% of the patients, and the *lower end* represents 25% of the patients.

TABLE E1. Patients with HLHS/UVH examined at a median age of 12.2 months (n = 37): Diagnoses and operations performed

	Age (d)		Operation	Diagnosis	n
	Median	Range			
Primary operation	7.0	1–37	Norwood	HLHS	23
			Norwood	DILV, HAA, CoA, RV hypo	1
			Norwood	TA, HAA, TGA, VSD	1
			Norwood	AVSD, HAA, LV hypo	1
			Norwood	Nonbalanced AVSD, CoA	1
			DKS, BT modification, rec. aortic arch	DILV, TGA, HAA, CoA	1
			CoA correction, PA banding	TA, dextrocardia, RV hypo, TGA, VSD	1
			BT shunt	AVSD, dextrocardia, TGA, RV hypo, heterotaxy	1
			BT shunt	PA+IVS, RV hypo	3
			PA banding	TA, VSD, PA, RV hypo	1
			BT shunt	TA, VSD, PS, RV hypo	1
			BT shunt, septectomy	PA+IVS, TA	1
			No operation	DORV, dextrocardia, VSD, PS, MS, ASD	1
BDG operation	171.0	63–394			37
Additional operation	108.5	1–287	CoA correction	HLHS	1
			LPA reconstruction, BT shunt	AVSD, dextrocardia, TGA, RV hypo, heterotaxy	1
			Aortic valve plasty	HLHS	1
			Re-BDG, thrombectomy	AVSD, LV hypo, HAA	1
			PA banding	TA, VSD, PS, RV hypo	1
			Septectomy and PA banding	HLHS	1
			Re-BT shunt	PA+IVS	1
			LPA plasty, aortic arch plasty	HLHS	1
Second additional operation	203.5	99–308	SVC plasty	HLHS	1
			Reconstruction of aorta and PA	HLHS	1

HLHS, Hypoplastic left heart syndrome; UVH, univentricular heart; DILV, double-inlet left ventricle; HAA, hypoplastic aortic arch; CoA, coarctation of the aorta; RV hypo, hypoplasia of the right ventricle; TA, tricuspid atresia; TGA, transposition of the great arteries; VSD, ventricular septal defect. AVSD, atrioventricular septal defect; LV hypo, hypoplasia of the left ventricle; DKS, Damus–Kaye–Stansel; BT, Blalock–Taussig; PA, pulmonary artery; PA+IVS, pulmonary atresia with intact ventricular septum; PS, pulmonary stenosis; DORV, double-outlet right ventricle; MS, mitral stenosis; ASD, atrial septal defect; BDG, bidirectional Glenn operation; LPA, left pulmonary artery; SVC, superior vena cava.