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ORIGINAL ARTICLE

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CONGENITAL

Neurocognitive development and behaviour in school-aged children after surgery for univentricular or biventricular congenital heart disease

Iemke Sarrechia[a,*], Marijke Miatton[b], Daniël De Wolf[c], Katrien François[d], Marc Gewillig[e], Bart Meyns[f] and Guy Vingerhoets[a]

[a] Department of Experimental Psychology, Ghent University, Ghent, Belgium
[b] Department of Neurology, Head, Neck and Nerve System, Ghent University Hospital, Ghent, Belgium
[c] Department of Pediatrics, Ghent University, Ghent, Belgium
[d] Department of Cardiac Surgery, Congenital Cardiac Surgery, Ghent University Hospital, Ghent, Belgium
[e] Pediatric and Congenital Cardiology, University Hospital Gasthuisberg, Leuven, Belgium
[f] Pediatric and Congenital Cardiothoracic Surgery, University Hospital Gasthuisberg, Leuven, Belgium

* Corresponding author. Department of Experimental Psychology, Clinical Developmental Psychology, Ghent University, Henri Dunantlaan 2, B-9000 Ghent, Belgium. Tel: +32-9-3313363; e-mail: iemke.sarrechia@gmail.com (I. Sarrechia).

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Abstract

OBJECTIVES: To assess the long-term neuropsychological and behavioural profile of school-aged children who were treated for univentricular heart (UVH) conditions or biventricular heart defect (BiVH) in infancy in a cross-sectional study design.

METHODS: Sixty-three patients, 17 UVH (13 males, 4 females) and 46 BiVH (19 males, 27 females), were assessed at a mean age of 9.1 years (2.2 years) with an intelligence and neuropsychological test battery. Results were compared between subgroups (UVH, BiVH and a healthy control group). Associations between cognitive outcome, medical and socio-demographic factors were explored. Parents completed the Child Behavior Checklist (CBCL).

RESULTS: Mean intelligence and neuropsychological scores were found within normal ranges for all diagnostic groups. Significant differences between UVH patients and controls emerged on auditory sustained and alternating attention, fine motor skills, visuospatial information processing, and to a lesser extent, memory performance. Parents of UVH patients reported more externalizing problems and school problems. Patient groups did not differ on neuropsychological outcome measures, nor on behavioural problems as rated by parents.

CONCLUSIONS: After Fontan completion, patients at school age display intelligence scores within normal population-based ranges. However, they were found at risk for subtle shortcomings in attention, fine motor skills, visuospatial information processing and externalizing behaviour problems. Considerations pertaining to neurobehavioural outcome in school-aged children are discussed.

Keywords: Congenital heart defect • Hypoplastic left heart • Tricuspid atresia • Neuropsychology • Neurodevelopmental outcome

INTRODUCTION

Advanced surgical staged palliation is the current treatment for children with a univentricular heart (UVH), a condition once considered fatal. The prevalence of this complex congenital heart disease (CHD) is estimated at 0.08–0.09 per 1000 births and represents ∼2% of all CHDs [1]. These children often present at birth with congestive heart failure, cyanosis, poor feeding and respiratory distress, making immediate intervention imperative.

With the growing number of survivors following treatment for complex CHD, neurodevelopmental outcome has been highlighted throughout the last decades. Of all cohorts with CHD, those with UVH suffer from the poorest cognitive outcome. At preschool age, these children exhibit mental and psychomotor developmental indexes in the low-to-average range as assessed by the Bayley Scales of Infant Development (BSID) [2–5]. At school age, when broader cognitive functions develop, low-to-average intelligence scores have been described in children treated for UVH in early and recent reports [6, 7]. Studies have documented subtle problems in attention and executive functioning, language, but predominantly in motor functioning and visuospatial information processing [4, 8–10]. Altogether, it puts subgroups of children with UVH at risk for academic underachievement and unemployment as they progress into adulthood [11].

Researchers have attempted to discover aetiological factors underlying adverse cognitive functioning, but with varying success rates. Pre- and postoperative brain injuries, as well as genetic

anomalies are common in this clinical population [5, 7, 12]. Intraoperative management and postoperative events possibly adversely affecting developmental outcomes have all been the focus of previous research efforts [5, 12]. Recently, evidence has been found for non-modifiable factors such as socio-economic status, genetics, neurological anomalies and parenting style to explain the adverse development of these children [5, 13]. The present study was set up to delineate and update the cognitive profile of children diagnosed with and treated for hypoplastic left heart (HLH) or tricuspid atresia (TA), considered as the UVH cohort. We compared cognitive outcomes with those of a matched healthy control group (UVH controls) and with those with surgical repair of a biventricular heart defect (BiVH), for an atrial septum defect secundum type (ASD-II) or ventricular septum defect (VSD) in infancy. We hypothesized that children treated for UVH would display more adverse neuropsychological functioning, due to preoperative hypoxia, prolonged cyanotic state, haemodynamic instability, multiple surgical procedures and subsequent long hospitalizations in infancy and early childhood.

METHODS

Patients

Patients treated surgically for UVH (HLH/TA) and BiVH (ASD-II/VSD) were selected in two specialized heart centres, Ghent University Hospital and University Hospital Gasthuisberg Leuven (Flanders, Belgium). They were assessed with an intelligence screening and an extensive neuropsychological test battery at school age (6–12 years).

Exclusion criteria for the UVH cohort were severe genetic abnormalities, developmental syndromes and cerebral palsy. BiVH patients were excluded if there was evidence for perinatal problems, preterm gestational age (<37 weeks), birth weight <2000 g, other cardiac malformations, genetic abnormalities or developmental syndromes. Out of 107 invited, 63 parents of CHD patients (59%) responded positively to our appeal and participated. In Ghent University Hospital almost all parents of every eligible UVH patient agreed to participate in the study (12/14). In Leuven University Hospital, other studies competing for participation in the same clinical sample of UVH patients resulted in participation of 5 from 8 invited. Non-responders did not provide any demographic data, nor gave permission to review their medical files. Included patients completed all steps of the assessment procedure. The clinical population consisted of 17 patients who had UVH treatment (HLH: 8/TA: 9) and 46 BiVH patients (VSD: 28/ASD-II: 18).

Surgical palliation or defect repair was performed in both groups according to diagnosis- and institution-specific protocols.

The UVH group underwent staged surgical palliation during 2000–2009, initialized with the Norwood operation or pulmonary artery banding and concluded with the Fontan/total cavopulmonary connection operation. In the HLH cohort, 6 of 8 patients had antegrade flow in their aortic arch prior to the Norwood procedure.

Patients with BiVH were treated during 1999–2010 with one single open-heart surgery with mild-to-moderate hypothermic (25–37°C) cardiopulmonary bypass.

The healthy control group was recruited through approval of primary school boards and was matched with each patient in terms of gender, age and parental education level. Parents completed demographic surveys.

The Hollingshead Four-Factor Index [14] was calculated for socio-economic status (SES) by combining parental occupational and educational level. Raw scores ranged from 24 to 66, a higher score indicating higher social status. Both the medical ethics committee of Ghent University Hospital and Gasthuisberg Leuven approved the study and parental written consent for the study and publication of the results was obtained.

Neurodevelopmental testing

Intelligence was assessed with a short version of the WISC-III-NL (3rd edn, Dutch version). Two verbal subtests (Similarities and Vocabulary) and two performance tasks (picture arrangement and block design) constituted a reliable measure of overall intelligence [15].

The NePsy (a Developmental Neuropsychological Assessment, 2nd edn, Dutch version) [16] is a customizable test battery to assess an extensive range of neurocognitive skills in school-aged children. In a scientific statement of the American Heart Association, the NePsy was listed as a valid and reliable instrument to assess a variety of neuropsychological functions in children treated for CHD [17]. Domains of Attention and Executive Functioning, Language, Memory and Learning, Sensorimotor Integration, Social Perception and Visuospatial Processing were assessed. Table 1 gives an overview of the selected tasks.

Outcome scores are expressed as age-adjusted standardized scores (mean: 10, standard deviation [SD]: 3), or percentile scores, which are considered to be process scores (pc < 2–pc75). These scores assess specific abilities or error rates that enable the clinician to evaluate a child's performance in more detail.

Behavioural assessment

The Achenbach Child Behavior Checklist for Children aged 6–18 (CBCL-6/18) [18] was used to obtain standardized measures of behavioural, social and emotional functioning of the children, rated by their parents. This questionnaire contains problem behaviour scales and competence scales, to be rated in frequency on a three-point scale. Three composite scales are computed: internalizing scale, externalizing scale and grouped together, these scales constitute the total problem behaviour.

Statistical analysis

Data were analysed using the SPSS version 21.0 statistical Package (SPSS, Inc., Chicago, IL, USA). Normality was checked by Kolmogorov–Smirnov tests. Normally distributed data are presented as means with standard deviation; median and interquartile ranges are given for data that did not meet normality assumptions. Demographic characteristics and cognitive outcome measures are compared between patient groups and the matched controls. Nominal data were compared using Fisher's exact test. For data derived from the medical charts, median and interquartile ranges were calculated.

For matched samples (UVH vs controls), paired *t*-tests and Wilcoxon signed-rank tests were applied to study group differences. Analysis of variances (ANOVAs) and Mann–Whitney *U*-tests were used to examine differences between patients (UVH vs BiVH). In the latter analyses, ANOVAs were adjusted for gender.

In addition, effect sizes were calculated to examine clinically meaningful differences next to statistical significance. For parametric

Table 1: Selected NePsy tasks [16]

NePsy domains	Ability assessed
Auditory attention and executive functioning	
Auditory attention and response test	Selective auditory attention; vigilance; shifting; inhibition
Design fluency	Planning; problem-solving skills
Inhibition	Shift and maintenance of new visual set; inhibition
Language domain	
Comprehension of instructions	Receiving, processing and executing oral instructions
Repetition of nonsense words	Phonological encoding and decoding
Speeded naming	Rapid semantic access and production of names
Word generation	Verbal productivity
Memory and learning domain	
Memory for faces	Encoding of facial features; immediate and long-term memory for faces
Memory for names	Name learning; short recall and long-term memory for names
Narrative memory	Encoding of story details; free and cued recall
Word list inference	Verbal working memory; repetition and recall after inference
Sensorimotor domain	
Imitating hand positions	Visuospatial analysis and motor programming
Manual motor sequences	Imitation of rhythmic manual movement sequences
Fingertip tapping	Rapid motor programming
Visuomotor precision	Graphomotor speed; accuracy
Social perception domain	
Affect recognition	Recognize and compare emotional affect
Theory of mind	Ability to understand mental functions and another's point of view
Visuospatial processing domain	
Block construction	Ability to reproduce 3D from 2D drawings
Design copying	Motor and visuoperceptual skills in copying 2D designs
Geometric puzzles	Visuospatial analysis; mental rotation
Route finding	Visuospatial relations; directionality

data, Cohen's *d* was computed to indicate the standardized difference between two means. For data that did not meet normality assumptions, Mann–Whitney's or Wilcoxon's *r* was calculated. Effect sizes are defined as small, $d = 0.20/r = 0.10$; moderate, $d = 0.50/r = 0.30$; large, $d = 0.80/r = 0.50$ and very large, $d = 1.3/r = 0.70$.

RESULTS

Patient population

Patients with HLH and TA did not differ significantly on demographic characteristics, neuropsychological or behavioural outcome; they were therefore considered as one group (UVH) in further analyses.

The comparison of the total group of UVH patients and controls did not elicit significant differences in demographics due to matching efforts (Table 2). When comparing the UVH group and the BiVH group, there was a significant difference in gender distribution. We controlled for this variable in further analyses by adding it as an extra between-subjects factor. The mean SES was middle class.

When compared with BiVH patients, the UVH patient group was significantly younger and weighed less at the time of first intervention. Cumulative lifetime durations of hospitalization, intensive care unit (ICU) stay, surgery, extracorporeal circulation, clamp time, duration of anaesthesia and postoperative intubation time elicited significant group differences (Table 3). We identified one child (with TA) with postoperative convulsions. Additional brain imaging data showed bilateral posterior lesions. The patient was treated successfully with anticonvulsant medication. No other neurological problems were noted in the UVH cohort.

Neurocognitive assessment

Univentricular heart vs controls. Mean estimated intelligence in the UVH group was 101 (range: 73–130); most intelligence scores were within normal ranges and did not differ from controls (Table 4).

Table 2: Demographics

	UVH patients		UVH controls		*P*-value[a]	BiVH patients		*P*-value[b]
No.	17		17			46		
Sex	♂: 13	♀: 4	♂: 13	♀: 4	$1.0\chi^2$	♂: 19	♀: 27	**$0.013^*\chi^2$**
Mean test age (years.months) (SD)	9.1	(2.1)	9.2	(2.1)	0.220	9.0	(2.2)	0.964
Mean birthweight [g (SD)]	3269	(446)	3593	(564)	0.133	3250	(476)	0.884
Mean birth length [cm (SD)]	49.2	(3.1)	51.4	(2.6)	0.110	49.5	(2.1)	0.583
Mean pregnancy duration [days (SD)]	276	(12)	279	(10)	0.486	273	(11)	0.484
Apgar score 1 (min)	<4: 7.1%		<4: 0%		1.0[c]	<4: 0%		0.199[c]
	4–6: 14.3%		4–6: 11.1%			4–6: 5.4%		
	7–10: 78.6%		7–10: 88.9%			7–10: 94.6%		
Apgar score 5 (min)	<4: 0%		<4: 0%		0.502[c]	<4: 0%		0.071[c]
	4–6: 14.3%		4–6: 0%			4–6: 0%		
	7–10: 85.7%		7–10: 100%			7–10: 100%		
Hollingshead SES [mean (SD)]	37.6	(6.2)	39.4	(9.6)	0.374	39.7	(8.4)	0.372

UVH: univentricular heart patients; BiVH: biventricular heart defect patients.
[a]Paired samples *t*-test, *P*-value for UVH vs UVH controls.
[b]ANOVA, *P*-value for UVH vs BiVH.
[c]Nominal data: χ^2 test (Fisher's exact test).
$^*P < 0.05$.
P value reached statistical significance is indicated in bold type.

Table 3: Hospitalization characteristics

	UVH patients		BiVH patients		*P*-value
No.	17		46		
Mean age at initial surgery (years.months) (SD)	0.07	(0.06)	1.5	(1.9)	<0.000**
Mean weight at first surgery (g) (SD)	3655	(1004)	8591	(5822)	<0.000**
Hospital stay (lifetime−days)	39	(28–48)	7	(7–9)	<0.000**
ICU stay (lifetime−days)	8	(7–11)	2	(1–3)	<0.000**
Duration of surgery (lifetime−min)	565	(447–716)	125	(105–170)	<0.000**
Duration of ECC (lifetime−min)	192	(140–280)	56	(41–69)	<0.000**
Duration of clamp (lifetime−min)	81	(48–110)	33	(26–44)	0.001**
Duration of anaesthesia (lifetime−min)	835	(685–1008)	230	(205–255)	<0.000**
Intubation duration (lifetime−min)	5555	(2698–7610)	705	(384–1560)	<0.000**

Age and weight at first intervention are expressed as mean (SD).
Medical characteristics are expressed as median (interquartile range).
Mann–Whitney (exact). **$P < 0.01$.

Considering the neuropsychological assessment, significant differences were found in the *Attention and Executive functioning* domain, in Auditory Sustained and Shifting Attention, and Design Fluency. These results elicited medium to large effect sizes ($d/r = 0.42–0.67$). A significant difference emerged between UVH patients and controls in the cued recall of a narrative in the *Memory* domain, with a medium effect size ($r = 0.39$). Significant differences were found in the domain of *Sensorimotor functioning* in fingertip tapping and manual motor sequences scores verged on significance ($P = 0.051$). These scores evoked medium to large effect sizes ($d = 0.47–0.83$). Patient *Visuospatial information processing* skills were found different from controls in Design Copying, Total, Motor and Local score, resulting in medium to very large effect sizes ($d/r = 0.39–1.2$). Performance on block construction elicited a clear trend towards significance ($P = 0.058$).

Besides these significant group differences, it should be noted that the majority of mean and median scores were within normal ranges of population-based norms.

Univentricular heart vs biventricular heart defect. UVH patients obtained significantly lower scores when memorizing and recalling faces, but these scores reflected a small effect size ($d = 0.13$). Biventricular heart patients scored lower than the UVH group on a task of route finding, demonstrated by a small to medium effect size ($r = 0.26$) (Table 4).

Behavioural functioning

Completing the CBCL, parents of UVH patients reported significantly more externalizing and total behaviour problems when compared with ratings of the matched control group (Table 5). A trend towards more internalizing behaviour problems was demonstrated ($P = 0.056$). These results were accompanied by medium to large effect sizes ($r = 0.32–0.42$). School functioning was found worse for the UVH group when compared with controls. Forty-seven percent of the parents of the UVH group reported school problems, which translated into repeating a grade and receiving special education in ∼12% of the cases. No significant differences appeared when comparing the UVH and BiVH patients; small to medium effect sizes were demonstrated ($d = 0–0.33$).

Associations with clinical and demographic variables for univentricular heart treatment

Spearman's rho analysis revealed a negative association between cumulative lifetime ICU stay and performance of auditory sustained attention ($r_s = −0.587$, $N = 17$, $P = 0.013$) and the aforementioned trend towards significance of the scores on block construction ($r_s = −0.589$, $N = 17$, $P = 0.013$). A negative relationship was found between cumulative intubation time and the ability to shift attention and inhibit preplanned and on-going response mechanisms ($r_s = −0.556$, $N = 13$, $P = 0.048$). The total duration of mechanical ventilation during lifetime also showed an inverse association with fingertip tapping scores ($r_s = −0.509$, $N = 17$, $P = 0.037$).

Of the innate patient characteristics, pregnancy duration seemed to explain some of the variance in outcome scores of design copying; the motor score ($r_s = −0.607$, $N = 17$, $P = 0.01$).

Fingertip tapping scores were significantly related to birth weight ($r_s = 0.737$, $N = 17$, $P = 0.001$). Memory performance on a task of recalling a narrative with given cues was positively associated with SES ($r_s = 0.515$, $N = 16$, $P = 0.041$).

Cumulative lifetime duration of hospital stay, duration of surgery, prolonged time on ECC or aortic cross-clamp, nor duration of anaesthesia elicited significant relations with adverse cognitive outcome scores. In addition, no correlations were found between patient characteristics or medical data and the composite scales of the CBCL.

DISCUSSION

A univentricular physiology is a severe form of CHD and constitutes ∼2% of all CHDs [1]. This multicentre study presents an up-to-date evaluation of neurobehavioural outcome in children treated for UVH at a mean age of 9 years, aiming to extend knowledge on long-term development of these children after completion of staged palliation.

From a neuropsychological viewpoint, UVH patients are doing relatively well when compared with healthy controls. Full estimated IQ scores were found to be in normal ranges for the majority of the UVH patients, corroborating previous findings [6, 7, 19, 20], but contradicting other results [4]. In the latter study, the UVH cohort had a

Table 4: Neuropsychological performance

	UVH patients		UVH controls		*P*-value [a]	Effect size *d*/*r*	BiVH patients		*P*-value [b,c]	Effect size *d*/*r*
No.	17		17				46			
WISC-III-NL										
Estimated full scale IQ	101.1	(13.5)	107.8	(12.2)	0.288	0.52	102	(13.6)	0.175	0.06
Similarities	11.6	(2.4)	12.2	(2.4)	0.608	0.25	12.1	(2.7)	0.335	0.19
Picture arrangement	9.5	(2.8)	10.7	(2.6)	0.244	0.44	9.4	(3)	0.080	0.03
Block design	10.3	(2.6)	11.6	(2.9)	0.293	0.47	9.9	(2.9)	0.878	0.14
Vocabulary	9.4	(2.8)	10.5	(2.5)	0.496	0.41	9.9	(2.3)	0.178	0.20
NEPSY-II-NL										
Auditory attention and executive functioning										
Auditory attention (pc)	50	(25–75)	75	(75–75)	**0.016***	0.42	75	(50–75)	0.086	0.21
Response test (pc)	50	(17.5–50)	50	(37.5–75)	**0.047***	0.42	50	(25–50)	0.526	0.09
Design fluency	9.1	(2.6)	10.8	(2.4)	**0.024***	0.67	9.4	(2.1)	0.538	0.12
Inhibition (pc)	50	(25–75)	50	(50–75)	0.176	0.25	50	(50–75)	0.509	0.09
Inhibition time	9.5	(3.6)	11.2	(1.9)	0.098	0.59	9.6	(1.9)	0.129	0.03
Language domain										
Comprehension of instructions	10.5	(2.3)	12.1	(3)	0.136	0.59	10.7	(2.8)	0.380	0.07
Repetition of nonsense words	11	(3)	11	(2)	1.0	0	9.7	(2.3)	0.483	0.48
Speeded naming										
Total (pc)	25	(25–75)	50	(25–62.5)	0.344	0.19	25	(25–50)	0.976	0
Speeded naming time (pc)	75	(75–75)	75	(75–75)	1.0	0.17	75	(75–75)	0.677	0.04
Word generation										
Semantic	9	(2.7)	9.9	(3.1)	0.414	0.31	9.3	(2.3)	0.535	0.12
Linguistic (pc)	50	(25–62.5)	50	(37.5–62.5)	0.391	0.21	25	(10–50)	0.509	0.10
Memory and learning domain										
Memory for faces	9.4	(3.3)	10.6	(2.6)	0.157	0.40	9.8	(2.6)	**0.013***	0.13
Delayed	10.8	(3.5)	11.4	(2.5)	0.524	0.19	10.7	(3.6)	0.142	0.02
Memory for names	8.4	(2.9)	9.2	(2.4)	0.342	0.30	9	(2.5)	0.820	0.22
Narrative memory	10.2	(2.1)	11	(1)	0.154	0.48	11	(2)	0.127	0.39
Cued recall (pc)	50	(25–75)	75	(50–75)	0.033*c	0.39	50	(25–75)	0.676	0.05
Word list inference										
Working memory	11.7	(2.2)	10.6	(1.7)	0.252	0.56	10.2	(1.9)	0.776	0.73
Word recall	11	(1.7)	11.8	(2.2)	0.406	0.40	11.3	(2.3)	0.212	0.14
Sensorimotor domain										
Imitating hand positions	9.6	(1.8)	10.5	(1.7)	0.172	0.47	9.2	(2.5)	0.589	0.18
Manual motor sequences	11.2	(3)	12.9	(1.3)	0.051	0.73	11.4	(3.2)	0.952	0.06
Fingertip tapping	8.4	(1.7)	9.9	(1.9)	0.018*	0.83	–	–	–	–
Visuomotor precision										
Time (pc)	50	(25–62.5)	75	(50–75)	0.124	0.29	50	(25–75)	0.518	0.08
Error (pc)	25	(10–37.5)	25	(5–50)	0.946	0.01	25	(10–50)	0.539	0.07
Social perception domain										
Affect recognition (pc)	10	(10–50)	25	(6–50)	0.145	0.25	17.5	(4.25–50)	0.885	0.01
Theory of mind										
Verbal task	11.2	(2.7)	12	(2.7)	0.316	0.29	10.5	(2.6)	0.170	0.26
Contextual task	10.4	(2.3)	11	(2)	0.322	0.27	9.8	(2.5)	0.400	0.25
Visuospatial processing domain										
Block construction	10.4	(2.5)	12.5	(2.3)	0.058	0.87	10.4	(2.2)	0.909	0
Design copying (pc)	10	(3.5–10)	10	(10–25)	**0.019***	0.39	10	(2–25)	0.869	0.02
Motor	9.8	(2.3)	12.3	(1.8)	**0.000****	1.2	9.2	(2.9)	0.923	0.22
Global (pc)	25	(7.5–37.5)	25	(10–50)	0.125	0.27	25	(10–50)	0.422	0.10
Local	7.7	(1.9)	9.6	(1.3)	**0.002****	1.1	7.8	(2.1)	0.623	0.05
Geometric puzzles (pc)	50	(25–75)	50	(25–75)	0.809	0.05	50	(25–50)	0.149	0.18
Route finding (pc)	50	(25–50)	50	(25–50)	0.688	0.09	25	(10–25)	**0.035***	0.26

Standard scores: mean (SD); *P*c-scores: median (interquartile range).
[a]Paired *t*-test and Wilcoxon signed-rank test.
[b]ANOVA and Mann–Whitney *U*-test (Exact).
[c]Gender was added as a covariate in ANOVA.
*$P < 0.05$.
**$P < 0.01$.
P value reached statistical significance is indicated in bold type.

particularly long hospital stay after the Norwood procedure (median 25 days) or heart transplant (median: 46 days), which correlated negatively with intelligence. In our study, only attentional scores were found to be associated with lifetime ICU stay. This might suggest that children who experienced an eventful post-operative course, with prolonged mechanical ventilation and

Table 5: Behavioural functioning: CBCL

CBCL	UVH patients Mean (SD)	UVH Controls Mean (SD)	*P*-value[a]	Effect size *r*	BiVH patients Mean (SD)	*P*-value [b,c]	Effect size *d*
No.	17	17			46		
Composite problem behaviour scales							
Internalizing	55.9 (−8.7)	48.7 (−10.6)	0.056	0.32	52.8 (−9.6)	0.48	0.33
Externalizing	52 (−10.1)	47.1 (−9.2)	**0.017***	0.41	49.1 (−9.7)	0.309	0.29
Total problem score	53.9 (−8.7)	47.3 (−10.3)	**0.013***	0.42	51.8 (−9.1)	0.179	0.23
Total competence	42.4 (−11.8)	46.3 (−8.7)	0.351	0.16	42.4 (−8.4)	0.109	0
Competence scales							
Special education	Yes: 11.8% No: 88.2%	Yes: 0% No: 100%	0.485[d]		Yes: 8.7% No: 91.3%	1.0[d]	
Repeating school year	Yes: 11.8% No: 88.2%	Yes: 0% No: 100%	0.485[d]		Yes: 13% No: 87%	1.0[d]	
School problems	Yes: 47.1% No: 52.9%	Yes: 11.8% No: 88.2%	**0.024** χ^{2}*		Yes: 32.6% No: 67.4%	0.290 χ^{2}	

[a]Wilcoxon signed-rank test.
[b]Analysis of covariance.
[c]Gender was added as a covariate in ANOVA.
[d]χ^{2} test (Fisher's exact test).
*$P < 0.05$.
P value reached statistical significance is indicated in bold type.

subsequent longer ICU stay, are the ones that perform more poorly during neuropsychological assessment.

In addition to an intelligence screening, we also assessed a comprehensive neuropsychological test battery, with encouraging outcomes. When compared with age- and gender-matched controls, UVH patients showed similar neuropsychological outcomes. Despite optimistic scores for several neuropsychological domains, results indicated subtle deficiencies in auditory sustained and alternating attention, fine motor skills, visuospatial information processing, and to a lesser extent, memory performance. Effect sizes indicated clinically meaningful differences.

Shortcomings in attention regulation, processing speed and impulse control may influence general school functioning as attention is essential for each cognitive and motor task. UVH survivors seem to be at a disadvantage for these cognitive skills, demonstrated by recent research [9] and the current results. Attentional problems have been described in a sample of 7 HLH patients in ∼57% of patients, and for other UVH lesions ($n = 19$) in up to ∼53% [21].

Deficient gross and fine motor functions are among the most described long-term outcomes after complex cyanotic CHD repair [8–10]. UVH patients in the current study displayed inefficient eye–hand coordination, motor programming and deficient tactile/kinaesthetic information processing when performing fingertip tapping and rhythmic manual motor sequences. Central nervous system anomalies and ongoing perioperative hypoxaemia in UVH patients may affect the developing young brain [22]. Moreover, reduced total brain volume, including deviant white matter development, are suggested to be accountable for deficient motor functioning [23]. It remains uncertain if these patients suffered from mild covert neurological injury due to ongoing insufficient systemic blood flow and multiple interventions to explain the current findings. The cause and location of brain regions that are particularly vulnerable for delayed/altered development and ongoing hypoxaemia remain to be determined.

Impaired visuospatial skills have been found consistently among complex CHD populations [8–10, 24]. Our results suggest a continuity of these problems throughout childhood. It has been postulated that complex visuospatial tasks pose a specific challenge for children with CHD, and impaired visual–perceptual abilities are thought to explain poor performance [24]. Pronounced reduced hippocampal volume (>8% when compared with controls) in cyanotic CHD patients without overt lesions have been found to correlate with perceptual reasoning task scores [23]. This region may be particularly vulnerable to the chronic hypoxaemia and (post-)operative events these children are exposed to.

It remains unclear in what way these cognitive difficulties in attention, motor skills and visuospatial information processing persist and evolve throughout adolescent life and affect or hamper school choice, sports engagement and future career options.

Only few differences were found in long-term neurobehavioural functioning in UVH patients or BiVH patients. These differences were accompanied by small-to-medium effect sizes. Previous studies demonstrated that intellectual and neuropsychological functioning between cyanotic or acyanotic CHD is comparable [2, 8, 9].

With respect to behaviour, parents report that UVH patients are burdened with more externalizing and total problem behaviour, suggesting that patients have difficulty in regulating their behaviour and may display aggressive, hyperactive, non-compliant and undercontrolled behaviour (e.g. disobedience, impulsivity and swearing), corroborating previous research [8]. Parents also indicated a higher frequency of school problems when compared with controls. Repeating a grade was reported ∼in 12% of the UVH group. The internalizing problem score verged on significance, suggesting that some of these children are also burdened with anxious, depressive and overcontrolled behaviour (e.g. fearfulness, headaches, social inhibition and worry), ratifying other results [3, 8]. Remarkably, parents of UVH and BiVH patients display similar rates of repeating a grade (12 and 13%), suggesting that school problems are also evident in the latter diagnostic group. Problems in emotional regulation can be considered as the

common denominator for behavioural issues. This might manifest in poor self-regulation (e.g. irritable negative emotional tone and poor adaptability) and subsequent attention deficiencies [3]. In addition, the protective and overly concerned nature of parenting may have caused behaviour to deviate from the norm. Awareness should be raised in teachers too, because these behavioural manifestations may be mistakenly considered as Attentional Deficit Hyperactivity Disorder symptoms.

It is noteworthy that neuropsychological performance of children and behavioural ratings by parents of those who required aortic arch reconstruction for HLH did not differ significantly from those who had staged surgical repair for TA. This validates previous research efforts that showed intellectual, motor outcome and behaviour between HLH and other UVH lesions to be quite similar [3, 6, 10]. These results shed a different light on the theory that, in HLH patients, prenatal brain injury occurs through diminished cerebral and aortic perfusion as their long-term outcomes are equivalent to those with an underdeveloped or absent right ventricle.

Our positive findings are somewhat surprising given multiple and long hospitalizations, consecutive periods of cardiopulmonary bypass with deep hypothermic cardiac arrest in the surgical management and chronic hypoxaemia in UVH patients. Associations with these parameters and cognitive outcome have been highlighted in previous research [4, 5].

Other known aetiological considerations pertaining to adverse neuropsychological functioning in CHD patients imply altered cortical brain development [25], the high frequency of genetic anomalies [5, 12] and low parental education or socio-economic status [5, 20].

The fairly good neuropsychological results of our patients should be observed in light of the general healthy condition of these children. Our UVH patients were born at term, had normal birth weight and had no known or suspected genetic abnormalities, developmental syndromes or neurological diagnoses. The former are innate elements for a rather smooth development. Other studies showed that the latter factors comprise certain risks for poor long-term cognitive outcome [3, 5].

Cumulative time of ICU stay and mechanical ventilation was associated with long-term developmental outcome. These factors may reflect an eventful postoperative course and intensified ICU monitoring in subsamples of our patients. Intrinsic characteristics such as pregnancy duration, birth weight and SES were also found to influence long-term cognitive development. Other research has promoted delayed elective delivery to 39–40 weeks to improve birth weight [5], but the negative relation between cognitive outcome and pregnancy duration in the current study suggests a cumulative intrauterine impact of adverse foetal circulation. It is very challenging to find a balance in improving outcome scores by modifying these factors.

Hoskoppal *et al.* [2] showed that neurodevelopment in UVH children is improving, on the premise that they are non-syndromic. Pre- and postoperative neurological injury, specifically ischaemic insults, occurs often in complex CHD populations [21, 23]. Brain plasticity is plausibly an important factor in countering early ischaemic injury before and after staged palliation that occurs in critical periods of neurological development, warranting the preservation of certain higher cognitive functions.

In addition, it is possible that parents of these patients are now highly attentive to possible cognitive problems and seek early consulting services, anticipating cognitive delay. Nevertheless, clinicians and parents share responsibility in addressing and signalling school functioning during the follow-up visits for early identification of high-risk conditions. Limitations of this study include the retrospective, rather than longitudinal, study design, a lack of neuroimaging data and a small sample size of the UVH group. The power of the study was limited because of sample size. The power to detect a difference in full scale estimated IQ, for example, was 36%. The sample size required to achieve power of 80% would have been 53 participants for each sample separately. In addition, population-based Dutch norms for the NEPSY-II-NL might be rather low for our study group of Belgian children, overrating performance and possibly missing clinically meaningful observations.

CONCLUSION

With increasing perioperative survival in children with complex CHD, greater emphasis is placed on neurodevelopmental comorbidity and behavioural outcome of children palliated for severe CHD. Over the last years, surgical techniques and postoperative management have changed significantly. UVH patients undergoing staged palliation nowadays have different outcomes compared with children having the same treatment a few decades ago. Our results suggest that adverse neurodevelopmental outcome in school-aged children treated for UVH is less compromising than expected in the current era of surgical palliation. All outcome scores were within normal ranges. Subtle shortcomings in attention, fine motor skills and visuospatial information processing characterize the neuropsychological profile of UVH patients. These children were also found at risk for internalizing and especially externalizing problem behaviour and more school problems by parental reports. It becomes advisable to screen UVH and BiVH patients during the follow-up visits using short questionnaires and identify those at greater risk for cognitive and/or behavioural problems. In this way, specific longitudinal patterns can be observed. Tailored referral for a comprehensive neuropsychological evaluation could be implemented, promoting improved developmental trajectories.

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