Chronic Neuromotor Disability After Complex Cardiac Surgery in Early Life

M. Florencia Ricci, MD, John C. Andersen, MD, Ari R. Joffe, MD, Man-Joe Watt, MB, BS, Elham Khodayari Moez, MSc, Irina A. Dinu, PhD, Gonzalo Garcia Guerra, MSc, MD, David B. Ross, MD, Ivan M. Rebeyka, MD, Charlene M.T. Robertson, MD

Abstract

BACKGROUND AND OBJECTIVES: Little is known about chronic neuromotor disability (CND) including cerebral palsy and motor impairments after acquired brain injury in children surviving early complex cardiac surgery (CCS). We sought to determine the frequency and presentation of CND in this population while exploring potentially modifiable acute care predictors.

METHODS: This prospective follow-up study included 549 children after CCS requiring cardiopulmonary bypass at ≤6 weeks of age. Groups included those with only 1 CCS, mostly biventricular CHD, and those with >1 CCS, predominantly single ventricle defects. At 4.5 years of age, 420 (94.6%) children received multidisciplinary assessment. Frequency of CND is given as percentage of assessed survivors. Predictors of CND were analyzed using multiple logistic regression analysis.

RESULTS: CND occurred in 6% (95% confidence interval [CI] 3.7%–8.2%) of 4.5-year survivors; for 1 CCS, 4.2% (CI 2.3%–6.1%) and >1, 9.8% (CI 7%–12.6%). CND presentation showed: hemiparesis, 72%; spasticity, 80%; ambulation, 72%; intellectual disability, 44%; autism, 16%; epilepsy, 12%; permanent vision and hearing impairment, 12% and 8%, respectively. Overall, 32% of presumed causative events happened before first CCS. Independent odds ratio for CND are age (days) at first CCS, 1.08 (CI 1.04–1.12; P < .001); highest plasma lactate before first CCS (mmol/L), 1.13 (CI 1.03–1.23; P = 0.008); and >1 CCS, 3.57 (CI 1.48–8.9; P = .005).

CONCLUSIONS: CND is not uncommon among CCS survivors. The frequency of associated disabilities characterized in this study informs pediatricians caring for this vulnerable population. Shortening the waiting period and reducing preoperative plasma lactate levels at first CCS may assist in reducing the frequency of CND.

WHAT'S KNOWN ON THIS SUBJECT:
Neurodevelopmental outcomes after cardiac surgery in early life provide critical information for understanding and improving care. Studies show these children are at risk for arterial ischemic stroke and acquired brain injury; further characterization of motor impairment is needed.

WHAT THIS STUDY ADDS: This study focuses on the presence of chronic neuromotor disabilities including cerebral palsy and motor impairments after acquired brain injury in children surviving early complex cardiac surgery, providing information on the frequency, characteristics, and predictors that may assist in prevention.
Survival rates after complex cardiac surgery (CCS) in early infancy have increased. Disabilities have become a concern as studies show children with Congenital Heart Disease (CHD) often demonstrate deficits in cognitive abilities, social interaction, language, behavior, permanent hearing loss, and health-related quality of life. Neuromotor delays have also been described as possible long-term outcomes after cardiac surgery; and acquired brain injury (ABI) has been recognized as a complication. Domi estimated that 1 of 185 children with CHD are at risk for stroke within the first 72 hours postsurgery, after which hemiparesis may occur. Brain injury as detected by neuroimaging has been found in up to 30% of infants with CHD before surgery. Generally motor impairments have been studied as part of a description of neurologic deficits, resulting in lack of clarity on the frequency and characteristics of neuromotor disabilities.

"Cerebral palsy (CP) describes a group of permanent disorders of the development of movement and posture, causing activity limitation, attributed to non-progressive disturbances that occurred in the developing fetal or infant brain." Twenty-four months is considered the maximum age that an acquired injury to the developing brain may be called CP, thereafter the term ABI with motor impairment is used. CP is classified according anatomic distribution and typology of the motor disorder, functional motor abilities, accompanying impairments, neuroimaging findings, and the causation and timing whenever possible. For this study, chronic neuromotor disability (CND), a term modified from Golomb, is used as an umbrella term to include CP and ABI (including stroke). The aims of this study are to determine the frequency of CND among 4.5-year-old survivors of early CCS requiring cardiopulmonary bypass, to describe CND presentation according to the current CP classification, and to identify potentially modifiable acute care predictors that may lead to a reduction in the frequency of CND.

METHODS

This inception cohort outcomes study is part of a follow-up project conducted in 6 Developmental/Rehabilitation referral sites in western Canada: Vancouver, British Columbia; Edmonton and Calgary, Alberta; Regina and Saskatoon, Saskatchewan; and Winnipeg, Manitoba. Infants were identified at the time of first CCS and followed prospectively. At the time of CCS, predetermined demographic, preoperative, intraoperative, and postoperative variables were collected. The study was approved by health research ethics boards at each site; parental or guardian consent was obtained.

Participants
All infants ≤6 weeks of age with CHD who were considered at greatest risk for adverse outcome because of the need for CCS requiring cardiopulmonary bypass between September 1996 and December 2009 at the Stollery Children's Hospital, Edmonton, Canada, were included. Children were divided into 2 groups, those with only 1 CCS, mostly biventricular CHD, and those with >1 CCS, predominantly those with single ventricle defects. Children who died before the 4.5-year assessment and those lost to follow-up were excluded.

Childhood Clinical Assessments
Multidisciplinary assessments were performed at 4.5 years at the referral sites. Each child was seen by a developmental pediatrician; if CND was suspected, a pediatric neurologist confirmed diagnoses. The CND nature, typology (spastic, dyskinetic, ataxic, hypotonic), anatomic distribution (unilateral-bilateral) of the motor disorder; functional motor abilities, (including oromotor involvement); accompanying impairments (intellectual disability: communication, vision, hearing impairments; epilepsy; autism spectrum disorder); and neuroimaging findings were recorded. Medical records of children with confirmed CND diagnoses were independently reviewed by 2 investigators (MFR, CMTR). Chronological information within all clinical notes and neuroimaging reports was sought to identify presumed timing of likely causative events (including description of acute illness) that lead to the final diagnoses of CND. If the opinions of the 2 reviewers differed, then a third joint review was completed until consensus was reached. Accompanying impairments, recorded prospectively in the database as previously described, were confirmed. Visual impairment, corrected visual acuity in the better eye of <20/60, was determined by ophthalmologic reports. Hearing was evaluated by certified pediatric audiologists; sensorineural loss or auditory neuropathy bilateral loss at >25 dB HL from 500 to 4000 Hz was considered permanent hearing impairment. Epilepsy was defined as the need for antiepileptics at 4.5 years of age obtained by history and confirmed by medical reports. The diagnosis of autism spectrum disorder was made by multidisciplinary teams after standardized testing. Intellectual disability was defined by the presence of both (1) intellectual impairment (scores <70) as determined by formal psychological assessment by certified pediatric psychologists and (2) parent-completed questionnaire of adaptive functioning deficit (scores <70).

Measures
Standardized age-appropriate developmental measures and...
questionnaires used normative data from the United States. Each neurocognitive and functional measure has a mean score of 100, and SD of 15; a score under 2 SD below mean (<70) is considered impairment.

Wechsler Preschool and Primary Scales of Intelligence—Third Edition, a gold standard measure, provides individualized assessment for children 3 to 7.25 years of age giving performance, verbal, and full-scale IQs. The Beery-Buktenica Development Test of Visual-Motor Integration, Fifth Edition, measures the ability of children aged 2 to 18 years to copy geometric designs, an important preschool learning skill.

The Adaptive Behavioral Assessment System—Second Edition assesses independent and realistic-for-age behaviors using 9 skill areas grouped into 3 composite domains: conceptual, practical, and social. The motor skill is separate and included in the General Adaptive Composite score. Each age-based skill area scaled score has a mean of 10 and a SD of 3; scores <4 are 2 SD below mean and show impairment.

The Gross Motor Function Classification System (GMFCS), a 5-level classification system based on the gross motor function of children with CP, with interrater reliability of 0.93, was documented at age 4.5 years.

The Blishen Index is an indicator of socioeconomic status dependent on employment, education, and prestige value of an occupation, with a population mean of 43 and SD of 13. Maternal education was recorded in years of schooling at the time of the 4.5-year assessment.

Acute Care Variables

Acute care information in relation to CND (Table 1) includes surgical year, birth gestation (weeks), birth weight (grams), gender, multiple birth, chromosomal abnormality, antenatal diagnosis, and preoperative ventilation days; preoperative and postoperative highest plasma lactate, inotrope score, and lowest base deficit; age (days), weight (kg), cardiopulmonary bypass time (minutes), X-clamp time (minutes), and use of deep hypothermic circulatory arrest (duration in minutes) at first CCS; single or biventricular cardiac defect; the presence of pre- or postoperative sepsis, seizures, cardiopulmonary resuscitation, dialysis; and the number of ventilated, ICU, and hospital days. Overall events recorded were the number of CCSs with cardiopulmonary bypass for each child before the 4.5-year assessment, presence of sepsis, cardiopulmonary resuscitation, dialysis, extracorporeal membrane oxygenation, heart transplant, ventricular assist device support, extracorporeal cardiopulmonary resuscitation, and having more than one CCS.

Statistical Analysis

Continuous variables are presented as mean (SD) or median (interquartile range) and categorical variables as counts and percentages. The frequency of CND is given as percentage of assessed survivors, using 95% confidence intervals (CIs). Demographic, operative, and perioperative predictors of CND for all 25 children and for a subset of those with unilateral CND were analyzed using univariate and stepwise multiple logistic regression analysis. A total of 28 predictors were initially screened, complying with the regression model-building rule of at least 10 patients for each predictor, given our sample size of 420 children. Multiple logistic regression analysis included variables significant at $P < .10$ and clinically relevant variables after screening for multicollinearity. Results are expressed as odds ratios (OR) with 95% CI; significance was considered $<.05$. Data analyses were performed using the Logistic procedure in SAS version 9.3.

RESULTS

From September 1996 to December 2009, 549 infants of ≤6 weeks of age had their first CCS requiring cardiopulmonary bypass; 105 (19.1%) children died and 24 were lost to follow-up by assessment age, leaving 420 (94.6% of survivors) to receive multidisciplinary assessment at a mean age of 55.2 months (6.6) (Fig 1). At first CCS, 117 (27.9%) had single ventricle anatomy (74 had Norwood surgery for classic hypoplastic left heart syndrome), 157 (37.4%) had transposition of great arteries (TGA; 99 with intact ventricular septum), 54 (12.9%) had total anomalous pulmonary venous connection repair, and 135 (32.1%) had other cardiac abnormalities. The age at first CCS for all 420 children was 12 (8.6) days; for those with single ventricle, 11.3 (6.9); and with biventricular defects, 12.3 (9.5) days. Of the 420 children, 288 had only 1 CCS, and 132 had ≥2 CCSs.

Frequency of CND

CND occurred in 25 (6%; CI 3.7%–8.2%) of assessed children; 4.2% (CI 2.3%–6.1%) of those who had 1 CCS, and 9.8% (CI 7%–12.6%) of those with >1 CCS. CND occurred in 10.3% (CI 7.4%–13.2%) of those with single ventricle defect. Five children with CCS at ≤6 weeks had late death after 2 years of age and before the 4.5-year assessment; none of these had suspect motor impairment.

Characteristics of Children With CND

Table 2 shows the description of the 25 children with CND at 4.5 years; 18 of 25 (72%) had unilateral motor impairment, half with right hemiparesis; 20 of 25 (80%) had spasticity; 18 of 25 (72%) had GMFCS I or II; and 4 of 25 (16%) had bulbar and oromotor involvement requiring gastrostomy. The presumed timing of the events leading to CND occurred within the first 5 days postoperatively for only 2 children, and none occurred on the operative day. Those
TABLE 1 Description of 4.5-Year-Old Children With and Without Chronic Neuromotor Disabilities After Early CCS (n = 420): Mean (SD), Median (Interquartile Range), n (%)  

<table>
<thead>
<tr>
<th>Description</th>
<th>Total (n = 420)</th>
<th>CND No (n = 395)</th>
<th>CND Yes (n = 25)</th>
</tr>
</thead>
</table>

A. Preoperative first CCS  
- Family SES: 43.6 (13.6); 42 (18)  
- MCHS: 13.4 (2.8); 13 (3)  
- Birth region within northern Alberta: 167 (39.6%); 160 (40.5%)  
- Birth gestation (wk): 35.8 (1.7); 39 (2)  
- Birth wt (g): 3328.5 (577.2); 3310.5 (738)  
- Gender, male: 275 (65.1%); 252 (63.9%)  
- Multiparous: 14 (3.3%); 12 (5%)  
- Chromosomal abnormality: 32 (7.6%); 29 (7.3%)  
- Antenatal diagnosis: 123 (29.3%); 112 (28.4%)  
- Ventilation days: 5.7 (5.8); 5.3 (5.4)  
- Inotrope score: 7 (14.1); 6.6 (12.6)  
- Highest plasma lactate level (mmol/L): 3.5 (3.4); 3.3 (3.2)  
- Lowest base deficit: −4.5 (4.5); −4.4 (4.3)

B. Intraoperative first CCS  
- Year of surgery: 2003.9 (3.6); 2004 (6)  
- Age at surgery (d): 11.6 (8.2)  
- Single ventricle: 117 (27.9%); 105 (26.6%)  
- Wt (kg): 3.39 (0.59); 3.4 (0.8)  
- X-clamp time (min): 53.8 (24.7); 54.0 (24.5)  
- DHCA, yes: 298 (71%); 280 (70.9%)  
- DHCA time (min), n = 298: 24.5 (17.4); 24.4 (17.5); (n = 280) 26.2 (16.8); (n = 18)  

C. Postoperative: first CCS  
- Day 1–5 highest plasma lactate (mmol/L): 5.8 (3); 5.8 (2.9)  
- Day 1–5 highest inotrope score: 14.9 (13.4); 14.8 (13.1)  
- Day 1–5 lowest base deficit: −2.5 (3.4); −2.5 (3.4)

D. Overall first operation  
- Sepsis: 75 (17.9%); 70 (17.7%)  
- Seizures: 41 (9.8%); 39 (9.9%)  
- CPR: 15 (3.6%); 15 (3.6%)  
- ECMO: 20 (4.8%); 18 (4.6%)  
- Dialysis: 42 (10%); 41 (10.4%)  
- All ventilated days: 16.6 (15.5)  
- All ICU days: 19.5 (17.7); 19.4 (17.9)  
- All hospital days: 31.4 (29.4); 31 (29.5)

E. Overall before 4.5 y assessment  
- Sepsis: 80 (19%); 72 (18.2%)  
- CPR: 20 (4.8%); 14 (3.5%)  
- Dialysis: 45 (10.7%); 43 (10.5%)  
- ECMO: 24 (5.7%); 20 (5.4%)  
- Heart transplant: 10 (2.4%); 8 (2.5%)  
- VAD: 3 (0.8%); 1 (0.3%)  
- E-CPR: 5 (1.2%); 3 (0.8%)  
- CPB interventions before 4.5 y: 1.6 (1.0); 1.6 (1.0)  
- S1 intervention with CPB: 132 (31.4%); 119 (30.1%)  

CPB, cardiopulmonary bypass; CPR, cardiopulmonary resuscitation; DHCA, deep hypothermic circulatory arrest; ECMO, extracorporeal membrane oxygenation; E-CPR, extracorporeal cardio pulmonary resuscitation; SES, socioeconomic status; VAD, ventricular assist device.

b Blishen Index.25  
Inotrope score.26

25 with CND had their first CCS on day 17.9 (12.1), on average 6.3 days after those without CND. For the 8 children with the presumed timing happening before first CCS, half of which had TGA, the age at surgery was 24.6 (15.1) days, on average 13 days after those without CND, only 2 of these 8 children had antenatal CHD diagnoses. For those 7 with presumed timing of causative event happening after the first CCS but before any further CCS, the age at first surgery was 14.8 (10.7) days, on average 3.2 days later than those without CND. In addition, 10 children had the presumed causative event at a subsequent surgery (Fig 2).

Thirty-six (8.6%) of 420 children were born prematurely; 5 had CND. Presumed causative events for 3 of...
these were not directly related to gestation. Neuroimaging of 2 of these children suggests the causative insult may have been antenatal. Both were born at 36 weeks (Cases 1 and 4; Table 2).

**Childhood Growth, Health, and Accompanying Impairments**

Accompanying impairments for the 25 children with CND are found on Table 3. Intellectual disability occurred 20 times more commonly than the expected 2.23% determined from population normative values.

**Prediction of CND**

Univariate and stepwise multiple logistic regression analyses are shown in Table 4. According to the multiple regression model, OR for CND is 1.08 for each day the first CCS is delayed beyond the date of birth, and 1.13 for each mmol/L of plasma lactate elevation in the preoperative period at first CCS. Adjusting for the presence of these predictors, OR for unilateral CND is 12.23 (CI 3.38–44.23; P < .001) if >1 CCS is needed.

**DISCUSSION**

This study presents information relevant to practitioners caring for newborns with CHD, those assessing and assisting young survivors with CCS, and those meeting their rehabilitative needs. Frequency information on CND after CCS is not readily available, a classification including accompanying impairments of these specific children has not been reported, and little is known about the causation and potentially modifiable predictors that may assist prevention.

We have shown CND is not uncommon among preschool survivors of CCS, especially for those needing >1 CCS. This supports the role of reoperation in stroke as reported by Domi.11 After early CCS, motor disability is more common than that in the general population, where the prevalence of CP remains ~2 to 3 per 1000 live births27–32 and similar to CP among premature infants.28,31,32 Our results support others: “among children who acquire cerebral palsy postnatally, there is an excess of non-cerebral birth defects, particularly cardiac defects.”28 Overall, postnatal-acquired CP is ~5.5% of all CP: for 1998, it was reported as 0.41 (CI 0.14–0.67) per 10 000 live births.33

The majority of our patients presented with spasticity, the most common motor disorder type of CP.34 Unilateral distribution was the most common presentation, contrasting with the literature where bilateral spastic CP is most prevalent.28,31 Our findings align with results from a study by Golomb showing 87% of children with CP after perinatal arterial ischemic stroke present with hemiplegia.15 We have found 72% of the children with CND have GMFCS levels of I or II with somewhat more ability to ambulate than previous findings in children with CP in the general population both in Europe and North America.29,30

In our study, children after CCS with CND presented with a higher rate of accompanying impairments including intellectual disability, autism, epilepsy, and vision impairment than those without CND. This supports other studies showing children with CP have a higher frequency of associated impairments than in the general population.29,30 We found that CCS survivors with CND, have a greater percentage of intellectual disability and autism but a lower rate of epilepsy compared with children with CP in the literature.31,32 including less epilepsy and visual impairment than children described in the European Registry with postnatally acquired CP.33 The frequency of permanent hearing impairment among those with CND and those without was similar in our study; this may have been associated to ototoxicity as previously reported.6
<table>
<thead>
<tr>
<th>Cases</th>
<th>Dominant Type of Tone or Movement Abnormality</th>
<th>Anatomic Distribution</th>
<th>GMFCS</th>
<th>Presumed Timing of Causative Event in Relation to Complex Cardiac Surgery</th>
<th>Chronological Age at Time of Attributed Event</th>
<th>Acute Illness at Presumed Timing of Causative Event</th>
<th>Investigative Neuroimaging at Acute Illness</th>
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<tbody>
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<td>Unilateral</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1</td>
<td>Spasticity</td>
<td>Right hemiparesis</td>
<td>II</td>
<td>Likely antenatal, pulmonary atresia—tricuspid regurgitation reconstruction</td>
<td>Uncertain</td>
<td>Uncertain</td>
<td>MRI: periventricular leukomalacia</td>
</tr>
<tr>
<td>2</td>
<td>Spasticity</td>
<td>Left hemiparesis</td>
<td>II</td>
<td>9 d before Norwood stage 1 for classic HLHS</td>
<td>2 d</td>
<td>Cardiac arrest requiring resuscitation</td>
<td>CT: right middle cerebral artery distribution infarct</td>
</tr>
<tr>
<td>3</td>
<td>Spasticity</td>
<td>Left hemiparesis</td>
<td>I</td>
<td>2 d before ASO with no ventricular septal defect</td>
<td>10 d</td>
<td>Cardiogenic shock</td>
<td>CT: right middle cerebral artery distribution infarct</td>
</tr>
<tr>
<td>4</td>
<td>Spasticity</td>
<td>Right hemiparesis</td>
<td>II</td>
<td>4 d before ASO with no ventricular septal defect</td>
<td>1 d</td>
<td>Cardiogenic shock</td>
<td>MRI: periventricular venous infarct</td>
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<tr>
<td>5</td>
<td>Spasticity</td>
<td>Left hemiparesis</td>
<td>I</td>
<td>1 d before ASO</td>
<td>1 mo</td>
<td>Seizures</td>
<td>MRI: periventricular leukomalacia</td>
</tr>
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<td>6</td>
<td>Spasticity</td>
<td>Left hemiparesis</td>
<td>II</td>
<td>11 d after ASO with no ventricular septal defect</td>
<td>16 d</td>
<td>Septic shock</td>
<td>CT: Haemorrhagic transformation of infarcts in the right hemisphere, MRI: Acute watershed infarcts in both cerebral hemispheres, most severe in the right frontal and parietal lobes.</td>
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<tr>
<td>7</td>
<td>Spasticity</td>
<td>Right hemiparesis</td>
<td>II</td>
<td>2.5 mo after pulmonary arterioplasty</td>
<td>3 mo</td>
<td>Cardiac arrest requiring resuscitation</td>
<td>MRI: Left parietal infarct</td>
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<td>8</td>
<td>Spasticity</td>
<td>Left hemiparesis</td>
<td>I</td>
<td>4 mo after ASO with ventricular septal defect</td>
<td>5 mo</td>
<td>Pneumococcal meningitis</td>
<td>CT: Hypodensity in right parietal area, MRI: Right parafalcine infarct in the occipital region</td>
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<td>9</td>
<td>Spasticity</td>
<td>Right hemiparesis</td>
<td>II</td>
<td>30 d before Glenn for classic HLHS</td>
<td>5 mo</td>
<td>Cardiac arrest requiring resuscitation</td>
<td>MRI: Infarcts in right and left frontal lobe</td>
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<td>10</td>
<td>Spasticity</td>
<td>Right hemiparesis</td>
<td>II</td>
<td>7 d after Glenn for classic HLHS</td>
<td>8 mo</td>
<td>E. coli sepsis - Disseminated coagulopathy</td>
<td>MRI: watershed lesions and acute areas of infarction bilaterally</td>
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<tr>
<td>11</td>
<td>Spasticity</td>
<td>Right hemiparesis</td>
<td>II</td>
<td>7 d after Glenn for classic HLHS</td>
<td>6 mo</td>
<td>Acute right sided weakness</td>
<td>MRI: watershed lesions and acute areas of infarction bilaterally</td>
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<tr>
<td>12</td>
<td>Spasticity</td>
<td>Left hemiparesis</td>
<td>II</td>
<td>17 d after Glenn, postcritical aortic stenosis repair</td>
<td>4 mo</td>
<td>Left focal seizure</td>
<td>MRI: no significant intracranial abnormality</td>
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<td>13</td>
<td>Spasticity</td>
<td>Right hemiparesis</td>
<td>I</td>
<td>4 mo after Glenn for classic HLHS</td>
<td>10 mo</td>
<td>Acute right sided weakness</td>
<td>MRI: left middle cerebral artery distribution infarct</td>
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<tr>
<td>14</td>
<td>Spasticity</td>
<td>Left hemiparesis</td>
<td>I</td>
<td>3 d after Fenestrated Fontan, for classic HLHS</td>
<td>3 y 11 mo</td>
<td>Acute left sided weakness</td>
<td>MRI: Large right middle cerebral artery distribution infarction and left watershed infarcts</td>
</tr>
</tbody>
</table>

Previous: 2.5 mo after Norwood

3 mo | Cardiac arrest requiring resuscitation | MRI: Left frontal subcortical infarct |
### TABLE 2 Continued

<table>
<thead>
<tr>
<th>Cases</th>
<th>Dominant Type of Tone or Movement Abnormality</th>
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<tr>
<td>15</td>
<td>Spasticity</td>
<td>Left hemiparesis</td>
<td>I</td>
<td>5 d after fenestrated Fontan for classic HLHS</td>
<td>3 y</td>
<td>Acute left sided weakness and hemianopsia</td>
<td>MRI: right anterior cerebral artery and middle cerebral artery distribution stroke with multifocal infarcts on both hemispheres</td>
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<tr>
<td>16</td>
<td>Spasticity</td>
<td>Right hemiparesis</td>
<td>III</td>
<td>8 d after fenestrated Fontan for classic HLHS</td>
<td>3 y 11 mo</td>
<td>Pneumonitis and desaturation</td>
<td>CT: acute ischemic injury in left hemisphere</td>
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<td>17</td>
<td>Spasticity</td>
<td>Left hemiparesis</td>
<td>II</td>
<td>9 d after fenestrated Fontan, for classic HLHS</td>
<td>4 y 6 mo</td>
<td>Acute left side weakness</td>
<td>CT: right frontal lobe hemorrhagic infarct</td>
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<td>18</td>
<td>Spasticity</td>
<td>Right hemiparesis</td>
<td>II</td>
<td>27 d after failed fenestrated Fontan for classic HLHS, and on day 15th of ventricular assistive device</td>
<td>3 y 3 mo</td>
<td>Acute right sided weakness</td>
<td>CT: left subdural hematoma</td>
</tr>
</tbody>
</table>

**Bilateral**

<table>
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<tr>
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<tbody>
<tr>
<td>1</td>
<td>Hypotonia with increased DTRs</td>
<td>Quadripareisis</td>
<td>IV</td>
<td>16 d before surgery for interrupted aortic arch</td>
<td>2 d</td>
<td>Pretransfer cardiogenic shock</td>
<td>MRI: enlargement of ventricles and extra axial cerebrospinal fluid spaces</td>
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<tr>
<td>2</td>
<td>Hypotonia with increased DTRs</td>
<td>Quadripareisis</td>
<td>IV</td>
<td>12 d before pulmonary artery reconstruction associated with AV canal</td>
<td>1 mo</td>
<td>Gram-negative sepsis</td>
<td>MRI: intracranial hemorrhage III−IV</td>
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<td>3</td>
<td>Spasticity</td>
<td>Left triparesis</td>
<td>II</td>
<td>9 d before ASO</td>
<td>14 d</td>
<td>Focal seizures</td>
<td>MRI: small frontal infarct and dural sinus thrombosis</td>
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<tr>
<td>4</td>
<td>Mild Hypotonia with increased Deep Tendon Reflexes</td>
<td>Quadripareisis</td>
<td>III</td>
<td>21 d after TOF repair</td>
<td>23 d</td>
<td>Cardiac arrest requiring resuscitation</td>
<td>MRI: atrophy of the white matter</td>
</tr>
<tr>
<td>5</td>
<td>Dyskinesia</td>
<td>Quadripareisis</td>
<td>V</td>
<td>2 mo post-TOF arterioplasty</td>
<td>1 1/2 mo</td>
<td>CA requiring resuscitation</td>
<td>MRI: diffuse cerebral ischemia</td>
</tr>
<tr>
<td>6</td>
<td>Dyskinesia</td>
<td>Quadripareisis</td>
<td>V</td>
<td>3 mo after simple TAPVC</td>
<td>3 mo</td>
<td>E. coli sepsis—disseminated coagulopathy</td>
<td>MRI: global ischemia</td>
</tr>
<tr>
<td>7</td>
<td>Spasticity</td>
<td>Diparesis</td>
<td>II</td>
<td>2 y post–complex TAPVC</td>
<td>2 y</td>
<td>Endocarditis and subclavian thrombosis</td>
<td>MRI: increased signal in peritrigonal regions</td>
</tr>
</tbody>
</table>

ASO, arterial switch operation; CT, computed tomography; HLHS, hypoplastic left heart syndrome; TAPVC, total anomalous pulmonary venous connection; TGA, transposition of great arteries; TOF, tetralogy of Fallot.
Of particular importance is our described association between the presumed timing of events leading to CND and timing of the CCS. We found that the presumed causative event for CND rarely occurred in the 0- to 5-day postoperative window, which has been considered a vulnerable period. Overall, 32% of presumed

**TABLE 3** Growth, Health, and Accompanying Impairments After Early CCS in Relation to CND (n = 420): Mean (SD), Median (Interquartile Range), n (%)

<table>
<thead>
<tr>
<th>Outcome Variables</th>
<th>Total</th>
<th>CND</th>
<th>t*</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Height, z score</td>
<td>–0.34 (1.45), –0.15 (–1.2 to 0.2)</td>
<td>–0.31 (1.5)</td>
<td>–0.8 (1.3)</td>
<td>1.842</td>
</tr>
<tr>
<td>Wt, z score</td>
<td>–0.19 (1.08), 0.0 (–0.8 to 0.6)</td>
<td>–0.18 (1.8)</td>
<td>–0.44 (1.0)</td>
<td>1.189</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>31 (7.4%)</td>
<td>24 (6.1%)</td>
<td>7 (28%)</td>
<td>.001</td>
</tr>
<tr>
<td>Gastrostomy at any time after first surgery</td>
<td>67 (16%)</td>
<td>57 (14.4%)</td>
<td>10 (40%)</td>
<td>.002</td>
</tr>
<tr>
<td>No. of hospitalizations not related to cardiac treatment</td>
<td>1.6 (2.5), 1 (0–2)</td>
<td>1.8 (2.4)</td>
<td>2.4 (1.9)</td>
<td>–1.553</td>
</tr>
<tr>
<td>No. of hospitalizations related to cardiac treatment</td>
<td>1.4 (2.1), 0 (0–2)</td>
<td>1.3 (2)</td>
<td>2.6 (2.9)</td>
<td>–2.229</td>
</tr>
<tr>
<td>No. of medical specialist in addition to pediatrician</td>
<td>2.2 (1.5), 2 (1–3)</td>
<td>0.3 (0.7)</td>
<td>0.7 (0.5)</td>
<td>–2.705</td>
</tr>
<tr>
<td>Medication for chronic pulmonary disease</td>
<td>58 (13.8%)</td>
<td>52 (13.2%)</td>
<td>6 (24%)</td>
<td>.14</td>
</tr>
<tr>
<td>Medication for chronic cardiac disease</td>
<td>140 (33.3%)</td>
<td>126 (31.9%)</td>
<td>14 (56%)</td>
<td>.02</td>
</tr>
<tr>
<td>Vision impairment</td>
<td>8 (1.9%)</td>
<td>5 (1.3%)</td>
<td>3 (12%)</td>
<td>.009</td>
</tr>
<tr>
<td>Permanent hearing impairment</td>
<td>24 (5.7%)</td>
<td>22 (5.6%)</td>
<td>2 (8%)</td>
<td>.05</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>8 (1.9%)</td>
<td>5 (1.3%)</td>
<td>3 (12%)</td>
<td>.009</td>
</tr>
<tr>
<td>Autism spectrum disorder</td>
<td>15 (3.6%)</td>
<td>11 (2.8%)</td>
<td>4 (16%)</td>
<td>.009</td>
</tr>
<tr>
<td>Full-scale IQ &lt;7019</td>
<td>61 (14.1%)</td>
<td>50 (12.7%)</td>
<td>11 (44%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Performance IQ &lt;7019</td>
<td>49 (11.7%)</td>
<td>38 (9.6%)</td>
<td>11 (44%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Verbal IQ &lt;7019</td>
<td>56 (13.3%)</td>
<td>45 (11.4%)</td>
<td>11 (44%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Visual-motor Integration &lt;7020</td>
<td>46 (11%)</td>
<td>37 (9.4%)</td>
<td>9 (36%)</td>
<td>.001</td>
</tr>
<tr>
<td>ABAS communication &lt;q21</td>
<td>44 (10.5%)</td>
<td>37 (9.4%)</td>
<td>7 (28%)</td>
<td>.01</td>
</tr>
<tr>
<td>ABAS motor: &lt;q21</td>
<td>37 (8.8%)</td>
<td>29 (7.3%)</td>
<td>8 (32%)</td>
<td>.001</td>
</tr>
<tr>
<td>ABAS GAC: &lt;7021</td>
<td>74 (17.6%)</td>
<td>59 (14.9%)</td>
<td>15 (60%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Intellectual disability</td>
<td>51 (12.1%)</td>
<td>40 (10.1%)</td>
<td>11 (44%)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

ABAS, adaptive behavioral assessment system; GAC, general adaptive composite.
* Student t test, 2-sided.
* Fisher's 2-sided test.
causative events took place before first CCS, TGA being the most common diagnosis among these children. This might be related to already described abnormalities of brain microstructure and metabolism.35–37 However, 40% of presumed causative events took place beyond first CCS, and in this group, single ventricle defects were overrepresented.

Our study shows an older age at first CCS, high preoperative lactate levels, and >1 CCS are predictors of CND. The analysis of the children with unilateral CND confirms the importance of similar predictors and adds high preoperative inotrope score and lower weight at first CCS as predictors. We found the OR for CND is 1.08 for each day added to the preoperative period of first CCS. These findings underlie the importance of further investigation of earlier CCS37–41 and lead to the question: are waiting times for surgery longer in infants with CND secondary to illness and therefore the child is not stable for surgery, or are other medical and social situations affecting the time of surgery? Special attention needs to be paid to this concept of “readiness to treat.” Mahle reported that antenatal diagnosis leads to a reduction of early perioperative neurologic insults in neonates with hypoplastic left heart syndrome.42 The lack of antenatal diagnosis in 6 of 8 children with presumed causative events before first CCS in this study supports this finding. Recent studies show antenatal diagnostic rates for CHD are increasing43; this may result in fewer adverse preoperative events.

Finally, the OR for CND is 1.13 for each mmol/L of preoperative plasma lactate elevation at first CCS. Increased preoperative lactate levels have been found to be associated with lower functional abilities after CCS,44 with mental and/or motor delay in children undergoing arterial switch operations,45 and as indicators of postoperative mortality and morbidity.46–48 Preoperative plasma lactate levels and age at surgery are modifiable variables that could potentially lead to a reduction in CND the same way other advances have affected specific prevalence rates of CP.29,33 Specific in utero and perioperative neuroprotective strategies to achieve these goals should be further investigated.49,50

The strengths of this study include the high proportion of children assessed at 4.5 years of age with detailed classification of each child with CND and evaluation of the presumed timing of likely causative events. The main limitations are the small number of children with CND, the single-center performing CCS, neuroimaging dictated by clinical need without uniform testing, and difficulty determining the timing of an earlier insult with manifestation as a sudden neurologic symptom. Other variables that may predict CND may not have been recorded; these potential confounders can limit the certainty about the potentially modifiable predictors found. Potential bias might have been introduced by excluding children who died, especially those who died before the 2-year
assessment, because we do not know whether these children had pre- or postoperative neurologic insults that may have manifested as CND had the child survived.

CONCLUSIONS

Our findings provide evidence that CND is not uncommon among CCS survivors. Health professionals need to be aware of this and complete careful neurologic examinations to allow for early, specific rehabilitative therapies. Ongoing surveillance with multidisciplinary assessments are paramount because these children may present not only with motor impairments but with high rates of additional associated impairments requiring intervention. Findings also suggest that presumed causative events infrequently happen in the early postoperative period and often occur while awaiting surgery. Strategies to shorten the waiting time for CCS and to prevent high plasma lactate levels before first CCS may assist in reducing the presence of motor impairments in this population. These study results can assist both general pediatricians and pediatric subspecialists in providing more informed antenatal and postnatal counseling, as well as anticipatory guidance for families. Larger studies to further explore the mechanisms and risk factors of CND in CCS survivors are needed.

ACKNOWLEDGMENTS

We thank the children and their parents for their willingness to attend developmental follow-up.

ABBREVIATIONS

ABI: acquired brain injury
CCS: complex cardiac surgery
CHD: congenital heart disease
CI: confidence interval
CND: chronic neuromotor disability
CP: cerebral palsy
GMFCS: Gross Motor Function Classification System
OR: odds ratio
TGA: transposition of great arteries

REFERENCES

1. Australian Institute of Health and Welfare (AIHW). Heart, stroke and vascular diseases—Australian facts 2004. AIHW Cat. No. CVD 27. Canberra, Australia: AIHW and National Heart Foundation of Australia (Cardiovascular Disease Series No. 22); 2004
3. Creighton DE, Robertson CMT, Sauve RS, et al; Western Canadian Complex Pediatric Therapies Follow-up Group. Neurocognitive, functional, and health outcomes at 5 years of age for children after complex cardiac surgery at 6 weeks of age or younger. Pediatrics. 2007;120(3). Available at: www.pediatrics.org/cgi/content/full/120/3/e478


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