Neurodevelopmental profiles of children with unilateral cerebral palsy associated with middle cerebral artery and periventricular venous infarctions

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PUBLICATION DATA

Accepted for publication 15th December 2020.

Published online 31st January 2021.

ABBREVIATIONS

CHEQ	Children's Hand-use Experience Questionnaire
MCA	Middle cerebral artery
PVI	Periventricular venous infarction
PWI	Periventricular white matter injury

AIM To compare the neurodevelopment of children with unilateral cerebral palsy (CP) with middle cerebral artery (MCA) and periventricular venous infarctions (PVIs).

METHOD In this cross-sectional study, children with unilateral CP completed a neurological exam, unimanual Quality of Upper Extremity Skills Test, hand usage questionnaires, and IQ test. Neuroimaging was obtained from health records.

RESULTS Two hundred and forty-five participants with unilateral CP had neuroimaging (151 [61.9%] male, ages 2–18y, median=7y 6mo, interquartile range [IQR]=6y 7mo, with 93.6% in Gross Motor Function Classification System level I/II and 78.8% in Manual Ability Classification System level I/II). Ninety-seven (39.6%) had MCA injuries and 106 (43.3%) had periventricular white matter injuries, of which 48 (45.3%) were PVIs. Median Quality of Upper Extremity Skills Test for the MCA group was 49.2 (IQR=55.8), PVI 79.9 (IQR=23.6) (Mann–Whitney U=988.50, p<0.001). Bimanual hand usage (Children's Hand-use Experience Questionnaire) (Mann–Whitney U=425, p<0.001) and light touch (odds ratio=9.12, 95% confidence interval 1.28–400.76, Fisher's exact test p=0.017) were lower in the MCA compared to the PVI group. Full-scale IQ median centile score for the MCA group was 18.0 (IQR=35.5) and 50.0 (IQR=30.0) for the PVI group (Mann–Whitney U=382, p<0.001).

INTERPRETATION Children with unilateral CP and MCA injuries demonstrated lower hand function and usage, decreased light touch, and lower IQs compared to the PVI group. This study aids in defining rehabilitation needs informed by brain injury patterns.

Unilateral cerebral palsy (CP) is characterized by a motor impairment predominantly on one side of the body and is a common type of limb distribution of CP occurring in 28% (gestational age <37wks) or 39% (gestational age >37wks) of cases in population-based studies.[1] Unilateral CP is frequently caused by an asymmetric brain injury or malformation.[2] We have a good understanding of the common clinical presentation of unilateral CP; however we lack information on whether there are different neurodevelopmental profiles of unilateral CP associated with different injury patterns. Understanding the link between developmental profiles and neurological injury is important because children with specific injury patterns may respond differently to interventions such as constraint therapy.[3] We have created a large database of children with unilateral CP called 'Hemi CP-NET' with data on neuroimaging and neurodevelopmental outcomes. This database creates a unique opportunity to correlate specific neurodevelopmental profiles with brain injury subtypes in unilateral CP.

Information on neurodevelopmental profiles of unilateral CP is available through existing population-based CP registries and case series.[1,4] The majority are ambulatory[1] and Kitai et al.[5] reported more impact on unimanual than gross motor function. Average intelligence is observed in the majority of individuals with unilateral CP, with between 3% to 25% having an intellectual disability.[6–8] A vision abnormality was reported in 31% of children with unilateral CP,[9] with visual field deficits identified as the most common impairment.[10] One-third of individuals with unilateral CP have epilepsy.[6]

© 2021 The Authors. *Developmental Medicine & Child Neurology* published by John Wiley & Sons Ltd on behalf of Mac Keith Press DOI: 10.1111/dmcn.14818
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Neuroimaging patterns in unilateral CP include arterial injuries such as middle cerebral artery (MCA) infarctions, periventricular white matter injury (PWI) including periventricular venous infarction (PVI),[11] and brain malformations.[12] The PVI subtype reflects a venous infarction secondary to the obstruction of deep medullary veins draining the periventricular white matter leading to a stereotyped pattern of focal encephalomalacia. In a systematic review of brain imaging in CP including 404 individuals with unilateral CP, focal vascular insults such as MCA and PVI were reported in 24.4%, PWI in 39.7%, and brain malformations in 13.2% of individuals.[13]

Earlier studies that examined neurodevelopmental outcomes with differing brain imaging patterns in unilateral CP have found conflicting results on hand function. In studies with small numbers of participants, Staudt et al.[14] and Holmström et al.[15] found that better hand function was associated with a PWI. However, in a larger study of children with unilateral CP born at term, Kitai et al.[5] found no difference in hand function between PVI and MCA subgroups. Compared to individuals with PWI or PVI, both Cioni et al.[2] and Kitai et al.[5] identified more seizures in the MCA subgroup. Jacobson et al.[10] identified more visual field deficits in individuals in the MCA subgroup.

An improved understanding of the specific neurodevelopmental profiles that result from brain injury subtypes in individuals with unilateral CP may help guide rehabilitation treatments by prioritizing specific monitoring strategies and tailored rehabilitation approaches with each subtype of brain injury. As such, the objectives of this work are to provide a descriptive overview of different neuroimaging patterns identified in a cross-sectional cohort of children with unilateral CP and compare neurodevelopmental profiles of the two most common vascular injury patterns of MCA and PVI.

METHOD

This cross-sectional sampling study was conducted across nine clinical centres throughout Ontario, Canada affiliated through the Cerebral Palsy Integrated Neuroscience Discovery Network (CP-NET: Holland Bloorview Kids Rehabilitation Hospital, McMaster Children's Hospital, the Hospital for Sick Children, Grandview Children's Centre, Erinoak Kids Centre, London Health Sciences Centre, Hotel Dieu Hospital, Ottawa Children's Treatment Centre, and Health Sciences North). The study occurred between April 2012 and October 2017. Research ethics board approval and written informed consent were obtained from the Holland Bloorview Research Ethics Board (Holland Bloorview Kids Rehabilitation Hospital, Erinoak Kids Centre, Grandview Children's Centre), Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (Hotel Dieu Hospital), the Research Ethics Board for The Hospital for Sick Children (the Hospital for Sick Children), the Research Ethics Board of Health Sciences North (Health Sciences North), the Hamilton Health Sciences/McMaster Health Sciences Research Ethics Board (McMaster Children's Hospital), the CHEO Research Ethics Board (Ottawa Children's Treatment Centre), and the Thames Valley Children's Centre's Research Advisory Committee (London Health Sciences Centre).

What this paper adds

- Developmental profiles of individuals with unilateral cerebral palsy (CP) differ according to infarction type.
- Children with middle cerebral artery (MCA) infarctions had more impact on their neurodevelopmental profile than those with periventricular venous infarctions (PVIs).
- MCA and periventricular white matter injury patterns were found in similar proportions in unilateral CP.
- Children with PVI were predominantly born at term.

Participants

Children were identified by screening health records. A child was eligible for enrolment if they were: (1) aged 2 to 18 years, and (2) had a diagnosis of unilateral CP.

Data collection and instrumentation

Information was obtained from six sources: (1) retrospectively from the child's health record; (2) electronic copies of clinically acquired source brain images (magnetic resonance imaging, computerized axial tomography, and head ultrasounds) with prospective categorization/scoring into prespecified brain injury patterns by a single neuroradiologist; (3) parent interview/questionnaires administered prospectively to record the presence of seizures within the past year, and to measure bimanual hand usage (Table S1, online supporting information) using the Children's Hand-use Experience Questionnaire (CHEQ) (Version 1.0)[16] for children 6 years of age or older or the Pediatric Upper Extremity Motor Activity Log for children younger than 6 years of age;[17] (4) an occupational therapist administered the Quality of Upper Extremity Skills Test prospectively, a validated measure to assess the quality of upper extremity unilateral hand functioning with a score of 100% representing typically developing unimanual hand function independent of the child's age,[18] and classified motor functioning using the Gross Motor Function Classification System[19] and the Manual Ability Classification System;[20] (5) a standardized neurological examination completed prospectively by a study physician who administered the Pediatric Stroke Outcome Measure, a validated measure[21] to assess grip strength, sensory measures for children older than 4 years of age, mirror movements, visual fields, selective motor control,[22] tone, and behaviour (Table S1); and (6) data extracted from previous psychoeducation assessments to obtain the participant's IQ. In cases where participants had no previous psychoeducational assessment and were 4 years of age or older, an age-specific psychoeducation assessment was conducted prospectively.[23]

Neuroimaging analysis

A scoring form (Appendix S1, online supporting information) was adapted using validated references for cerebrovascular pathology. Neuroimages were classified into MCA infarctions, PWI including PVI, non-MCA arterial infarctions, brain malformations, miscellaneous, and normal patterns.[11,24,25] PWI was characterized by foci of T2 hyperintensity in the white matter within the deep or subcortical regions and includes periventricular leukomalacia. PVI was defined as a unilateral periventricular focal encephalomalacia, presumed sequelae of the obstruction of the deep medullary veins, with relative sparing of the overlying cortex and basal ganglia.[11] Children who had an asymmetric PWI pattern with a unilateral PVI but bilateral white matter injury were categorized in the PWI group. Brain malformations included unilateral schizencephaly, polymicrogyria, focal cortical dysplasia, and lissencephaly. The miscellaneous category included hydrocephalus, encephalitis, and diffuse hypoxic ischemic insult. Interrater reliability was done on the neuroimaging scoring for the first 85 images which were 'double-scored' separately by two neuroradiologists with agreement across items averaging 93.6% (range 74–99%).

Statistical analysis

Data were analysed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA) and R version 3.4.3 (R Core Team 2017, R Foundation for Statistical Computing, Vienna, Austria). All continuous variables were assessed for normal distribution using the Shapiro–Wilk test. The majority of continuous measures had at minimum one group which was found to be non-normally distributed. As a result, medians and interquartile ranges (IQRs) estimated central values for all continuous data. Proportions and frequencies were used for categorical data. Descriptive statistics were calculated to summarize participant characteristics. Fisher's exact test and the associated odds ratios or non-parametric independent samples Mann–Whitney *U* tests were conducted to explore univariate relationships between MCA and PVI subgroups and neurodevelopmental outcome variables using R and SPSS respectively. In cases where there was a significant multi-level categorical variable, post hoc odds ratio analyses were conducted. All tests for significance were carried out at a significance level of 0.05. Because of potential bias caused by missing data, imputation approaches were explored for variables with at least 20% missing data in either the PVI or MCA infarction group. Further details are provided in Appendix S2, Figure S1 (online supporting information).

RESULTS

Participant characteristics

A total of 320 children were identified from nine Ontario paediatric rehabilitation centres. Seventy-five children were excluded as they did not have clinical neuroimaging available, leaving 245 (76.6%) participants for analyses. Table 1 outlines the total group participant characteristics and observed imaging classifications. The median age at registration was 7 years 6 months (IQR=6y 7mo) and 72.4% were born at term gestation. Most children with unilateral CP were ambulatory (Gross Motor Function Classification System levels I–III, 98.3%) and 78.8% were in Manual Ability Classification System level I or II. The two most common vascular injury patterns were MCA infarctions with 97 (39.6%) and PVIs with 48 (19.6%) children. The median age at registration for the MCA group was 6 years 11 months (IQR=7y 4mo) and the PVI group was 8 years 4 months (IQR=5y 8mo). The majority of children in the MCA (73 [82%]) and the PVI (37 [82.2%]) groups were born at term.

Outcomes comparing the neurodevelopmental profile of MCA and PVI subgroups

Comparisons between participants with PVI and MCA infarctions for neurological, manual function, cognitive, and behavioural outcomes are reported in Table S2 (online supporting information), and Figures 1 and 2. For neurological outcomes, differences in seizures, visual fields, grip strength, elbow flexor spasticity measured by the angle of spastic catch, and sensory light touch were detected on the unilateral side, with more neurological deficits identified in the MCA group (Table S2; Fig. 1). Results revealed that children with MCA infarctions were 8.61 times (95% CI 1.23–375.20) more likely to have seizures in the last 12 months, 7.20 times (95% CI 1.01–317.49) more likely to have abnormal visual fields on the unilateral side, and 3.83 times (95% CI 1.51–10.21) more likely to have lower

Table 1: Total group participant characteristics (*n*=245)

Variable		Participants (%)
Sex	Male	151 (61.9)
Missing: 1	Female	93 (38.1)
GMFCS level	I	181 (77)
Missing: 10	II	39 (16.6)
	III	11 (4.7)
	IV	3 (1.3)
	V	1 (0.4)
MACS level	I	82 (35.3)
Missing: 13	II	101 (43.5)
	III	33 (14.2)
	IV	11 (4.7)
	V	5 (2.2)
Imaging classifications	PWI patterns	106 (43.3)
	PVI	48 (19.6)
	MCA	97 (39.6)
	Unilateral brain malformations	19 (7.8)
	Miscellaneous	12 (4.9)
	Normal	8 (3.3)
	Non-MCA patterns of arterial infarction	3 (1.2)

GMFCS, Gross Motor Function Classification System; MACS, Manual Ability Classification System; PWI, periventricular white matter injury; PVI, periventricular venous infarction; MCA, middle cerebral artery.

grip strength than children with PVIs. Results for sensory status are shown in Figure 1. Odds ratios for sensory light touch revealed that children with MCA infarctions were 9.12 times (95% CI 1.28–400.76) more likely to have decreased light touch than those with PVIs. No differences in results were identified when missing data were imputed for categorical variables (Table S3, online supporting information), with the exception of sensory 2-point discrimination which became statistically significant in the imputation version restricted to participants over 4 years of age with children with MCA infarctions having decreased 2-point discrimination compared to children with PVIs. Comparing manual function, the quality of unilateral hand/arm movement measured by the Quality of Upper Extremity Skills Test total and grasp scores, and bimanual hand usage measured by the CHEQ (in children >6y) also showed lower function in the MCA compared to the PVI group (Table S2). Children with MCA infarctions performed significantly less activities of daily living independently on the CHEQ (median=17.0, IQR=10.0) compared to children with PVIs (median=26.0, IQR=7.0; Mann–Whitney U=308.00, p<0.001) (Table S2). Children with MCA infarctions had fewer independent activities performed bimanually (78.2%) whereas those with PVIs

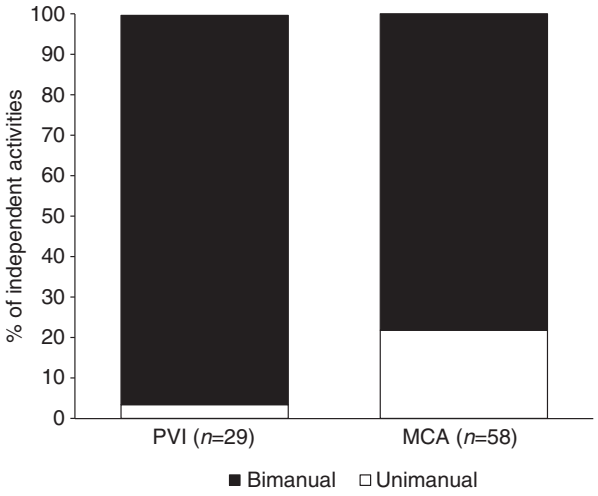

Figure 2: Percentage of unimanual and bimanual hand usage for activities performed independently for participants with periventricular venous infarctions and middle cerebral artery infarctions.

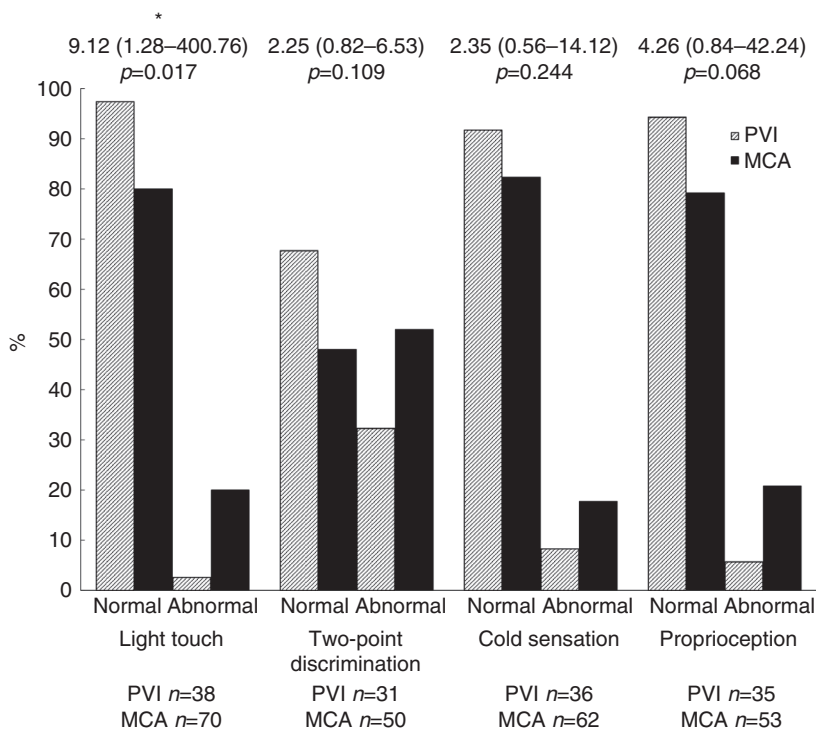

Figure 1: Comparison of the sensory outcomes for the participants with periventricular venous infarctions and middle cerebral artery infarctions. All p-values are reported for Fisher's exact test and * indicates significance. Missing data n (%) for all variables were as follows: light touch periventricular venous infarction (PVI) 10 (20.8), middle cerebral artery (MCA) 27 (27.8); two-point discrimination PVI 17 (35.4), MCA 47 (48.5); cold sensation PVI 12 (25.0), MCA 35 (36.1); proprioception PVI 13 (27.1), MCA 44 (45.4). Imputations for missing variables are reported in Appendix S2 (online supporting information).

performed 96.2% of independent activities bimanually (Mann–Whitney U=425, p<0.001) (Table S2; Fig. 2).

Cognitive outcomes (measured by full-scale, performance, and verbal IQ centiles) also showed lower scores in the MCA group compared to PVI (Table S2). No differences in IQ results were identified when missing data were imputed (Table S4, online supporting information). No differences were seen between the MCA and PVI group for behaviour; however a behavioural deficit was identified on the Pediatric Stroke Outcome Measure in 36 children, representing 33.6% of the group. These were further characterized by the physician completing the Pediatric Stroke Outcome Measure in 22 children. Fourteen were identified with inattention/hyperactivity, seven with social communication challenges, and one with anxiety.

DISCUSSION

In this study of children with unilateral CP, neuroimaging identified that the majority had either PWI (43.3%) or MCA infarctions (39.6%) in relatively equal proportions. The high prevalence of PWI in unilateral CP is consistent with other imaging studies.[12] Furthermore, a large proportion (45.3%) of the PWI group had a PVI. When considered as an independent imaging group, those with PVIs were the second most common vascular injury pattern, the only larger group being MCA infarctions. Eight per cent had brain malformations.

Importantly, this study identified significant differences in neurodevelopmental outcomes between the MCA and PVI groups. Children with a MCA infarction were more likely to have seizures, upper limb spasticity and lower unilateral hand/arm grip strength, sensory light touch, grasp (Quality of Upper Extremity Skills Test), hand usage and independence in bimanual function for activities of daily living (as measured by the CHEQ in children >6y), and cognitive functioning compared to those with PVIs. This is in contract to the large study by Kitai et al.[5] where no difference in motor hand function was detected between the 66 children with PVI compared to 44 children with MCA infarctions. This difference can be explained by the Kitai et al. study measuring hand function on a 4-point ordinal scale (pinch, grasp, press, disuse) compared to the Quality of Upper Extremity Skills Test (utilized in this study) which grades hand function on a scale from 0 to 100% allowing for a more sensitive hand function assessment. We did not detect differences in leg/foot outcomes between the two groups. Children in the MCA group also had more restrictions in visual fields on their unilateral side. In interpreting the neurodevelopmental findings, it is important to note that cognitive skills, sensory and motor processing, and hypertonia do not act in isolation and integrate to produce enhanced manual motor output, hand usage, and independence in activities of daily living in children with unilateral CP with a PVI.

The differences between the PVI and MCA group can be explained by neuroanatomical location and timing of injury during brain development. The MCA injury in the parietal cortex is frequently situated near the distal hand projections of the cortex and encompasses both the primary motor and sensory areas. Hence with MCA injuries, distal hand function is impacted and changes in both motor and sensory processing can be identified. The cortical projections to the legs are located near the longitudinal fissure separating the two hemispheres and therefore relatively outside the MCA infarction area. The area of the MCA infarction can also involve the optic radiation which explains the higher proportion of children with visual field cuts and is localized in the cortex, which explains the higher proportion of children with cognitive impairment and seizures. For individuals with PVI, the area of haemorrhagic infarction is predominantly located in the subcortical area which implicates the motor tracts of the arm and leg rather than the arm being preferentially targeted. The mechanism of sensory sparing in PVI has been elucidated by Staudt et al.[26] who identified that the ascending thalamocortical somatosensory axons at the time of the injury (typically at the beginning of the third trimester) have not yet reached their final destination. These tracts divert laterally/posteriorly around the periventricular injury eventually reaching the primary sensory cortex.

The majority of children in the PVI and MCA groups were born at term gestation (greater than 80%). The high proportion of term gestation in the PVI group is important to highlight as the mechanism of injury is widely attributed to a germinal matrix haemorrhage – an injury associated with the preterm brain – creating a blockage of 'outflow' in the deep medullary veins leading to a venous infarction.[27] However, it is increasingly recognized that this injury pattern can occur silently in utero with the term-born infant presenting in the first year of life with a presumed perinatal ischemic stroke.[11] This finding of a predominant term presentation of PVI is a unique finding of our study, as many of the registry studies do not have detailed neuroimaging findings to accurately identify PVI and there is variability of how PVI is categorized (focal vascular injury vs white matter injury).

This study has rehabilitation implications. Therapists developing hand programmes such as constraint and bimanual therapy should conduct a detailed sensory evaluation of the child. For children with impaired sensory function, building a variety of sensory experiences into the therapy may be helpful, as well as cueing the child to look visually at the hand when they are doing a task to enhance visual-spatial awareness. We detected more spasticity in the upper limb of children with MCA injuries and this subgroup may benefit from tone reduction interventions such as botulinum neurotoxin A injections. Learning challenges impact long-term independence highlighting the need for awareness that children in the MCA group had higher rates of cognitive impairment and may require specialized school services. It is important to highlight the presence of behavioural issues in one-third of children with unilateral CP in both PVI and MCA groups. Clinicians should screen for behavioural issues in all children with unilateral CP.

Our study has limitations. Neuroimaging was clinically ordered and therefore obtained at varying ages. Children who did not have imaging (n=75, 23.4%) were excluded from this analysis and this may introduce a bias. Some children had sequential neuroimaging allowing for an interpretation of injury evolution over time; however, many children had only a single neuroimage. In assessing differences in the neurodevelopmental profile of children in the two groups (MCA and PVI) we did not account for lesion size which is known to be a factor impacting neurological sequelae and warrants more research going forward.[28] In addition, children of a young age (<4y) or with a cognitive disability may not have been able to complete the neurodevelopmental assessments leading to missing data. It is important to highlight, however, that when imputation methods were explored to ascertain if bias was introduced by missing data, the results of the imputed analyses remained similar to the primary analyses. Although we saw a difference in bimanual hand usage and independence in manual activities in children over 6 years of age on the CHEQ, we did not detect a signal in hand-use efficacy, time needed, and 'bothersomeness', nor did we detect a signal in hand usage for children under the age of 6 years with the Pediatric Upper Extremity Motor Activity Log. The use of two different measurement tools (CHEQ and Pediatric Upper Extremity Motor Activity Log) based on age impacts the power to detect differences for this variable. Furthermore, data in the Hemi CP-NET database on behaviour were limited in detail.

In conclusion, this study revealed a difference in neurodevelopmental outcomes between groups of children with unilateral CP who had MCA versus PVIs. Children in the PVI group had fewer seizures and better sensorimotor and cognitive skills associated with enhanced hand function/some elements of hand usage and independence in manual activities of daily living. Utilizing neuroimaging patterns to better understand the child's neurodevelopmental picture can aid in therapeutic interventions geared towards a child's individual needs, representing a move towards precision health in rehabilitation. Future CP clinical databases that include neuroimaging and neurodevelopmental functioning will help to accelerate this progress.

ACKNOWLEDGEMENTS

The members of the CP-NET group are as follows: Craig Campbell (Department of Paediatrics, Western University, London, ON); Anne Kawamura and Lauren Switzer (Department of Paediatrics, Bloorview Research Institute, Holland Bloorview Kids Rehabilitation Hospital, University of Toronto, Toronto, ON); Dawa Samdup (Department of Pediatrics, Queens University, Kingston, ON); and Ilana Walters (Faculty of Medicine, Dalhousie University, Halifax, NS, Canada).

The authors wish to thank the participants and families who donated their time to this research study along with the numerous research staff, occupational therapists, psychologists, and physicians across Ontario, Canada who contributed their time, clinical expertise, and support to this study. This research was conducted with the support of the Ontario Brain Institute, an independent non-profit corporation, funded partially by the Ontario government. The opinions, results, and conclusions are those of the authors and no endorsement by the Ontario Brain Institute is intended or should be inferred. Furthermore, the Ontario Brain Institute was not involved in the study design, data collection, data analysis, manuscript preparation, or publication decisions.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

SUPPORTING INFORMATION

The following additional material may be found online:

Figure S1: Example of imputation approach.

Table S1: Details on outcome assessment

Table S2: Comparison of manual, neurological, cognitive, and behavioural outcomes for participants with PVI and MCA infarctions

Table S3: Summary of original data compared to imputed data for categorical variables

Table S4: Summary of original continuous data compared to imputed data

Appendix S1: CP-NET data collection sheet.

Appendix S2: Imputation approaches for missing data.

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