

Cognitive functioning over 2 years after intracerebral hemorrhage in school-aged children

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ABBREVIATIONS

ICH	Intracerebral hemorrhage
IQR	Interquartile range
PSOM	Pediatric Stroke Outcome Measure

AIM Previous research investigating outcomes after pediatric intracerebral hemorrhage (ICH) has generally been limited to global and sensorimotor outcomes. This study examined cognitive outcomes after spontaneous ICH in school-aged children with serial assessments over 2 years after stroke.

METHOD Seven children (age range 6–16y, median 13; six males, one female; 57% white, 43% black) presenting with spontaneous ICH (six arteriovenous malformations) were assessed at 3 months, 12 months, and 24 months after stroke. The Pediatric Stroke Outcome Measure (PSOM) quantified neurological outcome and Wechsler Intelligence Scales measured cognitive outcomes: verbal comprehension, perceptual reasoning, working memory, and processing speed.

RESULTS PSOM scales showed improved neurological function over the first 12 months, with mild to no sensorimotor deficits and moderate overall deficits at 1- and 2-year follow-ups (median 2-year sensorimotor PSOM=0.5, total PSOM=1.5). Changes in cognitive function indicated a different trajectory; verbal comprehension and perceptual reasoning improved over 24 months; low performance was sustained in processing speed and working memory. Age-normed centile scores decreased between 1- and 2-year follow-ups for working memory, suggesting emerging deficits compared with peers.

INTERPRETATION Early and serial cognitive testing in children with ICH is needed to assess cognitive functioning and support children in school as they age and cognitive deficits become more apparent and important for function.

Previous studies of intracerebral hemorrhage (ICH) and hemorrhagic stroke in childhood have simply reported neurological outcome qualitatively as 'normal', 'good', or 'poor'^{1,2} or have used disability scales or measures of global neurological outcome that are heavily influenced by sensorimotor function.^{3–7} One larger study by Lo et al.⁸ reported neurological outcome as well as quality of life after pediatric ICH. From a group of 59 children, there were 39 survivors; follow-up was available in 19 children at a median of 6 years 7 months after ICH. Children tended to have mild to moderate physical deficits, but many had significant impairment in quality of life, specifically in school functioning. Similar findings are also reported in two other patient cohorts.^{9,10} In addition, a study by Liu et al.⁶ of 70 Chinese children found that the level of disability improved significantly between 3 months and 6 months after ICH. Taken together, findings in previous studies generally suggest improvement in physical disability when assessed months to years after cerebral hemorrhage¹¹ but a significant reduction in quality of life persists.

However, less attention has been given to cognitive outcome after non-traumatic ICH in children. In one study of pediatric hemorrhagic stroke (parenchymal and subarachnoid hemorrhage), 17 out of 31 children demonstrated some level of cognitive impairment (10 mild, seven moderate to severe) 10 years after hemorrhage.¹¹ In a study of neonatal arterial ischemic stroke that tested preschool children and then 18 or more months later as school-aged children (up to 8y after stroke), there was a decline in Full-scale IQ with emerging deficits in working memory and processing speed during the school years.¹² Other studies of childhood brain injuries, such as survivors of newborn hypoxic-ischemic encephalopathy requiring cooling, have reported similar findings, suggesting that deficits may emerge later in development in children.¹³ However, previous studies have not conducted serial testing to examine the trajectory of cognitive function in children with non-traumatic ICH.

We investigated cognitive outcome after spontaneous ICH in school-aged children with serial assessments over

time, 3 months, 12 months, and 24 months after stroke. We expected that cognitive function would slowly improve at each time point in parallel with improvements in sensorimotor function and global neurological outcome.

METHOD

Procedure

Children born at term and aged greater than 28 days to 16 years at the time of spontaneous ICH, including those with primary intraparenchymal hemorrhage and/or intraventricular hemorrhage, were prospectively, consecutively enrolled from 2011 to 2015 at a single institution. The setting was a tertiary care center, located in a metropolitan area in the southeast of the USA. The Institutional Review Board of Vanderbilt University Medical Center approved this study. Consent was obtained from the participants' parents and assent from children 7 years or older. Children were excluded if hemorrhage was related to brain tumor or trauma, or if they died before hospital discharge. Of eligible patients approached, only two refused: one lived too far away to return for follow-up assessment, the other because of lack of interest. Cognitive assessments were only administered to children who were 6 years and older at time 1 (3mo after ICH) and native English speakers; children were excluded from this cognitive study if they were younger than 6 ($n=6$) or if they were not native English speakers ($n=3$). Two raters measured total brain volume and intraparenchymal hemorrhage volume using the validated ABC/XYZ method.¹⁴ Outcome was assessed with the Pediatric Stroke Outcome Measure and a cognitive testing battery at 3 months (time 1, hereafter T_1), 12 months (time 2, T_2), and 24 months (time 3, T_3) after ICH.

Measures

Neurological function

The Pediatric Stroke Outcome Measure (PSOM) is based on neurological examination and includes five subscale scores: sensorimotor left, sensorimotor right, expressive language, receptive language, and cognition/behavior. The subscales are scored as 0 (no deficit), 0.5 (mild deficit that does not interfere with function), 1 (moderate deficit that interferes with function), and 2 (severe deficit). In the current study, we report the PSOM sensorimotor average for the affected side, either right or left (no child had bilateral sensorimotor dysfunction) as well as total PSOM (range 0–10). Moderate disability has been defined as PSOM greater than or equal to 1 and severe disability as PSOM greater than or equal to 2.¹⁵

The Pediatric ICH Score is a clinical grading scale for outcome prediction in the acute period after ICH.¹⁶ These scores range from 0 to 4; scores greater than 1 have been shown to be predictive of moderate disability at 3 months after ICH.

Cognitive function

The Wechsler Abbreviated Scale of Intelligence (Second Edition)¹⁷ and select subtests of the Wechsler Intelligence

What this paper adds

- In children with intracerebral hemorrhage (ICH), motor function improved between 3 months and 24 months.
- Improvements in cognitive function were variable between 3 months and 24 months.
- Working memory centiles declined, suggesting emerging deficits compared with peers.
- Processing speed improved but remained significantly below the 50th centile.
- Cognitive impact of ICH may increase with age in children.

Scale for Children (Fourth Edition)¹⁸ or the Wechsler Adult Intelligence Scale (Third Edition)¹⁹ were administered to all participants. These are widely used and well-validated measures of cognitive function and intelligence. For current analyses, subtests that were not strongly dependent on graphomotor function were used. The vocabulary subtest was used as an index of verbal comprehension and the matrix reasoning subtest was used as an index of perceptual reasoning from the Wechsler Abbreviated Scale of Intelligence; the symbol search subtest was used as a measure of processing speed and the digit span subtest was used as measure of working memory from the Wechsler Intelligence Scale for Children or the Wechsler Adult Intelligence Scale. The same tests were given at each time point because parallel tests are not available for these Wechsler instruments. Cognition scores are reported as both raw scores and age-normed centiles.

Statistical analyses

Statistical analyses were conducted with R (RStudio, Inc., Boston, MA, USA). Mean, median, and interquartile range (IQR) were calculated. Power for a sample size of 7 was 0.20, much lower than the recommended 0.80.²⁰ Therefore, no formal statistical testing was conducted due to the relatively small sample size.

RESULTS

Participants included seven children, ages 6 to 16 years (median 13), six males, one female, 57% white, 43% black. See Table I for demographic and clinical data for the sample. Two participants had pure ICH and five had both ICH and intraventricular hemorrhage. One child had two rebleeds between the 12- and 24-month follow-ups (Table I, participant 2). Brain arteriovenous malformation was the cause of ICH in six out of the seven participants. In one child, etiology could not be determined with careful evaluation. Brain arteriovenous malformation was suspected on the basis of hemorrhage pattern, mixed ICH and intraventricular hemorrhage,²¹ but could not be confirmed. Cerebral angiography was performed in all children; in the child with etiology not determined, angiography was completed during the acute hospital stay as well as 3 months and 12 months after ICH. Angiography was negative for a vascular cause at all of these time points. Initial Glasgow Coma Scale values ranged from 3 to 14 (median 9). Median hemorrhage volume as a percentage of brain volume was 1.96, IQR 1.17 to 3.74. A hemorrhage of 2% of total brain

Table 1: Demographics and clinical information for children with spontaneous intracerebral hemorrhage (ICH)

Participant	Age at ICH (y:mo)	Hemorrhage cause	Hemorrhage location	Hemorrhage volume (% of brain volume)	GCS at presentation	Pediatric ICH score	Intracranial pressure concerns?	Treatment	Epilepsy	Total PSOM at 3mo	Total PSOM at 12mo	Total PSOM at 24mo
1	13:2	Idiopathic	Right parietal, IVE, subcortical	1.09	8	2	Yes, severe, EVD, hemicraniectomy required	Emergency surgery, hematoma evacuation	No	3	1	1
2	6:10	AVM	Left parietal, basal ganglia, IVE and recurrent ICH, subcortical	1.24	9	1	Yes, EVD required	Embolization ×2, radiation ×2	Yes, well controlled	5	3	2.5
3	16:11	AVM	Left parietal, large IVE, subcortical	0.06	6	1	Yes, EVD required	Surgery	No	3	1.5	2.5 ^a
4	6:6	AVM	Left frontal, IVE, subcortical	1.96	14	0	No	Surgery	No	0	0	0
5	12:0	AVM	Right frontal, cortical and subcortical	6.50	11	1	Yes	Embolization, surgery ×2	No	3	2.5	1.5
6	14:7	AVM	Left parietal, occipital, cortical and subcortical	2.48	14	1	Yes, EVD required	Surgery	Yes, well controlled	1.5	0.5	0.5
7	12:11	AVM	Left parietal, basal ganglia, cortical and subcortical	4.99	3	4	Yes, severe, hemicraniectomy	Emergency surgery	No	4.5	4	3

^aPSOM increased at 24mo on the basis of the PSOM behavior/cognitive subscale. GCS, Glasgow Coma Scale; PSOM, Pediatric Stroke Outcome Measure; IVE, intraventricular extension; EVD, extraventricular drain; AVM, arteriovenous malformation of the brain.

volume represents a moderate-sized ICH.^{4,22} All but one child had a Pediatric ICH Score of greater than or equal to 1. Total PSOMs improved over time from median of 3 (IQR 2.25–3.75) at 3 months to 1.5 (IQR 0.75–2.75) at 24 months. However, median PSOM did not change between 12 months and 24 months, indicating that improvement may slow after 6 months.

Sensorimotor and cognitive function

Table II shows median and IQRs for sensorimotor function (as measured by the PSOM) and cognitive function (as measured by Wechsler tests with age-normed centiles) over three time points.

Results from PSOM scores generally reflected improvement between the 3- and 12-month assessments, and then stability between the 12- and 24-month assessments. Sensorimotor performance largely improved over time, with a median of 0.5 at 24 months indicating mild deficit that did not interfere with function. The child who had an arteriovenous malformation that rebelled twice showed worsened sensorimotor function from 0.5 to 1.0 at 24 months; the median PSOM sensorimotor score for all study participants was 0.5 at both 12 months and 24 months but the IQR increased due to this child's worsening PSOM. PSOM expressive language, receptive language, and cognitive/behavioral each had a median of 0 at 24 months.

While results of serial cognitive testing with Wechsler tests also suggested general improvements between T_1 and T_3 (Table II, Table S1), this was not the case for each domain. Median verbal comprehension scores improved from the 13th to the 34th centile over time and median perceptual reasoning scores improved from the 45th to the 63rd centile over time. Upper and lower bounds of the IQR for both verbal comprehension and perceptual reasoning contained the published normative mean for age (50th centile) at T_3 .

However, there was sustained low performance in working memory and processing speed as the IQR remained below the 50th centile at T_3 for both domains. Median

processing speed scores improved from the 5th to the 37th centile over time, while median working memory scores declined from the 16th to the 9th centile over time. It is noteworthy that, for both verbal comprehension and working memory, there was a trend for T_2 scores to be higher than T_3 scores. However, no changes were tested for statistical significance.

Given that working memory remained the most impaired at the 24-month follow-up, we examined both raw scores and age-normed centiles (Fig. 1). Results in the figure indicate that children's raw scores improved over a 2-year period, yet this was not reflected in age-normed centiles, which declined over time.

DISCUSSION

This study presents, to the best of our knowledge, the first serial cognitive testing over three points in time after spontaneous ICH in school-aged children. The total PSOM and PSOM sensorimotor data fit the typical clinical impression and previous research in children with ischemic and hemorrhagic stroke, which is global improvement in physical disability during the first 12 months²³ or at 6-year follow-up.¹¹ However, serial cognitive testing suggests a different trajectory. Testing at 24 months indicated sustained low performance in processing speed and working memory. Results indicated that although individual performance continued to improve, children were not able to keep up with increasing demands of working memory, and remained behind peers in age comparisons at the 12- and 24-month follow-ups. These findings are similar to work in children with ischemic stroke showing that cognitive impairments may be more significant than motor impairments over time.²⁴ Further, in support of the fact that motor function is not a sensitive indicator of cognitive function, PSOM motor scores are not significantly correlated with intelligence measures for preschool or school-aged children with a history of neonatal arterial ischemic stroke.¹² Therefore, children with good motor function cannot always be assumed to have good cognitive function; formal cognitive testing is required.

Table II: Neurological outcome and cognition scores at 3mo, 12mo, and 24mo after intracerebral hemorrhage

	Median (IQR) at T_1 (3mo)	Median (IQR) at T_2 (12mo)	Median (IQR) at T_3 (24mo)	Change T_1 – T_3 (3–24mo)
PSOM total	3.00 (2.25–3.75)	1.50 (0.75–2.75)	1.50 (0.75–2.75)	–1.50
PSOM sensorimotor subscales	1.00 (0.75–1.50)	0.50 (0.25–0.75)	0.50 (0.25–1.25)	–0.50
PSOM expressive language	1.00 (0–1.50)	0 (0–0.50)	0 (0–1.00)	–1.00
PSOM receptive language	0 (0–0.50)	0 (0–0)	0 (0–0)	0
PSOM cognitive/behavioral	1.00 (0.25–1.00)	1.00 (0.25–1.00)	0 (0–0.50)	–1.00
Full-scale IQ ^a	18.0 (13.0–24.0)	34.0 (14.0–55.5)	45.0 (28.0–58.0)	+27
Verbal comprehension ^a	13.0 (6.5–22.0)	50.0 (23.0–58.0)	34.0 (34.0–72.5)	+21
Perceptual reasoning ^a	45.0 (12.0–69.0)	47.0 (20.0–70.0)	63.00 (48.5–68.0)	+18
Working memory ^a	16.0 (1.5–37.5)	25.0 (12.5–60.5)	9.00 (9.0–37.0)	–7.00
Processing speed ^a	5.0 (3.5–9.0)	25.0 (16.0–31.0)	37.00 (20.5–43.5)	+32

^aExpressed as centile on the basis of age norms. Verbal comprehension was measured with the Wechsler Abbreviated Scale of Intelligence (Second Edition) (WASI-II) vocabulary subtest; perceptual reasoning with the WASI-II matrix reasoning subtest; working memory with the Wechsler Intelligence Scale for Children (Fourth Edition) (WISC-IV) or Wechsler Adult Intelligence Scale (Third Edition) (WAIS-III) digit span subtest; processing speed with the WISC-IV or WAIS-III symbol search subtest. IQR, interquartile range; PSOM, Pediatric Stroke Outcome Measure.

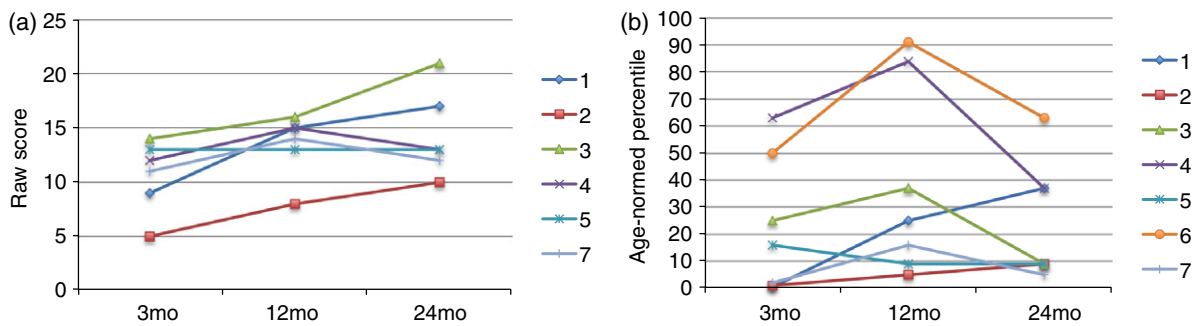


Figure 1: Working memory raw scores and age-normed centiles in children with intracerebral hemorrhage. (a) Raw scores at 3 months, 12 months, and 24 months for the seven study participants as measured by the Wechsler Intelligence Scale for Children (Fourth Edition) (WISC-IV) digit span subtest. (b) Age-normed centiles at 3 months, 12 months, and 24 months for these participants for the digit span subtest. Note: participant 6 was administered the WISC-IV at 3 months and 12 months, then the Wechsler Adult Intelligence Scale (Third Edition) at T_3 . For this reason, raw scores are not displayed in (a). [Colour figure can be viewed at wileyonlinelibrary.com]

Results from the current sample also indicate heterogeneity both across participants and across domains of cognitive function. This further demonstrates that a prognosis of gradual, slow improvement over time may not be the case for every child. Additionally, five of the seven children still had moderate deficits or greater according to the total PSOM score at 2 years after stroke.

In the current study, verbal comprehension and perceptual reasoning improved from T_1 to T_3 , with median centile scores in the average range compared with same-age peers at 24 months. This is similar to results from a previous study of pediatric hemorrhagic stroke that found that Verbal and Perceptual IQ were in the average range 10 years after stroke.¹¹ Median scores for processing speed were also within the average range, but IQR remained below the 50th centile, indicating sustained low performance but not worsening performance from 3 months to 24 months after ICH (Table II).

Unlike other domains, working memory failed to improve over time, with median score at the 9th centile at 24-month follow-up. This is similar to a study of children with ischemic stroke that found increasing deficits in this domain as children aged.¹² Although participants with ICH generally showed improvements in raw scores at each time point, age-corrected scores showed declines between 12 months and 24 months. This suggests that children with brain injury may not keep up with peers as cognitive demands increase developmentally with age. This phenomenon has been studied in pediatric cancer and congenital heart disease conditions where both subtle brain injury and stroke may occur, and is known as ‘growing into deficits’.^{25,26} Results from the current study show that although children with ICH may maintain individual levels of cognitive functioning over time, the performance gap with peers does not improve and worsens over time between 12 months and 24 months. Therefore, this phenomenon of growing into deficits could potentially be relevant to the current sample. This is especially salient to aspects of executive function, such as

working memory, which continue to develop during the periods of adolescence and early adulthood.²⁷ The present findings that suggest emerging deficits in working memory may reflect an interaction between insults associated with brain injury related to ICH and normative developmental processes in brain maturation.²⁸ This may suggest a sensitive period for development of working memory that is not similarly reflected in domains of verbal comprehension or perceptual reasoning.

Limitations of this work include the small sample size. Non-traumatic ICH has an incidence of 0.8 per 100 000.²⁹ To conduct more careful quantitative analyses, large multi-site studies will be needed to achieve the necessary sample size to increase generalizability. To minimize bias, we approached all eligible children about study participation; however, we did not have the ability to test non-native English speakers. In addition, owing to the small sample size, we did not exclude the participant with the recurrent hemorrhage. The patient’s total PSOM improved from 2.5 to 3 despite recurrent small hemorrhages. While serial testing over three points in time is a notable strength, practice effects may have inflated cognitive scores at 12 months as children were tested at both 3 months and 12 months after ICH. Most cognitive tests are not given more frequently than every 12 months, in order to avoid improvement in scores due to practice or familiarity with the test. It is our experience that children with ICH or other brain injuries typically receive cognitive testing at 2 to 3 months to guide educational placement as they return to school as well as about 1 year after ICH to reassess educational placement. This study design was therefore meant to mirror common clinical practice. Future studies should consider alternative, parallel tests. However, it is interesting to note that even with the potential for practice effects, the overall patterns of results still suggested sustained low performance in processing speed and in working memory. Indeed, results from parallel tests may find more prominent deficits.

In conclusion, this study suggests that neurological improvement occurs primarily during the first 12 months and becomes stable afterwards; however, trajectories of cognitive domains differ, as some improve while others remain stable or decline over time. The clinical implications of these findings include the need for early and serial cognitive testing to assess cognitive difficulties as children with a history of ICH age. Motor skills are visible and easy to assess in clinic, while cognitive function is subtler and requires neuropsychological assessment. Clinicians may see improvements over time during subsequent clinic visits, but neuropsychological testing is needed to better understand how children compare with peers. However, as obtaining insurance coverage for cognitive testing is increasingly difficult, many children are being assessed not by neuropsychologists but by school psychologists who may have limited experience with ICH or similar brain injuries.

These results suggest that although children with a history of ICH may have the capacity to perform as well as same-aged peers, as reflected in verbal and perceptual reasoning skills, their cognitive proficiency is limited, as indicated by sustained low performance in processing speed and worsening working memory compared with peers. This suggests that school-based supports may be needed,

such as individual learning plans and additional time on tests, which is consistent with a previous study of ICH indicating that, at 12 months after ICH, over 50% of children were receiving educational supports.¹⁰ Results of serial neuropsychological testing can inform referrals for and coordination of services, so that children can maximize their potential after ICH.

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SUPPORTING INFORMATION

The following additional material may be found online:

Table S1: Neurological outcome and cognition scores at 3 months, 12 months, and 24 months after ICH

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RESUMEN

FUNCIONAMIENTO COGNITIVO DOS AÑOS DESPUÉS DE PADECER HEMORRAGIA INTRACEREBRAL EN NIÑOS DE EDAD ESCOLAR

OBJETIVO Estudios previos que han investigado los resultados y evolución en niños que han padecido una hemorragia intracerebral pediátrica (HIC) se han limitado a describir los resultados globales y sensoriomotrices. El presente estudio examinó los resultados de la evolución cognitiva luego de una HIC en niños de edad escolar utilizando evaluaciones periódicas a lo largo de dos años luego del ictus.

MÉTODOS Siete niños (rango de edad 6-16 años, mediana de 13 años, 6 varones, 7% caucásicos, 43% afroamericano) que presentaron con HIC (6 con malformaciones arteriovenosas) fueron evaluados a los 3, 12 y 24 meses luego del episodio ictal. Se cuantificaron los resultados de la evolución neurológica con el instrumento "Pediatric Stroke Outcome Measure" (PSOM) y se utilizaron las escalas de Inteligencia de Wechsler para evaluar los resultados de la evolución cognitiva: comprensión verbal, razonamiento perceptual, memoria de trabajo y velocidad de procesamiento.

RESULTADOS Las escalas PSOM mostraron mejoría en el funcionamiento neurológico en los primeros 12 meses, con leve o ninguna deficiencia sensorio motriz y deficiencias globales moderadas al seguimiento, al año y a los dos años (a los 2 años la media PSOM = 0.5. Total PSOM = 1.5). Los cambios en las funciones cognitivas fueron adoptando trayectorias diferentes; la comprensión verbal y el procesamiento perceptual mejoraron a lo largo de los 24 meses post-ictus, pero se mantuvo un bajo performance en velocidad de procesamiento y memoria de trabajo. Los resultados expresados en puntaje normatizado según la edad, expresado en centilos, fueron descendiendo en los seguimientos entre 1 año y 2 años post ictus. Esto sugiere que emergen deficiencias en relación a sus pares.

INTERPRETACIÓN Es necesario administrar pruebas cognitivas en forma temprana y periódica en niños con HIC para poder evaluar el funcionamiento cognitivo y proveer el apoyo necesario durante la edad escolar y para detectar deficiencias cognitivas de funciones altamente necesarias para un buen desempeño y que pueden ir haciéndose más evidentes con el transcurso del tiempo.

RESUMO

FUNCIONAMENTO COGNITIVO DE CRIANÇAS EM IDADE ESCOLAR NO DECORRER DE 2 ANOS APÓS UM ACIDENTE VASCULAR ENCEFÁLICO HEMORRÁGICO

OBJETIVO Pesquisa anterior que investigou resultados após um acidente vascular encefálico hemorrágico (AVEH) pediátrico tem de forma geral sido limitada aos resultados globais e sensório-motores. Este estudo examinou resultados cognitivos após o AVEH espontâneo de crianças em idade escolar por meio de avaliações em série ao longo de 2 anos após o acidente encefálico.

MÉTODO Sete crianças (faixa etária de 6 a 16 anos, mediana = 13 anos, seis meninos, 57% brancos, 43% negros) com AVEH espontâneo (seis malformações arteriovenosas) foram avaliadas aos 3, 12 e 24 meses após o acidente encefálico. O *Pediatric Stroke Outcome Measure* (PSOM) quantificou o resultado neurológico e as Escalas Wechsler de Inteligência para Crianças (WISC) mediram os resultados cognitivos de: compreensão verbal, raciocínio perceptual, memória operacional e velocidade de processamento.

RESULTADOS A PSOM mostrou um aumento da função neurológica nos primeiros 12 meses, com déficits sensório-motores de moderados a inexistentes e déficits globais moderados no acompanhamento de 1 e 2 anos (mediana de 2 anos PSOM sensório-motor=0.5; PSOM global=1.5). As mudanças na função cognitiva indicaram uma trajetória diferente; a compreensão verbal e o raciocínio perceptual melhoraram até 24 meses; o baixo desempenho foi mantido na velocidade de processamento e na memória operacional. Os escores normativos diminuíram entre os acompanhamentos de 1 e 2 anos para a memória operacional, sugerindo déficits emergentes em comparação com os seus pares.

INTERPRETAÇÃO Testes cognitivos precoces e em série de crianças com AVEH são necessários para avaliar o funcionamento cognitivo infantil e fornecer suporte a escola na medida em que eles envelhecem e os déficits cognitivos tornam-se mais evidentes e importantes para a função.