Characterization of Neuropsychological Outcomes in a Cohort of Pediatric Patients with Moyamoya Arteriopathy

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Abstract

Introduction Moyamoya arteriopathy is a severe, progressive cerebral arteriopathy that places affected children at high risk for stroke. Moyamoya has been associated with a range of neuropsychological deficits in adults, but data on many cognitive domains remain limited in the pediatric population and little is known about the neuropsychological profile of children with syndromic moyamoya.

Methods This is a single-center, retrospective cohort study of children with moyamoya arteriopathy followed at our center who underwent neuropsychological testing between 2003 and 2021. Test scores were extracted from neuropsychological reports. Medical records were reviewed with attention to individual neuropsychological test results, medical comorbidities, presence of infarct(s) on neuroimaging, and history of clinical ischemic stroke.

Results Of the 83 children with moyamoya followed at our center between 2003 and 2021, 13 had completed neuropsychological testing across multiple cognitive domains. Compared to age-based normative data, children in this sample had lower scores in overall intelligence ($p = 0.003$), global executive functioning ($p = 0.005$), and overall adaptive functioning ($p = 0.015$). There was no significant difference in overall intelligence between children with ($n = 6$) versus without ($n = 7$) a history of clinical stroke ($p = 0.368$), though children with any radiographic infarct scored lower in this domain ($p = 0.032$).

Conclusion In our cohort, children with moyamoya demonstrated impaired intelligence and executive functioning, even in the absence of clinical stroke. Neuropsychological evaluation should be considered standard of care for all children with moyamoya, even those without a history of clinical stroke.

Keywords
- moyamoya disease
- stroke
- pediatric
- neuropsychology
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Introduction

Moyamoya arteriopathy is a progressive cerebral arteriopathy characterized by bilateral internal carotid artery stenosis and compensatory formation of collateral vessel networks.[1] Moyamoya is associated with up to 10% of childhood strokes and transient ischemic attacks, and roughly one-third of children with moyamoya who experience stroke has recurrent stroke within 1 year.[2,3] Moyamoya can occur in association with systemic conditions such as neurofibromatosis type 1, sickle cell disease, or trisomy 21, termed moyamoya syndrome (MMS), or without an associated condition, termed moyamoya disease (MMD).[4,5] Moyamoya is known to cause neuropsychological impairment in anywhere from 13 to 69% of affected children.[6–8] Prior studies are limited by exclusion or underrepresentation of children with MMS and often do not examine domains such as social and emotional well-being and adaptive functioning.

Currently, clinical management decisions (e.g., when to consider revascularization surgery) tend to focus on stroke or transient ischemic attack as the only relevant outcomes. However, one recent study of children with moyamoya found prominent executive dysfunction associated with altered cerebral hemodynamics in the right parietal and white matter regions, even in the absence of stroke.[9] As the first step in understanding how and when to incorporate risk of poor neuropsychological outcome in clinical treatment decision-making, it is important to first characterize long-term neuropsychological outcomes in children with moyamoya. Therefore, we sought to characterize the full complement of neuropsychological impairment in children with both MMD and MMS and to identify associations between clinical variables and cognitive outcomes. These data will allow us to begin to understand the role neuropsychological outcomes should play in treatment decision-making and to lay the foundation for future treatment studies that include cognitive and behavioral function as relevant outcome measures.

Methods

This study was approved by the Johns Hopkins Medicine Institutional Review Board and carried out under a waiver of consent. Patients with moyamoya seen at our center from 2003 to 2021 were identified retrospectively using International Classification of Disease codes.[5,10] Patients who underwent neuropsychological testing in multiple cognitive domains were included. Medical and neuropsychological testing records were reviewed with attention to demographic characteristics, comorbidities, occurrence of clinical and radiographic stroke, and neuropsychological test scores.

Radiographic Data

The magnetic resonance image (MRI) most proximate to the date of neuropsychological evaluation (either before or after) was analyzed. Clinical stroke was defined as an acute-onset neurologic deficit with associated acute infarct on MRI. Patients were classified as having radiographic infarct if there was any evidence of previous infarct on MRI.

Neuropsychological Measures

Standardized, age-normed neuropsychological measures were administered as part of clinical care. Overall intellectual functioning was assessed using either the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV)[11] or Fifth Edition (WISC-V)[12] full-scale intelligence quotient (FSIQ) or the Differential Abilities Scale, Second Edition (DAS-II)[13] general cognitive ability (GCA) score based on the child's age. The WISC-IV, WISC-V, and DAS-II FSIQ/GCA are strongly correlated ($r = 0.84–0.86$).[11–13] Scores are presented as standard scores (mean 100, standard deviation 15).

Verbal intelligence was assessed using WISC-IV/V verbal comprehension index or the DAS-II verbal reasoning composite, which are highly correlated ($r = 0.73–0.85$).[11–13]

Nonverbal intelligence was assessed using the WISC-IV/V perceptual/fluid reasoning index or the DAS-II nonverbal reasoning composite, which are moderately correlated ($r = 0.66–0.71$).[11–13] For all above-mentioned WISC and DAS indices, higher standard scores denote better performance.

Parent-reported executive functioning was assessed using either the Behavior Rating Inventory of Executive Functioning, Second Edition (BRIEF-2)[14] global executive composite (GEC), behavioral regulation index, and metacognition index scores or BRIEF-Preschool (BRIEF-P)[15] GEC and emergent metacognition index. BRIEF versions are well correlated ($r = 0.89–0.91$).[14,15] Scores are presented as T-scores (mean 50, standard deviation 10). Higher scores denote greater impairment.

Parent-reported adaptive functioning was assessed using the Adaptive Behavior Assessment System, Third Edition (ABAS-3).[16] The measure provides an overall adaptive score (general adaptive composite) as well as three subscales: conceptual, social, and practical skills. Higher standard scores indicate better adaptive functioning.

Social, emotional, and behavioral functioning were assessed using the composite scores from the Behavioral Assessment System for Children, Second (BASC-2)[17] or Third (BASC-3)[18] Edition. Indices associated with the BASC include externalizing symptoms (misconduct, aggression, defiance), internalizing symptoms (mood, anxiety), behavioral symptoms (inattention, hyperactivity), and adaptive skills (daily living and social skills). If a child was administered the Conners Comprehensive Behavior Rating Scale (CBRS)[19] in lieu of the BASC, the analogous scores were used. The BASC and CBRS subscales are moderately correlated ($r = 0.68–0.73$).[17–19] Scores are presented as T-scores; higher scores indicate greater impairment.

Visual-motor integration was assessed using either the Beery–Buktenica Developmental Tests of Visuomotor Integration, Sixth Edition[20] or the DAS-II copying subtest.[13] Higher standard scores indicate better performance.

Statistical Analysis

Statistical analysis was conducted using Stata 17.0 (StataCorp, College Station, Texas, United States). Normality of cognitive assessment distributions was assessed using the Shapiro–Wilk's test. Neuropsychological assessment scores were compared to age-based population means using one-sample *t*-tests. Scores

between the two groups (with and without clinical stroke) were compared using *t*-tests. Scores among syndromic groups were compared using one-way analysis of variance. A two-tailed *p*-value of <0.05 was considered statistically significant.

Results

Of 83 children with moyamoya assessed at our center, 13 had neuropsychological testing across multiple domains. This included four children (31%) with MMD and nine (69%) with MMS (three sickle cell disease, five neurofibromatosis type 1, and one hemophilia A). Median age at testing was 7.8 years (range: 5.3–16.5 years). MRI took place within a median of 43 (IQR: 19–195) days of neuropsychological testing. Six patients (46%) had a history of clinical ischemic stroke before testing, and 10 (77%) had prior infarct (including silent stroke) on MRI, including 4 (31%) with left hemispheric, 1 (8%) with right hemispheric, and 5 (38%) with bilateral infarcts. Seven (54%) had undergone surgical revascularization before testing.

Compared to age-based normative means, children in this cohort had significantly lower overall intelligence ($p = 0.003$), verbal intelligence ($p = 0.009$), and nonverbal intelligence ($p = 0.003$) scores (►**Fig. 1**). These children also had significantly elevated (impaired) BRIEF GEC ($p = 0.005$) and metacognition index ($p = 0.002$) scores. They demonstrated impairment in visual-motor integration ($p < 0.001$) and overall adaptive functioning ($p = 0.015$). There were no significant differences in social, emotional, or behavioral functioning.

We found no significant differences in overall intelligence, verbal intelligence, or visual-motor integration scores when comparing children with versus without history of clinical

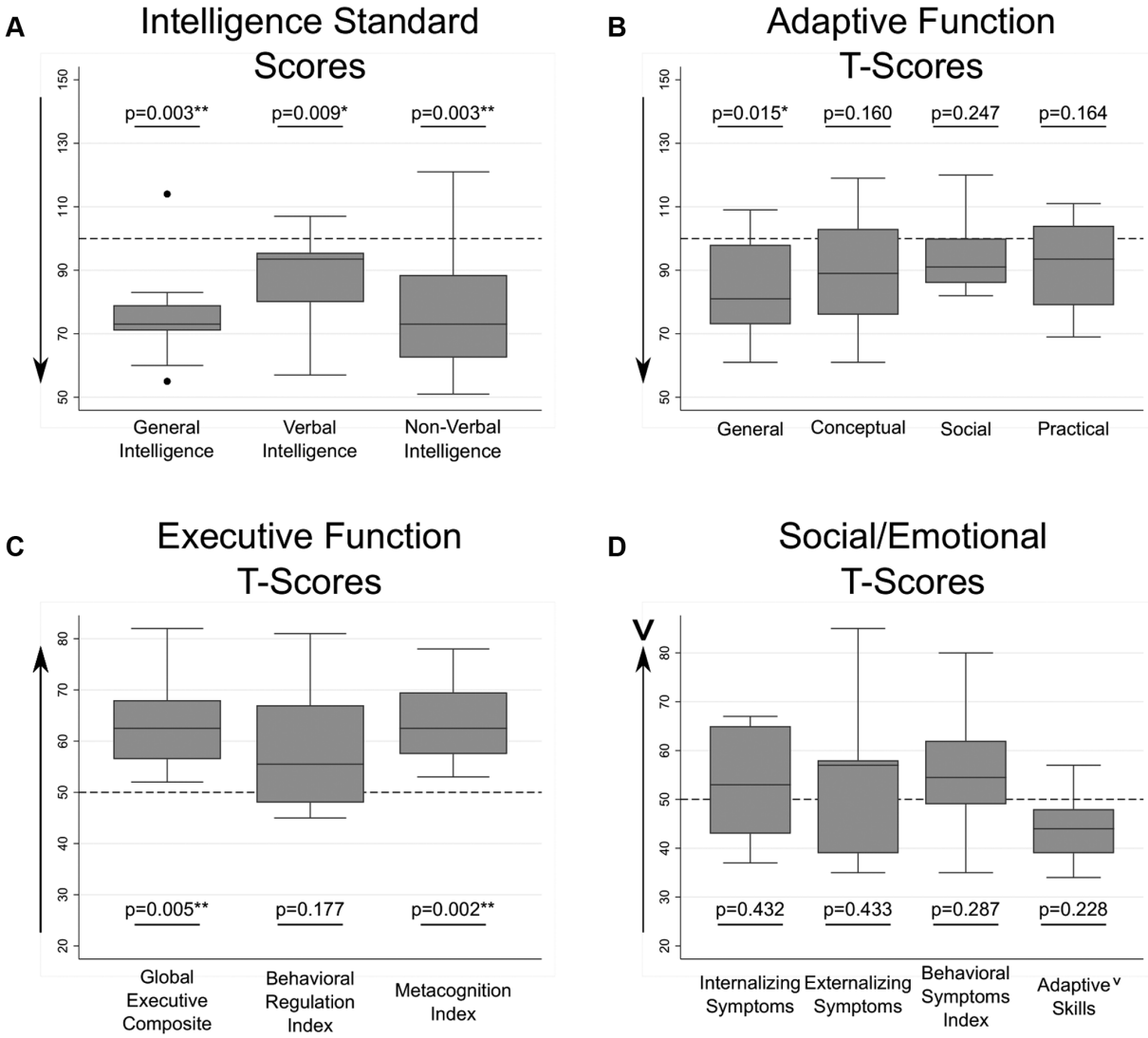

Fig. 1 Boxplots depicting cohort scores for test of intelligence (WISC-IV/V, DAS-II **[A]**), adaptive functioning (ABAS-3 **[B]**), executive functioning (BRIEF-2/P **[C]**), and social/emotional well-being (BASC-2/3, CBRS **[D]**). Arrow indicates direction of impairment. Dotted line represents age-appropriate population mean. Comparison to age-based population means using one-sample *t*-tests. $^{*}p < 0.05$, $^{**}p < 0.005$. v indicates that lower *t*-scores indicate impairment for the adaptive skills score of the BASC-2/3. ABAS-3, Adaptive Behavior Assessment System, Third Edition; BASC-2/3, Behavioral Assessment System for Children, Second/Third Edition; CBRS, Conners Comprehensive Behavior Rating Scale; DAS-II, Differential Abilities Scale, Second Edition; WISC-IV/V, Wechsler Intelligence Scale for Children, Fourth/Fifth Edition.

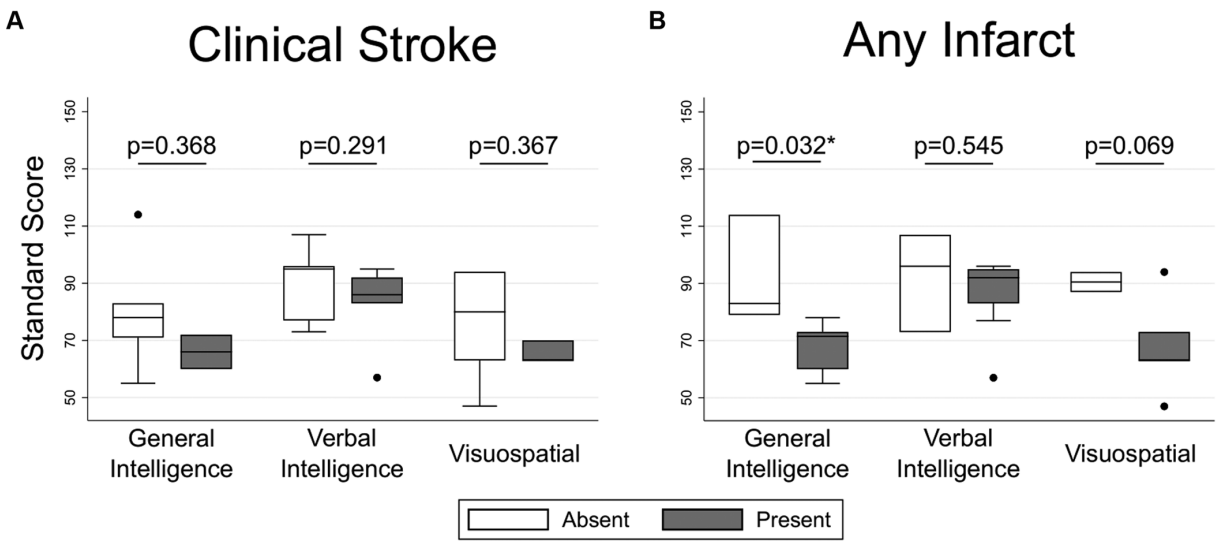

Fig. 2 Boxplots depicting differences in general intelligence (WISC-IV/V full-scale intelligence quotient or DAS-II general cognitive ability), verbal intelligence (WISC-IV/V verbal comprehension index or DAS-II verbal reasoning), and visual-motor integration (Beery VMI or DAS-II copying) standard scores between patients with and without history of clinical ischemic stroke **(A)** and any evidence of ischemic injury on MRI **(B)**. Standard scores compared using Student's *t*-tests. Standard score of 100 represents population mean. $^{*}p < 0.05$. Beery VMI, Beery–Buktenica Developmental Tests of Visuomotor Integration, Sixth Edition; DAS-II, Differential Abilities Scale, Second Edition; MRI, magnetic resonance image; WISC-IV/V, Wechsler Intelligence Scale for Children, Fourth/Fifth Edition.

stroke ($p > 0.05$, ►**Fig. 2A**). However, children with any evidence of infarct on MRI had significantly lower overall intelligence ($p = 0.032$) compared with children without radiographic evidence of infarct (►**Fig. 2B**). There was a trend toward decreased visual-motor integration abilities in children with radiographic infarcts (mean standard score 72.7, SD 16.1, $p = 0.069$). There were no significant differences in overall intelligence ($p = 0.568$), verbal intelligence ($p = 0.507$) or visual-motor integration ($p = 0.586$) among children in the MMD, sickle cell disease, and neurofibromatosis type 1 groups.

Discussion

In this single-center, retrospective cohort study, we found that children with moyamoya had impairments in overall intelligence, visual-motor integration, executive functioning, and adaptive functioning. Children with any infarct on MRI (including clinically silent stroke) had significantly lower general intelligence when compared with those without infarcts. This suggests that subclinical ischemic injury can affect neurocognitive functioning in children with moyamoya. While limited by small sample size, we did not detect differences in neuropsychological test scores among children in different syndromic groups.

Notably, we found prominent impairment in executive functioning, consistent with previous studies in children with moyamoya.[9,21] Chronic hypoperfusion in an anterior watershed distribution could contribute to executive dysfunction by limiting blood supply to the prefrontal cortex, even in the absence of stroke. Choi et al have reported that impaired cerebrovascular reactivity in the right parietal and subcortical white matter regions is associated with lower executive functioning.[9] Future studies investigating regional cortical thickness and/or using diffusion tensor imaging to interrogate white matter integrity may further elucidate the causal link between altered cerebral hemodynamics and changes in cognition.

Our study has some limitations. First, our small sample size limited statistical power for comparisons. As our cohort is retrospective, selection of patients for specific neuropsychological tests is subject to referral bias and may not be representative of all children with moyamoya. In particular, referral for neuropsychological testing may have been driven by neurocognitive symptoms resulting in a more severely affected cohort. Importantly, as most children in this sample underwent neuropsychological testing and MRI on different days, the possibility of silent strokes occurring in the time between testing and MRI cannot be excluded.

Conclusion

In conclusion, our study showed that impairment across multiple neuropsychological domains is common among children with moyamoya—even those without a history of clinical stroke. Specifically, we found notable deficits in intelligence, executive functioning, and visual-motor integration. Practitioners who care for these children should be aware of the prevalence of neurodevelopmental differences in this group, as screening and identification of challenges may allow for implementation of resources and accommodations that help children with moyamoya succeed. Finally, our results support future research that assesses the impact of different therapeutic strategies on long-term neuropsychological function in addition to stroke risk.

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Conflict of Interest
None declared.

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