pediatric stroke

Neuropsychological Outcomes in Pediatric Moyamoya Disease

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ABSTRACT

Neuropsychological assessment is an important part of clinical care for infants, children and youth with moyamoya disease (MMD). Challenges with aspects of executive control processes (including attention, working memory, speed of information processing and output) and perceptual reasoning have been reported in association with pediatric MMD, though existing studies are limited by retrospective design, small numbers, variability in outcome measures and underlying disease and neurological complications (e.g. stroke). Revascularization surgery is recommended for many children and youth with MMD, though little is known about neuropsychological outcomes following surgery and even less about cognitive changes pre-surgery that can be valuable in surgical decision-making. Early age at disease onset and longer time between onset and surgery have been associated with poorer neurocognitive outcomes. Anxiety, low mood, and somatic preoccupation are common among youth with MMD, and may impact the way in which disease-related symptoms are experienced, interpreted, and reported. In addition to reviewing the current literature on neuropsychological outcomes in pediatric MMD, we present a case study that highlights the essential contribution of neuropsychology to surgical planning and treatment evaluation in this population. We also discuss gaps in our current understanding and priorities for future research.

NEUROPSYCHOLOGICAL OUTCOMES IN PEDIATRIC MOYAMOYA DISEASE

Moyamoya disease (MMD) is a rare cerebrovascular disorder characterized by progressive occlusion of the distal internal carotid arteries supplying blood to the brain [1]. It is the leading cause of ischemia and stroke in children and youth, often requiring neurosurgical intervention to revascularize the brain [2, 3]. Neurologic and radiographic features of MMD have been well studied. However, little is known about neuropsychological outcomes [4, 5]. MMD can lead to cognitive impairment due to reduced blood flow to the brain, however, this has not been systematically studied, particularly in children. The unpredictability of the disease can also result in difficulties with emotional and mental health adjustment, particularly anxiety [6].

Neuropsychology is an integral part of clinical care for children and youth with MMD for several reasons. First, cognitive and social-emotional functioning are central to academic progress and quality of life and emphasize the importance for clinicians to adopt a holistic approach to the child (family, school) when providing medical care [7]. Second, neuropsychological assessment can inform diagnosis and neurosurgical treatment planning by documenting the functional impact of the disease and inferring which brain functions are most affected [8]. Post-surgical assessments are helpful in evaluating the effectiveness of surgical interventions, predicting long-term prognosis, and guiding further non-surgical treatment planning (medical, educational, psychological). Finally, neuropsychologists aid in exploring mental health and socio-demographic factors that may influence symptom reporting and compliance with medical recommendations. Anxiety, low mood, and somatic preoccupation are common among youth with MMD [7] and may impact the way in which disease-related symptoms are experienced, interpreted, and reported.

This paper aims to review the current literature on cognitive, behavioral and socio-emotional outcomes in children with MMD, the impact of surgical intervention on neuropsychological functioning, and the factors that appear to be most predictive of outcome. We also highlight the importance of neuropsychology in the care of MMD patients, address controversial issues in the field, and provide directions for future research.

Neurobiological mechanisms underlying cognitive symptoms.

MMD is a disease predominantly involving the distal internal carotid artery (ICA), proximal middle cerebral artery (MCA) and posterior cerebral arteries (PCA) in advanced disease. Clinical features may include transient ischemia attack (TIA), focal neurological deficit, headache or seizures. Chronic hypoperfusion puts the brain at risk of developing an ischemic stroke given the reduced cerebral blood flow (CBF). There are variations in the reported severity of arterial involvement and progression of macro- and microvascular arteriopathy neurocognitive sequalae in response to both acute and chronic hypoperfusion [9]. It is important to distinguish between MMD and moyamoya syndrome (MMS). MMD is primarily genetic in etiology and occurs independently, with no association to other conditions. In contrast, MMS occurs secondary to another underlying medical condition, such as Downs Syndrome, neurofibromatosis type I (NF1), or sickle cell disease [1].

The distal ICA, territories of MCA, and anterior cerebral arteries (ACA) are involved, which serve large cortical networks (frontal, parietal, and temporal) that can lead to significant cognitive impact. Ischemic microvascular disease can affect the white matter. In addition, the involvement of watershed zones in the various arterial territories and cortical-subcortical junction has been demonstrated in various studies. Chronic hypoperfusion in an anterior watershed distribution can limit blood supply to the prefrontal cortex even in the absence of stroke, resulting in executive dysfunction [4]. Impaired cerebrovascular reactivity in the right parietal and subcortical white matter regions has also been associated with diminished executive function [9].

Cognitive performance may be altered when the cerebrovascular system is under stress, and chronically insufficient CBF has been associated with long-term cognitive decline [10]. Anemia, hypoxia, and cardiovascular dysfunction all impact CBF and have been consistently associated with cognitive deficits. Although mild to moderate reduction in CBF in these populations do not appear to alter performance [11, 12, 13], the severe reduction has been associated with altered cognitive status [11, 14, 15]. It is important to highlight that altered CBF is not directly linked to neuronal dysfunction. Rather, CBF indirectly impacts neuronal function – and, by extension, cognitive performance – through its effects on cerebral metabolism [14]. The brain can adapt to severe CBF modification by

increasing its oxygen extraction capacity and, perhaps by using cognitive compensation mechanisms requiring less energy consumption [16].

Few studies have focused on cognitive function in MMD patients. Some studies have demonstrated that MMD patients without stroke experience cognitive impairment [17, 18]. Poorer performance on memory tasks has also been reported[19]. Other studies have found that MMD patients have impairments in prospective memory and attention, which correlate with white matter injury [20, 21]. Shi et al. showed that changes in regional CBF were directly correlated with neurocognitive changes using several neuropsychological tests. Therefore, normalizing CBF in MMD patients may prevent disability and improve functional outcomes. This could become a secondary objective alongside stroke prevention in the overall management [21].

Stroke is the main risk of MMD and can have catastrophic consequences on the patients' overall physical, cognitive and mental health. In pediatric onset MMD, younger age at diagnosis increases the risk of ischemic events. In addition to direct brain injury, the occurrence of a stroke in a developing brain has long-term consequences for future development [1, 4]. The age at stroke occurrence modifies the long-term prognosis. Early onset stroke (1 month to 6 years) corresponds to the main age at onset of MMD. This is correlated with less favorable outcomes [22, 23]. Early childhood is a critical time for attaining developmental milestones, and this is disrupted by having a stroke. As a consequence, it hinders learning and/or causes protracted development in acquiring new skills [24]. A large ischemic core also correlates with worse cognitive outcomes [25].

Neurological sequelae of a stroke may include seizures. The occurrence of seizures after a stroke is increased nearly 30-fold and 9-18% of MMD patients will experience seizures [26, 27]. Seizures have consistently been found to worsen cognitive outcomes in patients with stroke [25, 28]. Therefore, patients require close monitoring for signs of seizures or electroencephalogram (EEG) abnormalities. In the context of pediatric MMD and stroke, patients will require regular follow-up and rehabilitation to prevent secondary neurological complications and worsening disability.

Neurocognitive outcomes in pediatric MMD.

Reported incidence and prevalence of neurocognitive deficits in children and adults with MMD vary widely and depend on the population studied and cognitive assessment instruments used. Cognitive outcomes may also depend on whether children with MMD suffered a stroke or only a TIA, or suffered both TIA and stroke [8, 29, 30, 31]. Given the rare occurrence of this arteriopathy, most studies to date have used retrospective cross-sectional designs in smaller cohorts investigating short-term post-revascularisation cognitive outcomes. There is a paucity of longitudinal studies with larger population cohorts studying outcomes long-term or transitional cognitive changes associated with disease or treatment. Furthermore, there is a lack of studies looking at the relationship of neuropathology and neuroradiology of various brain structures with evolution of arteriopathy in MMD. Additionally, there are very few data integrating neuroimaging with cognitive outcomes.

In children with MMS, the exact epidemiology and clinical spectrum of neurocognitive abnormalities are difficult to study as it is often not possible to tease apart clinical features attributable to the arteriopathy itself versus the underlying primary syndrome causing the arteriopathy [8, 9, 30, 31]. These are important limitations in understanding the exact neurocognitive clinical syndromes, their natural history and evolution of this disease.

Most of the recent literature suggests that multiple neurocognitive domains are simultaneously affected in children with MMD, with significantly lower performance in a range of cognitive and adaptive domains when compared to age-based normative means. They predominantly demonstrate lower executive functioning (primarily basic processes such as attention, working memory, and processing speed), nonverbal abilities, and visual-motor integration [32].

A number of factors have been reported to impact neuropsychological outcomes in children with MMD, though existing data are limited by retrospective design, small sample size, variable assessment approach, and diverse outcome measures, limiting generalizability. A 2018 meta-analysis of 17 studies investigating cognitive impairment in adult and pediatric patients with MMD did not find a difference in the proportion of children (30%) versus adults (31%) with cognitive deficits as defined by an IQ <85, or -1.5 SD below the mean [29]; however, individual smaller studies have suggested that children are more often affected. Among the 11 included studies

analyzing the pediatric MMD population specifically, no association was found between patient sex or age and cognitive impairment [29]; earlier studies, however, have reported that earlier-onset MMD and longer duration of disease are both associated with poorer intellectual outcomes [5, 33, 34, 35, 36].

Several studies have examined whether the presence and/or distribution of strokes in children with MMD is associated with more severe neurocognitive deficits, with conflicting results [37]. A recent retrospective study of 13 children with MMD did not find significant differences in overall intellectual function between children with compared to those without history of stroke [32], however sample sizes were too small to draw any definitive conclusions. In contrast, an older study of 52 pediatric MMD patients found that those with stroke (17) had poorer intellectual function and with cortical infarcts may portend worse intellectual outcomes than subcortical/deep white matter-restricted infarcts [38]. Complicating matters, such as age at stroke may be an important modulator of neuropsychological sequelae, irrespective of stroke etiology. A cross-sectional study of 52 patients with neonatal or childhood arterial ischemic stroke revealed that the young childhood age group (>29 days to <6 years) had worse long-term cognitive outcomes than neonates or older children [23]. Another study of 30 pediatric MMD patients who underwent pre-operative assessment of intellectual abilities and ratings of executive functions found that overall patients performed more poorly in all cognitive subdomains than age reference normative samples, and patients with bilateral vasculopathy and bilateral strokes exhibited more pronounced neurocognitive deficits, though patients with unilateral disease and no stroke were still mildly affected [4]. However, sample size of bilateral vasculopathy was too small (n=7) to be conclusive, and changes in intellectual test measurement warrant caution in interpreting subdomain performance.

It is not known whether reduced CBF *without* stroke in MMD correlates with neurocognitive outcome. Again, existing studies report conflicting results with varying neuroradiological modalities used for assessment (e.g. xenon CT, SPECT, Arterial Spin Labeling) [39, 40, 35]. A recent study in children with MMD investigated the association between regional CBF (rCBF) and performance on measures of general intellectual ability (Wechsler Intelligence Scale for Children-WISC) and visual memory (Benton Visual Retention Test; BVRT) [41]. Findings suggest that rCBF in the right MCA territory in particular, was associated with both verbal and nonverbal intellectual performance, as well as working memory, while reduced rCBF in subcortical structures (bilateral basal ganglia, thalami,

cerebella, pons and vermis) was correlated primarily with working memory and to a lesser extent nonverbal reasoning, suggesting that the anatomical distribution of reduced blood flow may impact cognitive function differentially.

Multiple overlapping patient factors may compound neurocognitive impairment in children with MMD and MMS, making it difficult to parse out distinct associations. Japanese and Korean studies that excluded patients with MMS (e.g. Trisomy 21, Sickle Cell Disease, Neurofibromatosis-1 [NF-1]) reported age-appropriate intellectual ability, though with possible impairment in subdomains, particularly working memory [3, 5]. Western cohorts that included MMS patients have found lower overall intellectual functioning compared to age-matched controls, albeit still average for a large proportion of samples. Direct comparison of MMD and MMS did not find a significant difference [4, 42]. Additional factors, such as intractable epilepsy in NF1or cardiac dysfunction in sickle cell disease, may contribute to more significant cognitive deficits or intellectual disability in a subset of MMS patients [43].

Finally, the natural course of untreated MMD portends progressive cognitive decline [44, 45]. Surgical revascularization may slow or stabilize this decline in children with MMD and should serve as an additional rationale for treatment. Matsushima, et al retrospectively analyzed 65 children with MMD who underwent encephaloduroarteriosynangiosis (EDAS) and found that cognitive/intellectual performance stabilized post-operatively in most cases, except patients with earlier-onset MMD (<5 years); a subsequent study found that patients with pre-operative Full Scale IQ >70 had average IQ ~10 years post-operatively [46, 34, 47]. A meta-analysis of 8 studies evaluating the long-term impact of revascularization surgery on cognitive performance found that, among 199 pediatric patients, 33% had impaired intelligence (defined as 1.5 standard deviations below the mean) pre-operatively and 35% had impaired intelligence post-operatively. Overall, IQ improvement was seen in 27%, no change in 56%, and worsening in 13.5%, with a median follow-up period of 35.3 months (range 6.5-113 months) [29].

Taken together, the existing literature on factors affecting neurocognitive outcomes in children with MMD is challenging to interpret due to small numbers, retrospective design, variable inclusion criteria, nonuniform neurocognitive testing and outcome assessment methodology, as well as

interrelated pathologies (e.g. post-stroke epilepsy) potentially cofounding results. Although presence of stroke, early age at disease onset, bilateral disease, delayed surgical intervention, and decreased CBF in certain brain regions have all been linked to worse neurocognitive outcomes, larger, multicenter prospective studies are needed to accurately define prognosticators in this population. Table 2 and 3 highlight key findings with respect to factors that impact neuropsychological outcomes in pediatric MMD.

Structural and functional neuroimaging studies.

Structural MRI studies of MMD can better characterize the gross structural and microstructural abnormalities in this patient group. Few pediatric MMD imaging studies exist that have examined the association between neuroimaging variables and cognitive outcomes. An MRI study analysing diffusion-weighted imaging (DWI) of MMD patients younger than 20 years old, reported significantly increased apparent diffusion coefficient (ADC) values in patients with MMD compared to the control group in the white matter, cerebral cortex, caudate, putamen, and the nucleus accumbens [48]. Although no cognitive measures were administered in this study, the authors reported that there were no significant differences in brain volume between the patient and control group with brain volume in general associated with cognition [48, 48, 49]. Diffusion tensor MRI studies of adult MMD patients found that mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) in white matter pathways such as the uncinate fasciculus (UF), inferior-occipital fasciculus (IFOF), and superior longitudinal fasciculus (SFL) were correlated with nonverbal reasoning performance, suggesting that cognitive function in MMD are related to microstructural changes in the white matter [20].Functional brain imaging studies, such as cerebrovascular reactivity (CVR) and perfusion imaging can provide insights into the brain pathophysiology in MMD patients. Several studies examined the correlation between functional brain measures with cognition in pediatric MMD patients. Li and colleagues (2019) found significant correlations between subdomain performance on the Wechsler Intelligence Scale for Children (4th Ed.) (WISC-IV) and regional perfusion measured with arterial spin-labeling MRI in pediatric MMD patients 6-16 years [40]. Specifically, the authors reported that patients with cerebral infarction performed more poorly on

measures of nonverbal reasoning. Moreover, the left temporal lobe CBF was positively correlated with processing speed, and the Suzuki stage of the left hemisphere was negatively correlated with the FSIQ [40].

More recently, a breath-hold CVR BOLD MRI study of MMD patients 6-16 years showed a significant correlation between regional cerebral haemodynamics, such as in fronto-parietal cortex, and intellectual ability as measured by the Wechsler Intelligence Scales (WISC-III, WISC-IV, or WAIS-IV) [9]. Furthermore, parent ratings of executive function were correlated with frontal haemodynamic abnormality [9]. Another study reported that rCBF in the left dorsolateral prefrontal cortex was significantly correlated with nonverbal reasoning, processing speed, and general cognitive ability (FSIQ) as measured with WISC-IV, in children with MMD age 5-14 years and no apparent brain lesions [50]. Furthermore, a significant correlation was reported between the rCBF of the left medial frontal cortex and processing speed in the same study. The authors suggest that cerebral hypoperfusion was associated with mild cognitive dysfunction [50]. In addition to the pediatric studies, a PET imaging study in adults with MMD reported a significant correlation between perfusion in the right MCA territory and dysexecutive cognitive syndrome [51].

Although some studies report a strong correlation between brain imaging findings and cognitive measures as discussed above, there are studies that did not find such associations [37]. Further research is needed to understand these discrepancies.

Post-surgical outcomes.

There are a small number of studies evaluating pre-surgical and post-surgical neuropsychological outcomes in pediatric MMD. Comparison across studies is challenging because of variability in methodology, sample characteristics, length of follow-up time, and sample size, but some themes emerge from the available data. A systematic review paper by Mitchell and colleagues (2023) examined twelve studies of neuropsychological functioning following surgery for MMD; most studies found no evidence of cognitive change from pre-surgery to post-surgery, though some have found evidence of improvements [52] or declines [47]. When cognitive improvements were noted, they were most often observed for perceptual reasoning, visual-spatial processing, visual-motor speed,

and verbal memory [5, 35, 52, 53, 54]. When declines were noted, auditory attention and working memory appeared to be most common [47, 53]. Overall intellectual function was generally preserved and stable following surgery [34, 47, 55], but school performance was found to worsen following surgery in two of three studies that examined academic function [5,39, 54]. With respect to quality of life before and after surgery, findings are very mixed, with some evidence of improvement [39] but equal evidence of no change [55]. One study found that, despite successful disease control post-surgery, 17.9% of patients continued to have social difficulties following surgery [5]. Persistent mental health challenges, reduced academic attainment, and long-term interpersonal difficulties have also been reported in adults with pediatric MMD, even when the condition was successfully treated with surgery [56, 57].

Several factors have been found to impact post-surgical neuropsychological function. First, a shorter length of time between diagnosis and surgery appears to be associated with better cognitive and academic outcomes [5, 47], though it is difficult to determine if the observed cognitive improvements are related directly to surgical intervention, or some other factor. For example, variability in access to educational supports and rehabilitation therapy, comorbid medical factors, and overall family functioning can also impact a child's neuropsychological trajectory [8]. Second, female sex has been associated with better neuropsychological outcome following surgery [5, 58]. There is also evidence to suggest that patients who sustained a clinical stroke prior to surgery tend to have poorer cognitive outcome following surgery [59]. Further, among those with a pre-surgical stroke, younger age at stroke appears to be associated with poorer neuropsychological outcome following surgery [59].

The role of neuropsychology in surgical decision making.

Cerebral revascularisation (aka 'bypass') surgery is an important treatment for MMD in children because it is the only intervention that has been consistently demonstrated to improve the natural history of the condition [3, 60]. Revascularisation surgery, however, is highly invasive and carries a small, but not negligible, risk of peri-operative stroke and mortality [61, 62, 63]. Therefore, decision making regarding 1) which children should be operated and 2) which operation to perform is critical. These critical decisions have traditionally been informed by clinical neurological assessment

(history of lateralizing transient ischaemic attacks and/or strokes) and radiological evaluation (MRI, catheter angiography, tests of cerebrovascular reserve). These evaluations tend to concentrate on middle cerebral artery (MCA) perfusion and Rolandic function – i.e. lateralizing motor and sensory symptoms – and the revascularisation surgery aims to improve blood supply to the posterior frontal region to protect this region.

However, there is increasing realisation that, in addition to these clinically overt motor and sensory manifestations, the chronic hypoperfusion of MMD may cause more subtle cognitive and particularly executive dysfunction in children [9, 41, 64, 65]. Because MMD traditionally affects the entire anterior cerebral circulation, it is plausible that these effects are due to anterior cerebral artery (ACA) stenosis as this artery supplies most of the 'executive' regions of the frontal lobes. Traditional surgical techniques do not address hypoperfusion in the ACA territory, though several groups have now described methods of augmenting blood supply to this region [64, 66].

Therefore, it seems logical to include detailed neuropsychological analysis as the third component (along with traditional neurological and radiological evaluation) of pre-surgical assessment for children with MMD. Children showing executive or cognitive dysfunction commensurate with neuroradiological evidence of hypoperfusion of ACA territories are likely to benefit from targeted revascularisation as part of their surgical treatment. Careful post-operative neuropsychological evaluation is essential to monitor the outcome of surgery.

Case Study.

The case of a patient, LS, illustrates the important contribution of neuropsychology to surgical planning and evaluation in children with MMD. LS was born at full-term by emergency caesarean section due to fetal distress, weighing 7 lbs. There were no complications in the neonatal period, though LS was late in achieving developmental milestones, including sitting, crawling, and walking. He presented with seizures at six months of age, and brain imaging revealed an acute ischemic stroke affecting the right frontoparietal cortex with some extension into the temporal lobe. Further investigation led to a diagnosis of bilateral MMD, and he underwent bilateral revascularization surgery at 9 months of age. He experienced another arterial ischemic stroke a day

after surgery, with left middle cerebral artery involvement. At 13 years of age, EEG revealed seizure activity, and he was started on topiramate.

LS has undergone four neuropsychological assessments to track his development and identify any neurocognitive concerns that may emerge over time. An initial neuropsychological assessment at 3 years of age found that LS's school readiness skills and basic language functions were developing as expected for his age. However, his complex language skills were below age expectations. Concerns were also noted regarding his attention, impulsivity, and poor visual-spatial skills. This baseline assessment was valuable in evaluating the early impact of the stroke and highlighting areas of cognitive vulnerability for the surgical team to consider.

A second follow-up neuropsychological assessment was carried out at 5 years of age and revealed strong language and verbal reasoning skills. However, LS's visual-spatial and visual-motor skills remained below age expectations. Attention and impulsivity were mildly challenging, though LS did not meet the full diagnostic criteria for ADHD. LS's cognitive profile remained stable and consistent at his third neuropsychological assessment at 10 years of age, though some new subtle challenges with multi-tasking, planning, and error monitoring were noted. These follow-up assessments offered valuable insights into LS's cognitive development and reassured the medical team that his brain was receiving adequate blood flow to support this development. The emerging issues with attention and executive function were in line with predictions from his baseline assessment and did not indicate any new or unexpected problems. Thus the neuropsychological evaluation can help distinguish between cognitive findings that are stable versus those that are dynamic and more closely associated with blood flow sufficiency. At 15 years of age, LS's follow-up neuroimaging indicated progression of MMD, largely in the posterior circulation, which is an indicator of poor functional outcome [66] and increased risk for perioperative stroke. He additionally presented with nocturnal apneic episodes, which were subsequently diagnosed as seizures; topiramate was commenced with a good response. LS was referred for a follow-up neuropsychological assessment, which revealed much more pronounced challenges with attention regulation, executive functioning, working memory, and encoding of new information. Not only were there declines in standard scores from his previous assessment at 10 years of age, but some raw scores diminished as well – an indicator of true cognitive decline – and this was predominantly

noted for attention and working memory tests. Moreover, LS was observably more distracted, fidgety, and impulsive than he was in his prior assessment. These findings were seen as evidence of the functional impact of disease progression, strengthening the case for a second surgery. The neuropsychological data clearly showed that the changes observed in neuroimaging were linked to negative functional outcomes for the patient. Selected neuropsychological test scores from LS's last three neuropsychological assessments (ages 8, 10, and 15 years) are presented in Table 1.

Posterior circulation involvement in MMD is common; it is an adverse prognostic indicator pertaining to poorer functional outcomes. This is thought to be due to impaired collateral circulation [67, 68]. Often, children with posterior circulation involvement have irreversible brain injury at presentation, which poses a challenge in truly ascertaining whether the functional outcome is additionally affected by comorbidities, natural progression of disease, or epigenetic factors [68]. Subsequent CVR studies in this patient demonstrated a right frontal and interhemispheric vulnerability in keeping with disease progression, additionally reflected in the repeat catheter angiogram and neuropsychology assessment. The neuropsychological evaluation is particularly essential in situations where CVR studies are not available or cannot be obtained, because the cognitive profile can provide evidence that the disease is having a negative functional impact for the patient. This case highlights the importance of timely, harmonized multicomponent assessments for surgical decision-making in MMD.

Conclusions and Future Directions.

MMD can result in a range of cognitive and emotional changes, either as a consequence of neurological complications (e.g. stroke), or as a symptom of progressive stenosis of the underlying disease itself. We have provided a review of ways in which neuropsychological assessment can aide in both clinical care and research of pediatric MMD. Studying neuropsychological function in children with MMD provides important information on the extent and nature of these cognitive changes or deficits as well as their impact on daily functioning and cognitive, socio-emotional and academic development. As shown in this review, the primary cognitive changes may be found on measures sensitive to CNS injury, including attention, working memory, processing speed (often summarized as executive dysfunction), and, to some extent, nonverbal/perceptual reasoning.

However, larger scale studies are needed to confirm these effects. In general, intellectual ability is preserved, although findings vary largely in definition of what constitutes *impairment* and by comorbid conditions or complications of the disease. While variability in measurement, samples, and disease factors have limited definitive cognitive findings to date, neuropsychological assessment, if conducted uniformly, provides an important opportunity to study outcome in a more fine-tuned manner than neurologic examination alone.

In addition, neuropsychological studies can aide in tailoring treatment approaches, by assessing surgical intervention efficacy. We have highlighted the importance of neuropsychological assessment as an integral part of presurgical evaluation to inform treatment decisions, as well as to assess cognitive outcomes after surgery. Surgical interventions such as revascularization are performed to restore cerebral blood flow, and neuropsychological assessment pre-post surgery can elucidate the efficacy of these interventions in improving cognitive outcome. Furthermore, neuropsychological assessment can aide in predicting long-term prognosis and outcomes. A better understanding of the cognitive and behavioral trajectories of the disease can guide clinicians in developing appropriate and more tailored intervention plans (medical, rehabilitative, educational, psychological).

Importantly, research focused on neuropsychological outcomes in pediatric MMD can enhance our understanding of the extent of cognitive deficits, mechanisms and factors leading to cognitive or emotional impairment (e.g. disease itself, pre-existing learning or emotional disorders, familial and social factors), and hence inform the development of interventions aimed at improving long-term development in children and adolescents with MMD.

Along these lines, we outline the following priorities for future studies:

(5) *Prospective* studies using *uniform assessment tools or standardized protocols* to measure cognitive and behavioral function to allow for more definitive interpretation of cognitive findings. The literature to date provides primarily retrospective clinical data that uses a range of assessment tools, or different versions of the same test, that can introduce significant variability in findings, and hence limit interpretability. In particular, many studies have used measures of intellectual function (e.g. Wechsler Scales) as their main outcome,

relying on index scores that are comprised of notably different subtests supposedly measuring the same or a similar construct from one version to another, making direct comparison or combining of this data difficult. Using the same tests across all participants would eliminate this variation. An approach that measures cognitive domains or neurobehavioral constructs by area of function will be more fruitful – such as outlined in the Research Domain Criteria Initiative of the National Institutes of Mental Health https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc and in the NIH Common Data Elements.

In addition, several studies to date are based on historical samples that were ascertained often over a long timeframe. Changes over time in treatment protocols, normative population data, educational variation, etc. can all influence findings and hence limit their interpretability. Shorter study duration with prospective samples can counteract this limitation and improve interpretation of true cognitive changes/deficits vs. those introduced by design limitations. Importantly, study designs will need to include a standardized definition of cognitive "impairment" (e.g. true impairment or meaningful clinical difference vs. below average performance or purely statistical difference).

(2) *Large multi-centre studies* to increase sample size and be better able to investigate effects of MMD itself vs. that of neurological complication (TIA, stroke, seizure) on cognitive function. Because MMD is fortunately a rare disease, many studies to date have been plagued by small sample size, wide age ranges, and variability in measurement and study population (most notably patients with or without stroke), with sample sizes for subgroups of patients often in the single digits. This significantly reduces power of observed effects; findings from such studies are inconclusive at best and carry the risk to over- or underestimate cognitive deficits. Large-scale multi-site or multi-center efforts such as the International Pediatric Stroke Study (IPSS) provide an optimal background to mitigate these risks and homogenize study design and procedures.

(3) Careful *pre- and especially post-operative assessment* to study the influence of revascularization treatment on cognitive function. Integration of neuropsychological assessment data with that obtained from other diagnostic modalities, including measures of CBF, CVR, gray and

white matter structural (volumetric MRI, DWI) and functional changes (fMRI, rs-fMRI) will be critical for a more comprehensive picture of disease mechanisms and treatment outcomes. This should also include genetic studies and other phenotyping data of the disease (e.g. inflammatory/immune profiles) that have shown to be associated with cognition and emotional function in other conditions and have the potential to influence cognitive and emotional development.

(4) *Longitudinal neuropsychological assessment* at specified time points (e.g. yearly) to track development over time and aide in detection of cognitive changes as a function of progressive stenosis informing medical treatments, as well as facilitate prognostication of functional outcomes (educational, vocational, mental health) long term.

(5) More rigorous investigation of *determinants* of cognitive and emotional function to determine the cause of or their influence on cognitive deficits and/or deterioration. This should include medical (e.g. ischemia, seizure, comorbid medial conditions) and biomarker factors (e.g. genetic, immune) just as much as constitutional (e.g. pre-existing learning, intellectual, or behavioral disorders), familial (e.g. family history of learning or psychiatric disorders), and environmental factors (e.g. socio-economic, educational, neighborhood and intervention resources).

In summary, collaborative efforts are needed at a larger scale within the pediatric community to integrate expertise from neuropsychology with that of neurology, neurosurgery, neuroradiology, genetics, and other medical disciplines with the common goal to more rigorously study and provide care for children with MMD across development.

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Table 1: Factors that impact neuropsychological outcome in pediatric MMD.

Factor	Impact on Neuropsychological Outcomes
Age at Onset	Younger age at disease onset is linked to poorer outcomes
Duration of Symptoms	Longer symptom duration (>3 months [33]) before treatment is associated with greater impairments
Severity of Ischemic Events	More severe or recurrent ischemic events are associated with greater cognitive deficits
Posterior circulation involvement	MMD that extends to involve the posterior circulation has been associated with worse functional outcomes
Clinical Stroke	Stroke occurrence is associated with greater cognitive deficits
Seizure Disorder	Patients with seizure disorders are more likely to have poor cognitive outcome
Location of Brain Lesions	Lesions in frontotemporal areas appear to be particularly associated with cognitive impairments
Associated Conditions	Conditions like NF1, sickle cell disease, or Down syndrome can worsen cognitive outcomes
Surgical Intervention	Timely revascularization can improve outcomes, but results vary

Table 2 Neuropsychological Outcomes in Pediatric MMD

Domain	Symptoms and examples
Intellectual ability	Lower verbal comprehension and perceptual reasoning skills, particularly for those with early onset of the disease and/or stroke
Attention	Lower performance on standardized attention tests Everyday problems with attention and concentration based on parent/teacher reports
Working memory	Difficulty with mental manipulation of information based on standardized test performance and parent/teacher reports
Processing speed	Longer completion times for speeded tasks (verbal, visual, and motor)
Mental health	Increased likelihood of experiencing symptoms of anxiety, low mood, and somatic preoccupation
Quality of Life	Motor deficits, stress of chronic illness, cognitive impairments, missed school due to appointments, and mental health issues all reduce quality of life

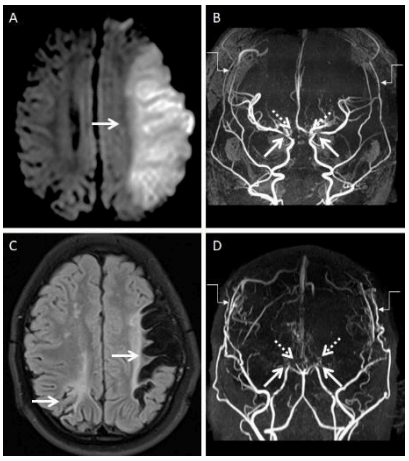
Table 3: Neuropsychological test scores from LS's assessments at 8, 10, and 15 years of age

Test Name	Skills Measured	8 years	10 years	15 years
COGNITION			**Standard/Scaled Scores (Percentile)**	
WISC-V Verbal Comprehension Index	Index of verbal comprehension skills	106 (66th)	106 (66th)	90 (25th)
WISC-V Visual-Spatial Index	Index of visual-spatial skills	66 (1st)	58 (<1st)	56 (<1st)
WISC-V Fluid Reasoning Index	Ability to reason with unfamiliar information in novel ways	103 (58th)	94 (34th)	94 (34th)
WISC-V Working Memory Index	Index of attention and mental manipulation skills	93 (32nd)	105 (63rd)	83 (13th)
WISC-V Processing Speed Index	Index of visuomotor processing speed	80 (9th)	75 (5th)	62 (1st)
WISC-V Full Scale IQ	Overall intellectual abilities	91 (27th)	85 (16th)	74 (4th)
ACADEMICS				
WIAT-III	**Academic achievement**			
Reading Comprehension	Measures untimed reading comprehension of text	106 (66th)	95 (37th)	102 (55th)
Math Problem Solving	Untimed math problem solving skills	111 (77th)	100 (50th)	105 (63rd)
Word Reading	Single word reading skills	111 (77th)	102 (55th)	106 (66th)
Numerical Operations	Measures untimed written math computational skills	100 (50th)	106 (66th)	106 (66th)
EXECUTIVE FUNCTION				
DKEFS Colour Word				
Colour Naming	Processing speed	12 (75th)	10 (50th)	7 (16th)
Word Naming	Processing speed	12 (75th)	12 (75th)	8 (25th)

Inhibition	Inhibitory control and processing speed	7 (16th)	10 (50th)	5 (5th)
Inhibition/Switching	Inhibitory control, set shifting, processing speed	11 (63rd)	11 (63rd)	5 (5th)
DKEFS Trail Making				
Visual Scanning	Visual scanning speed and accuracy	9 (37th)	6 (9th)	2 (4th)
Number Sequencing	Attention and visual speed	6 (9th)	8 (25th)	3 (1st)
Letter Sequencing	Attention and visual speed	6 (9th)	9 (37th)	3 (1st)
Number-Letter Switching	Set shifting, attention, and visual speed	3 (1st)	5 (5th)	3 (1st)
Motor Speed	Motor speed	5 (5th)	7 (16th)	3 (1st)
WCST	Flexible problem solving and hypothesis testing	n/a		
Categories Achieved		n/a	>16th (6)	<1st (2)
Total Errors		n/a	98 (45th)	3 (1st)
ATTENTION				
CPT-3	**Test of attention, vigilance, and inhibitory control**	2 impaired scores	1 impaired score	5 impaired scored

Abbreviations: WISC-V: Wechsler Intelligence Scale for Children – version V; WIAT-III: Wechsler Individual Achievement Test -3rd Edition; DKEFS: Delis Kaplan Executive Function Systems, WCST: Wisconsin Card Sorting Test; CPT-3: Continuous Performance Test – 3rd Edition.

Figure 1: Brain imaging for patient LS



MR imaging (A, B) at 7 months of age. Axial diffusion weighted imaging (DWI; A) reveals a large wedge-shaped area of restricted diffusion involving the left MCA in keeping with an acute infarct. Maximum intensity projection (MIP) of the time-of-flight MR angiogram (TOF-MRA) through the anterior circulation shows severe steno-occlusion along the terminal ICAs, extending into the ostia of the M1-MCAs on both sides (solid arrows). Severe steno-occlusion of the A1-ACAs is also noted (worse on the right; dotted arrows). Note the prominence of the superficial temporal arteries related to the pial synangiosis (stepped arrows). Follow up imaging (C, D) at 14 years of age. Axial FLAIR image © areas of encephalomalacia in the the both the MCA territories (left larger than right) (solid arrow). MIP of the TOF-MRA (D) reveals interval marked progression of the ICA stenoses with no distal flow within the ACA or MCAs. Additionally, there is severe steno-occlusion along the PCAs on both sides (dotted arrows). The previously performed pial synangiosis has remained patent (stepped arrow).

Focus Box: Case Synopsis

- 15 year-old boy with large right frontotemporal AIS at 6 months of age, associated with seizures at onset
- Subsequently diagnosed with moyamoya disease and underwent revascularization at 9 months of age; left MCA stroke one day post-surgery
- Repeated neuropsychological assessments at 3, 5, 10, and 15 years
- Stable deficits in visual-spatial and visual-motor processing noted across all assessments, consistent with the initial right MCA stroke.
- New deficits in attention, working memory, and executive functioning noted on the 15-year-old assessment, which were consistent with evidence of disease progression on brain imaging
- Neuropsychological assessment highlighted the functional impact of the disease, providing increased rationale for a second surgery