

# Neuropsychiatric Symptoms of Moyamoya Disease: Considerations for the Clinician

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**Abstract:** Neurocognitive impairment in moyamoya disease is common, under recognized, and potentially devastating. The purpose of this paper is to provide an updated overview on this topic for the practicing clinician. We searched PubMed for keywords including cognitive impairment, neurocognitive dysfunction, and neuropsychological recovery in moyamoya disease. We summarized the literature to provide a concise review of the treatment and management of neuropsychiatric symptoms associated with moyamoya disease. Neuropsychiatric sequelae have conventionally been attributed to chronic cerebral hypoperfusion and/or stroke. Cognitive dysfunction in adults with moyamoya disease is most commonly in the form of impaired executive function, whereas intelligence is the predominant impairment in children with moyamoya disease. Pharmacotherapy for treatment of the neuropsychiatric symptoms associated with moyamoya disease is appropriate and can improve quality of life; however, careful consideration is needed to avoid adverse cerebrovascular events. It remains unclear as to whether surgical revascularization improves or stabilizes cognitive performance and outcomes. Additional prospective studies are warranted to better understand the long-term impact of revascularization on cognitive functioning in moyamoya disease.

**Keywords:** moyamoya disease, moyamoya angiopathy-associated cognitive dysfunction, neuropsychological outcomes, neuropsychiatric comorbidity, revascularization, neurocognitive recovery

## Introduction

Moyamoya disease (MMD) is characterized by progressive narrowing of the intracranial terminal portions of the internal carotid arteries and their proximal branches within the circle of Willis, which, in turn, leads to the formation of abnormal networks of collateral vessels near the stenotic lesions.<sup>1</sup> “Moyamoya” is Japanese for “puff of smoke”, which is how these collateral vessels appeared on early conventional angiography.<sup>1</sup> The incidence of MMD in the United States is 0.086 per 100,00 person-years.<sup>2</sup> It is more prevalent in women than men.<sup>3</sup> MMD has a bimodal age of onset, with a peak in the first decade of life and a second peak at 30–40 years.<sup>4</sup> While the pathophysiology of MMD is not fully understood, MMD is distinct from cerebrovascular steno-occlusive disease due to atherosclerosis.<sup>5</sup> When the characteristic vascular changes of MMD occur in the setting of autoimmune disease, meningitis, brain tumor, Down syndrome, neurofibromatosis type 1, prior radiation, or another identifiable etiology the vasculopathy is termed moyamoya syndrome. Pediatric patients receiving radiation therapy, including proton beam therapy, for brain tumors are at increased risk of developing radiation-induced moyamoya syndrome.<sup>6,7</sup>

MMD predisposes to not only cerebral ischemia (ie, transient ischemic attacks and ischemic strokes) due to compromised cerebral perfusion through the stenotic arteries but also intracerebral hemorrhage as the compensatory collateral vessels are fragile and prone to rupture.<sup>8</sup> Therefore, MMD most often presents with focal neurologic deficits including lateralizing weakness, hemisensory loss, aphasia, dysarthria, visual disturbance, and decreased consciousness.<sup>9,10</sup> Other common symptoms include headache, seizures, and movement disorders.<sup>11,12</sup> MMD can also cause neuropsychiatric sequelae, which are not only common but perhaps some of the most disabling and difficult

symptoms to treat in MMD.<sup>13–15</sup> While rare, MMD has been reported to present with psychosis resembling schizophrenia in both children and adults.<sup>16–18</sup>

## Neurocognitive Dysfunction

MMD has been implicated to cause progressive cognitive decline, with cognitive dysfunction reported in 30% to 73% of patients with MMD.<sup>19,20</sup> The most commonly reported neurocognitive impairments in MMD differ by age group, as summarized in Table 1. Early age at onset and longer duration of disease have been associated with worse cognitive outcomes.<sup>21,22</sup> In pediatric patients with MMD, irreversible ischemic brain damage can have a profound impact on intellectual and functional outcomes.<sup>23,24</sup> Intelligence is the domain most often affected in children with MMD.<sup>25,26</sup> However, impairments in memory, processing speed, and visuospatial functioning have also been observed and reported.<sup>19,20</sup>

In adults with MMD, ischemic and hemorrhagic strokes can obviously contribute to neurocognitive dysfunction.<sup>27–29</sup> However, cognitive impairment has also been observed in adults with MMD in the absence of stroke.<sup>30</sup> MMD has a significant impact on cognition after accounting for not only the presence of stroke but also age, medical comorbidities, and medication effect.<sup>31</sup> In contrast to children with MMD, intelligence is typically normal in adults with MMD while executive dysfunction is most pronounced.<sup>32</sup> Impairments in processing speed, verbal memory, and verbal fluency have also been described.<sup>31</sup>

Utilization of acetylcholinesterase inhibitors such as donepezil, galantamine, and rivastigmine for treatment of cognitive symptoms in patients with MMD remains largely unexplored. However, it should be noted, there are currently no FDA-approved medications for vascular cognitive impairment. Stimulants, on the other hand, should generally be avoided given lack of efficacy data and the risk for hypertension and vasoconstriction.<sup>33</sup>

## Psychiatric Manifestations

It is extremely rare for MMD to present with isolated psychiatric symptoms.<sup>33</sup> The literature on this is limited to a few case reports. In adults, MMD has been discovered in cases of refractory depression and psychosis.<sup>34–36</sup> A 26-year-old woman diagnosed with schizophrenia in the setting of a 15-year history worsening psychotic symptoms after exercise was eventually found to have MMD.<sup>17</sup> Similarly, a 12-year-old boy was diagnosed with MMD after he developed episodes of acute transient psychosis triggered by physical exertion.<sup>37</sup> In another case, an 11-year-old boy experienced sudden onset aggression and abnormal behaviors and was initially diagnosed with schizophrenia; he was only found to have MMD after his psychotic symptoms failed to respond to phenothiazines.<sup>16</sup> A 23-year-old gentleman was diagnosed with schizophrenia in the context of 2-year history of recurrent psychotic episodes complicated by neuroleptic malignant syndrome and severe extrapyramidal side effects to conventional antipsychotic medications and was later diagnosed with MMD.<sup>18</sup> A 16-year-old boy was diagnosed with MMD following a 4-month history of mania without psychotic symptoms; this atypical presentation of mood disorder prompted further diagnostic evaluation and led to the subsequent diagnosis of MMD.<sup>38</sup> These cases highlight the importance of considering alternative etiologies, including MMD, in children and adults with atypical or treatment-resistant psychiatric disorders, particularly if in the setting of marked neuroleptic sensitivity.

**Table 1** The Most Commonly Reported Neurocognitive Impairments in MMD by Age Group

Children	Adults
Intelligence	Executive function
Processing speed	Memory
Attention	Language
Visuospatial functioning	Processing speed

Depression and anxiety are the most common psychiatric comorbidities in MMD.<sup>33</sup> Up to 64% of adults with MMD endorse depressive symptoms.<sup>31</sup> While stroke can significantly impact emotional adjustment, even in the absence of stroke, 28% of adults with MMD experience clinically significant depression, 29% experience clinically significant anxiety, and 33% experience significant behavioral abnormalities and apathy.<sup>30</sup> Irritability, emotional lability, hyperactivity, and inattention have been observed in children with MMD, even in the absence of an established mood disorder.<sup>39</sup>

While psychotropic medications are frequently utilized, to date there have been no studies dedicated to the medical treatment of psychiatric symptoms in patients with MMD. No absolute contraindications exist for any individual psychotropic medication; however, careful consideration for a medication's ability to alter cerebral hemodynamics, lower the seizure threshold, and contribute to confusion or paradoxical disinhibition is necessary.<sup>33</sup> Lamotrigine and divalproex sodium have been utilized in MMD to reduce irritability and impulsivity while limiting some of the cognitive and behavioral side effects associated with older mood stabilizers.<sup>36,38,40</sup> While antidepressants are considered to be relatively safe for MMD-associated anxiety and depression, treatment response is variable.<sup>41</sup> Selective serotonin reuptake inhibitors, such as sertraline, are favored given their relative lack of anticholinergic activity as compared to tricyclic antidepressants and because they are less likely to affect blood pressure as compared to serotonin-norepinephrine reuptake inhibitors.<sup>33</sup> Benzodiazepines appear to be safe for treatment of acute MMD-related anxiety and agitation, but long-term monotherapy is not recommended given the risk of tolerance and paradoxical disinhibition.<sup>31,42</sup> While antipsychotic agents are reported to be effective in reducing hallucinations and paranoia in MMD, it should be noted that patients with MMD are typically highly sensitive to neuroleptics.<sup>16,37,38</sup> If necessary, second-generation antipsychotics such as quetiapine are favored over first-generation agents, given the lower risk of adverse extrapyramidal side effects.<sup>33</sup>

## Pathophysiology of Neuropsychiatric Symptoms

Stroke is a well-described cause of cognitive and affective disorders.<sup>43,44</sup> However, even in the absence of stroke, increased burden of white matter hyperintensities caused by ischemic microvascular disease has been correlated with reductions in global cognition, memory, semantic memory, and executive function – particularly in adult women with MMD.<sup>45,46</sup> Perhaps not surprisingly, then, the particular pattern of neurocognitive impairment observed in MMD is reminiscent of vascular cognitive impairment due to diffuse small vessel disease.<sup>31</sup> Other studies have shown a lack of association between severity of infarcts and white matter disease and cognitive impairment.<sup>20,31,47</sup> Alternatively, long-standing cerebral hypoperfusion has been linked to MMD-associated cognitive disorders.<sup>30,48</sup> It has been demonstrated that radiographic evidence of frontal lobe hypoperfusion is associated with executive dysfunction in adults with MMD.<sup>49,50</sup> Similarly, decreased cerebral blood flow has been correlated with reduced intelligence in children with MMD.<sup>51</sup> This has important implications for neurosurgical revascularization, which is performed to restore cerebral blood flow and improve cerebral perfusion.

## Impact of Revascularization on Neurocognitive Outcomes

Surgical revascularization via direct or indirect bypass is the most successful treatment to improve cerebral hemodynamics and reduce the risk of stroke in MMD.<sup>52–54</sup> Surgical candidacy and the most appropriate bypass technique are determined on a case-by-case basis taking into account the patient's age, neurologic status, and preoperative imaging.<sup>55</sup> However, prospective studies on the impact of revascularization on cognitive function in MMD are limited as summarized in Table 2. There is some evidence to suggest revascularization may improve cognitive function in adults and intellectual prognosis in children.<sup>22,56,57</sup> Intelligence scores in children typically stabilize after surgical revascularization.<sup>24,58–60</sup> In children with MMD who had improved intelligence following revascularization, this corresponded with improvement in cerebral blood flow.<sup>58</sup> In one study, in the absence of a major preoperative stroke, all pediatric patients who underwent bypass surgery had a normal or borderline intelligence quotient at 9.5 years post-revascularization follow-up.<sup>61</sup> One prospective study demonstrated improved memory function after surgery.<sup>62</sup> In another prospective study, children showed a significant improvement in language functioning following revascularization.<sup>63</sup> Significant improvement in verbal memory was observed following indirect revascularization in a third prospective study in children with MMD.<sup>64</sup> Improvement in frontal lobe functions, including attention, have also been observed following indirect revascularization in children with MMD.<sup>65</sup> Poor cognitive outcomes in children have been attributed to completed stroke prior to revascularization surgery and small

**Table 2** Literature Review of Prospective Studies on Cognitive Outcomes Following Surgical Revascularization in MMD

Authors	Size	Age	Population	Surgical Revascularization	Tested Neurocognitive Domains	Postoperative Follow-Up Testing	Outcomes
Lee <sup>62</sup>	65	Children	Korea	EDAS and EDPS	Intelligence and visual memory	10–55 months	Significant improvement in performance IQ and visual memory.
Baek <sup>67</sup>	5	Adults	Korea	STA-MCA bypass	Attention, working memory, verbal memory, visuospatial function and visual memory, and language	3 months	Significant improvement in memory.
Zeifert <sup>68</sup>	84	Adults	United States	STA-MCA bypass	Intelligence, memory, executive function, expressive language, processing speed, and depression	6 months	Cognitive improvement – 11% Improved depression – 19% Cognitive decline – 14% Worsened depression – 11% No cognitive change – 75% Unchanged depression – 70%
Yanagihar <sup>69</sup>	32	Adults	Japan	STA-MCA bypass	Intelligence, memory, visuospatial function, and visual memory	2 months	Cognitive improvement – 31% Cognitive decline – 44% No significant change – 25%
Kim <sup>65</sup>	55	Children	Korea	EDAS	Intelligence, memory, visuospatial function, executive function, and attention	10 months	Significant improvement in performance IQ, perceptual organization, memory, executive function, and visual attention.
Kazumata <sup>70</sup>	25	Adults	Japan	STA-MCA bypass and EDAMS	Intelligence, memory, verbal comprehension, perceptual organization, working memory, executive function, attention, and processing speed	12–44 months	Significant improvement in the full-scale IQ, performance IQ, perceptual organization, processing speed, and attention-related cognition.
Ando <sup>57</sup>	17	Adults	Japan	STA-MCA bypass and EDMS	Intelligence, memory, visuospatial function and visual memory	6 months	Cognitive improvement – 35%
Hsu <sup>64</sup>	23	Children	Taiwan	Bilateral EDAS	Intelligence, verbal comprehension, perceptual organization, working memory, progressing speed, verbal learning and memory, and executive function	6+ months (average 22 months)	Significant improvement in verbal memory function.
Deckers <sup>63</sup>	32	Adults (11) and children (21)	Netherlands	STA-MCA bypass and EDMS	Intelligence, memory, working memory, language, attention and executive function, processing speed, and visuospatial function	10–27 months	Significant improvement in language in children. In adults, none of the domain scores significantly changed after surgery.

**Abbreviations:** IQ, intelligence quotient; STA, superficial temporal artery; MCA, middle cerebral artery; STA-MCA bypass, superficial temporal artery to middle cerebral artery anastomosis; EDMS, encephalo-duro-myo-synangiosis; EDPS, encephalo-duro-periosteal-synangiosis; EDAMS, encephalo-duro-arterio-myo-synangiosis.

craniotomy in indirect surgical bypass.<sup>22</sup> A retrospective review of moyamoya vasculopathy associated with a group neurodevelopmental disorders known as RASopathies suggested patients with neurofibromatosis type 1 may benefit from prophylactic surgical revascularization in order to prevent future cognitive impairment due to progression of the vasculopathy, particularly if exposed to radiation therapy.<sup>7,66</sup>

Revascularization surgery may improve processing speed and attention in adults with MMD.<sup>70</sup> One small prospective study showed remarkable improvement in memory following direct bypass (superficial temporal artery-to-middle cerebral artery anastomosis).<sup>67</sup> There are also reports of more global cognitive improvement following revascularization correlating with improved cerebral perfusion of the affected hemisphere.<sup>71,72</sup> However, acutely, cerebral hyperfusion following bypass surgery impairs cognitive function in adults with symptomatic ischemic MMD and misery perfusion, whereas increased cerebral blood flow in the chronic stage, months after bypass surgery, improves cognitive function.<sup>69</sup> The improvement in cognitive function after bypass surgery may ultimately relate to recovery of cerebral oxygen metabolism.<sup>73</sup> As for the affective symptoms, six months following revascularization, 19% of adults with MMD reported

improved depression while the large majority, 70%, experienced no change in depressive symptoms.<sup>68</sup> There is no data on the effects of revascularization on psychotic symptoms in patients with comorbid MMD and schizophrenia.

## Conclusion

Neuropsychiatric symptoms are common yet complex sequelae of MMD. Given the progressive nature of MMD, it is important clinicians are familiar with MMD-associated cognitive and affective symptoms, as early recognition and treatment can significantly improve quality of life. Surgical revascularization is effective for reducing the risk of future strokes in patients with MMD and may improve cognitive outcomes; however, additional prospective studies are needed to better characterize long-term neuropsychiatric outcomes following revascularization.

## Disclosure

The authors report no conflicts of interest in this work.

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