Chapter

Neuropsychology of Moyamoya Disease

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Abstract

Moyamoya disease (MMD) is an occlusive cerebrovascular disease characterized by progressive stenosis or occlusion in the terminal portion of the bilateral internal carotid arteries, and affect both children and adults. In this pathology, which presents itself through ischemia or cerebral hemorrhage, an unusual compensatory vascular network (moyamoya vessels) develops at the brain's base in the form of collateral channels. MMD can present clinically as hemiparesis, dysarthria, aphasia, headache, seizures, visual deficits, syncope, or personality changes. Neuropsychologically, and even in the absence of obvious stroke, patients often present impaired attention, memory, behavior, and executive functions. This book chapter reviews the current literature regarding the neuropsychological deficits of MMD both in children and adults.

Keywords: Moyamoya disease, neuropsychology, cognitive outcome, pediatric moyamoya

1. Introduction

Moyamoya disease (MMD) is a rare vascular syndrome most commonly found among the Japanese and other Asiatic peoples, its is chareacterized by the angiographic appearance of widespread cerebral collaterals due to occlusion of one or both internal carotid arteries [1]. The aetiology is unclear, but is perhaps related to an acquired lesion of the blood vessels at the brain's base. MMD was first described in Japan in 1957 by Takeuchi and Shimizu [2]. Although it is more common in Japan, clinical cases of the pathology have been reported in other parts of the world [3]. The incidence of MMD peaks in two age groups: int those around 4 years-old (pediatric MoyaMoya Disease, pMMD), and those in their 40s (adult MoyaMoya Disease, aMMD) [4]. There are almost twice as many female patients as there are male [5]. MMD is the most common pediatric cerebrovascular disorder in Japan, with a prevalence of about three cases per 100,000 children [6], while the incidence in Europe is approximately one- tenth of that observed in Japan [7]. A 2005 review result suggest an incidence of 0.086 cases per 100,000 people in the U.S. [8]. There are two main etiological categories of symptoms: those due to cerebral ischemia (stroke, transient ischemic attacks, and seizures, more frequent in pMMD) [9], and hemorrhagic symptoms due to the secondary effects of compensatory mechanisms that are triggered in response to the ischemia (hemorrhage of fragile collateral vessels and headache due to dilated transdural vessels, more frequent in aMMD). Individual variations in the degree of arterial involvement, the progression of stenosis, the regions of the ischemic cortex, and the response to reduced blood supply

explain the wide range of clinical presentations of the disease [10]. This chapter reviews the literature on moyamoya disease, specifically on neuropsychological aspects, in both pediatric and adult populations.

2. Pediatric Moyamoya disease (pMMD)

During the onset of Pediatric Moyamoya disease (pMMD), progressive occlusion occurs at the end of the intracranial internal carotid artery, and compensatory net-like abnormal vessels develop in the skull base, generating several clinical symptoms. These collateral vessels mimic a "puff of smoke" when revealed by and angiogram [11]. pMMD can affect both children and adults, but pediatric patients exhibit distinct clinical features, and treatment and prognosies differ from those in adult patients [12].

The distinctive clinical profile of pMMD includes headache, cognitive impairment, hypertension, temporary or permanent blindness, hemiplegia, general paresis of the insane, loss of sensation, aphasia, and mechanisms related to ischemia in the frontal, parietal, and temporal lobes [13, 14]. Children are at a higher risk of suffering Moyamoya Disease (MMD) and the condition is more severe in young children, especially those under four years, in whom the prognosis is often poor [15]. In children, the disease mainly manifests as ischemia, while bleeding is the primary symptom in adults [16]. Despite normal general intellectual functioning, some children with moyamoya disease exhibit cognitive deterioration, primarily learning disability, attention deficit, episodic memory, slow processing speed and neurological abnormalities [17]. Cognitive impairment is not generalized in all children, since some show neuropsychological alterations and others do not. The worst prognosis tends to be seen in children who have had a stroke or cerebral infarction. In contrast, Transient Ischemic Attack (TIA) usually has a better cognitive prognosis [18, 19], with only 15% of patients exhibiting single-domain impairment and 23% showing multiple cognitive domains to be affected after a TIA [20]. The affected area usually includes the terminal portions of the Internal Carotid Arteries (ICAs) and the proximal areas of the anterior or middle cerebral arteries, although Posterior Cerebral Arteries (PCAs) can be affected in some cases [21]. The pattern of cognitive dysfunction is often associated with lesions in frontotemporal areas, with young age [22] and young onset of the disease [23] proving to be the main risk factors for poor neuropsychological outcomes.

Moyamoya disease is characterized by progressive cerebrovascular stenosis with recurrent cerebral ischemic events. TIA attacks are often associated with hyperventilation in children with moyamoya, pointing to hypoperfusion rather than thrombotic vaso-occlusion as a prominent mechanism. The patterns of ischemia and severity of steno-occlusive disease in such children may hold clues to these mechanisms. In this sense, Rafay et al. studied twenty children (between 1 month to 18 years) with MMD in a neuroradiological MRI and angiography [24]. The initial clinical presentation revealed neurological deficits in 17, recurrent TIA in 7, headache in 8, seizures in 8, and alteration in consciousness in 4 children. Infarcts were bilateral in 13 (65%) children (ischemia alone was observed in 14, ischemic stroke with hemorrhagic transformation in two, and primary hemorrhage in two). Infarcts were cortical and/or subcortical in 13 (65%), both deep and cortical watershed in 11 (55%), and cortical watershed alone in 5 (25%) children. The predominant vascular territory involved was the middle cerebral artery. The internal carotid arterial system was involved in all cases, with stage IV being the most frequent angiographic stage. The authors concluded that ischemic injury in deep watershed zones is common in pMMD and may reflect non–vaso-occlusive ischemic mechanisms. They

also concluded that the location and severity of the vascular involvement might correlate with various ischemic infarction patterns in MMD and require further study.

In pMMD, a state of chronic ischemia persists in the developing brain, and the possibility of persistent neurologic events and progressive intellectual impairment has been recognized, with no significant correlation detected between age at onset and intellectual quotient (I.Q.) when patients have been monitored from childhood into adulthood [25]. I.Q. begins to decrease after the onset of pMMD, and often stabilizes ten years later [26]. Some studies have reported that 10–30% of patients experience difficulties in school life due to intellectual impairment [27–29]. An analysis of 410 consecutive cases revealed that the overall clinical outcome was excellent in 66%, good in 15%, fair in 15%, and poor in 4% of the patients. According to these results, 81% of the patients had a favorable clinical outcome (excellent or good). Multivariate analyses revealed that infarction on presentation was associated with an unfavorable clinical outcome and decreased vascular reserve only on single-photon emission computerized tomography, with favorable clinical outcome. These results indicate that an early diagnosis and active intervention before irreversible hemodynamic changes take place are essential to achieve a favorable clinical outcome in children with MMD [30]. In 2016 Titsworth, Scott and Smith published a U.S.A. national analysis of 2454 pMMD admissions and the effect of hospital volume on stroke outcome. They concluded that high-volume centres provide significantly improved care and reduced mortality in pediatric moyamoya patients, with the most substantial benefit observed in admissions for surgical revascularization [31].

Tho-Calvi et al. described the characteristics and clinical course of a large UK cohort (eighty-eight) of children with moyamoya attended in multiple centres. When they examined prognostic predictors they concluded that pMMD is associated with multiple recurrences, progressive arteriopathy, and poor outcome in half of patients, especially those who present with arterial ischemic stroke (AIS) and posterior circulation involvement [32]. Cooper et al. evaluated the relationship between neurologic outcome one month after diagnosis of pediatric AIS and motor and adaptive behaviour outcomes at 12 months. Their prospective longitudinal observational cohort study recruited sixty-four children (27 neonates, 19 preschool, and 18 school-aged) from a single children's tertiary hospital who were diagnosed with first AIS between December 2007 and November 2013. Neurologic impairment was evaluated at four time points following AIS diagnosis (at 0 months and 1, 6, and 12 months) using the Pediatric Stroke Outcome Measure (PSOM) or the Recovery and Recurrence Questionnaire. Motor function and adaptive behaviour were assessed at 12 months using standardized measures. Children were grouped for analysis according to age at diagnosis (neonates vs preschool vs school-aged). They concluded that PSOM has value as a predictive tool concerning motor and adaptive behavior when it is used one month after the first AIS has been diagnosed, with variation according to age [33]. In the same line, Funaki, Takahashi and Miyamoto reviewed the long-term outcome of pMMD, focusing on late cerebrovascular events and social outcome of pediatric patients once they reach adulthood. Long-term follow-up data for Asian populations suggested that the incidence of de novo hemorrhage increased at the age of 20 or later, even when 10 years has passed since bypass surgery. According to these authors, social adaptation difficulty, possibly related to cognitive impairment caused by frontal ischemia, continues in 10–20% of patients after they reach adulthood, even though no significant disability is evident in daily life [34].

The pathogenesis of pMMD is unknown. It can result in progressive, irreversible brain function impairment, and an earlier onset corresponds with a worse neuropsychological prognosis. Therefore, evidence-based medical treatment of affected

children at an early stage is highly recommended. These treatments consist of direct (intra and extracranial vascular reconstructions, usually involving superficial temporal artery-middle cerebral artery anastomosis) or indirect (multiple burr-hole surgery, encephalomyosynangiosis, and encephaloduroarteriosynangiosis) neurosurgical procedures. This surgery aims to improve the cognitive prognosis, increase the quality of life and reduce the risk of ischemic diseases thanks to improved cerebral hemodynamics [35]. Therefore, compared to adult patients, children with MMD can enjoy a good prognosis if diagnosis and surgical treatment are achieved as soon as possible [36].

In 2018, Kim et al. studied the neuropsychological impacts of indirect revascularization (pre-postoperative) in fifty-five children with MMD. The study was carried out to show that temporal encephaloduroarteriosynangiosis (EDAS) has a positive neuropsychological impact on pMMD patients [37]. The mean age at preoperative evaluation was 9.5 years and the mean age at postoperative evaluation was 10.4. The average interval between initial and follow-up test was ten months. K-WISC-III, the Rey-Kim memory test, the Children's Color Trails Test (CCTT), the Wisconsin Card Sorting Test (WCST), and the Advanced Test of Attention (ATA) were employed to assess patient's neurocognitive profile. Prior to the operation, patients displayed a 54.2% inattention deficit, but only around a 2.5% deficit in verbal memory recall function. After surgery there was a significant increase in performance I.Q. and an improvement of approximately ten scores in memory quotient (M.Q.). The study also reported parietal activation following surgical treatment, which enhanced the ability to interpret visual materials and, which enchanced the ability to interpret visual materials, record, and retrieve visual information. Interestingly, there was a significant improvement in performance in the WCST and CCTT, wich measured prefrontal executive function. Concerning failure to maintain set, no significant postoperative improvements were evident. However, simple and selective visual attention was significantly improved post-operation. The results of neuropsychological field comparison testifies to the effectiveness of temporal EDAS in pediatric MMD patients. This surgical intervention enhances the blood flow in operative areas and improves general cerebral function, including that in frontoparietal domains, leading to an overall improvement in the cognitive function impaired by MMD.

In a sample of thirty children with MMD, Williams et al. [38] examined intellectual and executive functioning. They evaluated the impact of moyamoya type, stroke (clinical or silent), vasculopathy laterality, and disease duration on neurocognitive abilities. All the subjects completed Wechsler Intelligence Scales before therapeutic revascularization procedures were carried out. Reports of executive function were obtained from parents and teachers using the Behavior Rating Index of Executive Function. The children scored significantly lower than the test standardization samples on all indices of intelligence and ratings of executive functioning. The patients did not differ by type of moyamoya or history of stroke. Those with bilateral disease and stroke scored significantly lower than those with unilateral disease on overall intellectual function and verbal comprehension measures. According to teacher ratings, deficits in metacognitive executive functions were even more pronounced in bilateral patients than unilateral ones. Finally, the authors concluded that children with MMD are at risk of intellectual and executive problems, which are exacerbated by bilateral disease and clinical stroke history [38].

Gutierrez-Martignon et al. analyzed the cognitive, academic, and emotional profile of a pediatric case of MMD at diagnosis, on three occasions during evolution (from 9 to 15 years old), before surgery, and after EDAS. An evident cognitive decline in visual attention, processing speed (PS), memory, and visual perception was detected between the first and second evaluations during evolution, while the

third evaluation revealed a fluctuating evolution. Executive function, PS, total I.Q., perceptual reasoning, and calculation were most consistently affected during the three assessments, which is consistent with the rest of the literature [39].

The impact on the quality of life of 30 children with MMD (with a median age of 13,5 years) was studied by Ball, Steinberg and Elbers using the Pediatric Quality of Life 4.0 Measurement Model [40]. The authors compared their quality of life to that of chronically ill children and children with stroke in order to better understand the impact of a diagnosis of MMD. The results showed that, even in the absence of stroke, children with moyamoya disease had a lower quality of life than healthy controls and a similar quality of life to chronically ill children and those with non–moyamoya disease stroke. The concluded that hildren with moyamoya disease would benefit from mental health support beyond what a mild physical presentation may indicate.

Assessment of neurological and neuropsychological outcome following revascularization, shows that surgical procedures are effective in halting the neurological progression and results in neuropsychological improvement in some patients [41]. For example, Nehra and Kaur in 2015 reported a male diagnosed with MMD at eight years old and, referred for neuropsychological evaluation at 12 years due to, impaired intellectual functioning with moderate retardation in adaptive social functioning. Two years after psychosocial intervention, the patient showed a remarkable upward trend in his adaptive social functioning and, a jump of 21 I.Q. points in his intellectual functioning [42]. In the same line, Cusin-Lamonica et al. reported the case of a girl of seven years old who suffered two episodes of stroke in the left and right temporal-parietal and left frontal areas that occurred until the age of six years and five months [43]. She presented signs of deterioration in oral and written language (syllabic-alphabetic), non-naming of all graphemes, low arithmetic and writing means, pre-first-grade reading skillsand psycholinguistic delay, and pre-school-level phonological processing skills. The psychological evaluation indicated a satisfactory intellectual level. Revascularization surgery and medication were prescribed.

Considering the infant's brain's developmental plasticity, extrinsic influences, such as psychological interventions for speech-language pathology, coupled with intrinsic influences, can alter the cortical organization and regenerate damaged connections, thus improving the compromised skills of children. A recent systematic review and metaanalysis of pMMD and aMMD, assessed the presence, severity, and nature of cognitive impairments in children and adults with MMD [44]. The authors revised data (collected between 1969 and 2016) pertaining to mean intelligence quotient and standardized z-scores of cognitive tests, and determined percentages of children and adults with cognitive deficits, before and after conservative or surgical treatment. In the case of pMMD, they included 11 studies reporting on a total of 281 children. In children, the median percentage with impaired cognition was 30% (range, 13% to 67%); the median I.Q. was 98 (rang: 71 to 107), and the median z-score was –0.39 for memory, and –0.43 for speed processing. The investigators concluded that many children (30%) with MMD suffer cognitive impairment, with modest to large deficits across various cognitive domains. Thus, extensive prospective studies with a standardized neuropsychological test battery are needed to determine the severity of cognitive impairment and the domains affected.

Recently, Kazumata et al. aimed to investigate cognitive function in the presurgical phase of pediatric patients with MMD with no apparent brain lesions in order to explore an association between cognitive function and cerebral blood flow [45]. They designed a prospective, observational, single-centre study, of 21 children (mean age 10 ± 3.0 years, range 5–14 years) diagnosed with MMD at Hokkaido

University Hospital between 2012 and 2018. A cross-sectional evaluation of intellectual ability was performed using the Wechsler Intelligence Scale for Children. rCBF was measured using [123I] N-isopropyl p-iodoamphetamine/SPECT. The associations among clinical factors, disease severity, regional cerebral blood flow (rCBF), and intelligence test scores were also examined. Results showed that the mean full-scale intelligence quotient (FIQ) was 101.8 ± 12.5 (range 76–125) in children with no apparent brain lesions. A significant difference in the intelligence scale index score was observed most frequently (42.9%) between the working memory index (WMI) and verbal comprehension index. Regional CBF was significantly reduced both in the left and right medial frontal cortices compared to the cerebellum. There was a significant association of rCBF in the left dorsolateral prefrontal cortex (DLPFC) with FIQ, perceptual reasoning index, and processing speed index. Although average intellectual ability was not reduced in the children with MMD, the association of reduced rCBF in the left DLPFC and medial frontal cortex with FIQ, perceptual reasoning and processing speed suggests mild cognitive dysfunction due to cerebral hypoperfusion. Li et al. [46] studied the cognitive performance profile of twenty-one pMMD and its relationship with regional cerebral blood perfusion using arterial spin-labeling magnetic resonance and the Wechsler Intelligence Scale for Children. Results showed that six patients (28.6%) had no cognitive deficits in any index score, while 15 (71.4%) displayed cognitive deficits of varying severity. Nine (42.9%) patients showed overall cognitive impairment, and all cognitive index scores except for Verbal Comprehension Index were significantly lower than the mean scores of normative data than controls of the same age. Perceptual reasoning index was statistically lower in patients with radiologically confirmed cerebral infarction. The area of interest analysis revealed that the left temporal lobe's cerebral blood flow positively correlated with processing speed [46].

The causes of Moyamoya vasculopathy are still unknown, though it has been associated with various genetic conditions, including Neurofibromatosis type 1 (NF1). When moyamoya vasculopathy is present in the context of an associated condition, it is called "moyamoya syndrome," whereas moyamoya pathology in the absence of known associated risk factors is called "moyamoya disease" [47]. Studies have shown that a subset of patients with NF1 experience associated vascular conditions, with moyamoya syndrome representing one of the most common comorbidities. While NF1 and moyamoya syndrome are associated with neurocognitive deficits, very few neuropsychological data ara available for cases of comorbid NF1 and moyamoya syndrome, particularly pre- and post-re-vascularization surgery. To shed light on this topic, DeDios-Sterna and Ventura published in 2019 a single case-study of a bilingual girl of Latin-American descendency with NF1 and moyamoya syndrome, who was assessed pre- (age five years, 9months) and post neurosurgery intervention (age six years, 1month). The pre-neurosurgical cognitive evaluation results documented significant deficits in sustained attention, daily executive functioning, and academic abilities, and the girl met ADHD-combined type criteria. Post- evaluation results revealed generally stable abilities with relative improvements in social, emotional, and behavioral functioning, but a relative decline in visuospatial skills, visual-spatial learning/memory, and executive functioning [48].

Existing literature supports attentional deficits in pMMD, but the clinical presentation of ADHD has rarely been reported. Due to chronic ischemic hypoxic insults to the cerebrum, these patients have poor working memory and experience difficulty sustaining attention, which is thought to be due tohypoperfusion of the frontal lobe. In this sense, Patra and Patnaik reported a clinical case of mental retardation and hyperactivity and inattention five years before the diagnosis of MMD. A definitive diagnosis was made at 11 years of age by means of digital subtraction angiography. The low intellectual functioning and ADHD might have

been explained by the chronic cerebral hypoperfusion caused by bilateral internal carotid artery involvement. The neurosurgical procedure had relieved the patient of headaches, but attention deficits and behavioural problemsremained after the operation and required specialized intervention. The decline in the patient's ADHD scores after the neurosurgical procedure might have been due to the persisting cognitive dysfunction caused by the early onset, bilateral arterial involvement, and chronic cerebral hypoperfusion [49].

In rare cases, Moyamoya syndrome is associated with clinical features of movement disorders, like Tourette's syndrome. In this context the first reported clinical case was that of a 5-year-and-9-month-old boy who developed repetitive episodic involuntary winking of the right eye along with ipsilateral shoulder-shrugging movements associated with paroxysmal shouts and loud laughs and punctuated with abusive verbal expressions (coprolalia), progressive regression of verbal and cognitive milestones, emotional lability and aspects of attention deficit hyperkinetic disorder [50]. The child was evaluated by MRI, which showed characteristic ischaemic areas involving the basal ganglia and fronto-parietal cortical regions and the middle cerebral artery territory, predominantly on the left side. Subsequent cerebral angiography revealed extensive stenosis of bilateral (predominantly left-sided) internal cerebral arteries and middle cerebral arteries, with evidence of diffuse leptomeningeal collaterals. The patient was eventually diagnosed with Moyamoya disease with associated Tourette's syndrome. Subsequently, he underwent left-sided superficial temporal artery to middle cerebral artery anastomosis along with encephalo-duro-arterio-myo-synangiosis. Significant clinical-radiological improvement was noted after three months, at which point, the clinical deficiencies had dramatically resolved. There was evidence of an excellent development of direct and indirect surgical collaterals and the left middle cerebral artery territory. The incidence of Moyamoya syndrome associated with intracranial aneurysms ranges from 3% to 14% in adult patients, whereas it is complication rarely reported in children. Noureldine et al. recently reported the first case of an infrequent subarachnoid haemorrhage a child with a ruptured anterior cerebral artery-dissecting aneurysm secondary to a newly discovered, unilateral Moyamoya-like pathology. These authors argued that prompt intervention is essential to exclude the risk of the ruptured aneurysmrebleeding due to persistent hemodynamic stress [51]. Reports on patients with pMMD who present cerebral ischemic complications after intraventricular haemorrhage (IVH) and/or intracerebral bleeding (ICB) are minimal. In this sense, Inoue et al. reported a case of a 7-year-old girl with moyamoya disease with severe cerebral vasospasm and delayed cerebral infarction following an IVH. The authors stressed that, though such cases are rare, the potential for vasospasm-induced cerebral infarction should be considered and, intensive treatment initiated immediately if suspected [52].

We can conclude, based on published evidence, that less neurological insult will lead to better cognitive outcomes. However, the impact of MMD on cognition remains unclear. Even though surgical treatment generally results in positive neurological outcomes, the relationship between the two needs to be investigated. Further clinical studies should focus on a wide range of neuropsychological tests and measurements ofcerebral blood flow and metabolism in large series.

3. MoyaMoya syndrome in adults (aMMD)

Adult MMD patients usually complain of experiencing difficulties in the normal development of their work, typically due to subtle cognitive deficits, but sometimes because of an apparent intellectual disability [53], including occasionally reported

cases of progressive dementia associated [54]. Growing interest in patients' neurocognitive profiles can be observed in the scientific literature published in recent years, including those with no neuroradiological evidence of a marked ictus [55–57]. The most recent works suggest that the cognitive impairment in adult MMD is the result of ischemic stroke, but the presence and extent of cognitive decline in asymptomatic patients (those who do not show evidence of ictus, but show some cognitive impairment due to subtle hypoperfusion sustained over years) is an aspect that requires exploration [58]. Some authors have highlighted the absence of a methodological consensus regarding neuropsychological evaluation in MMD as a limitation to definite conclusions [55, 56, 59]. In this sense, the COSMO-JAPAN multicentric prospective study, with 60 adult MMD patients [60] proposed a protocol for cognitive evaluation based on the WAIS-III (intelligence) and WMS-R (memory) tests together with an instrument to measure executive function, such as the FAB (Frontal Assessment Battery), the WCST (Wisconsin Card Classification Test), the Stroop test, the Verbal Fluency Test (FAS) or the TMT A/B (Trail Making Test), and including behavioural scales such as the BDI II (Beck depression scale), the STAI (state-trait anxiety scale), the FrSBe (Frontal behaviour scale), and the WHOQOL26 (a quality of life questionnaire). The results obtained in this study indicated an evident impairment of executive functions, which showedgood correlation with functional neuroimaging data, as a result of vascular involvement (hemodynamic ischemia measured with SPECT at rest) of the anteromedial branches of the anterior cerebral arteries, even in the absence of overt stroke. Functional neuroimaging data has helped to clarify brain-symptomatology relations in MMD. Nakagawara et al. [61] indicated that, even if infarction has not yet occurred, brain dysfunction is associated with persistent hemodynamic compromise in the medial frontal lobes that can be visualized by means of [123I] iomazenil (IMZ) single-photon emission C.T. (SPECT). They highlighted the tremendous potential of this technique as a tool for diagnosing cognitive impairment in adult patients with MMD in whom extensive abnormalities are not revealed by computed tomography (CT) or magnetic resonance imaging (MRI) [61].

In this way, the characterization of the cognitive profile of MMD patients has been the focus of much research in recent years. However, the literature has always indicated that the incidence and severity of cognitive alterations are highly variable among adult patients. In 2008, Karzmark et al. published a survey intended to document more comprehensively the nature of cognitive impairment in moyamoya disease by assessing a larger number of adult cases [57] with a neuropsychological assessment test battery. They demonstrated that the highest rate of impairment corresponded with executive functioning and the lowest rates with memory and perception [62]. Cognitive impairment was present in 31% of the patients, and was severe in 11%. The authors claimedthat MMD can impair cognition in adults, but that the effect is not as severe as in pediatric cases (not the case according to the meta-analyses by Kronenburg et al., which we will address later, which show that the proportion of adult patients with impaired cognitive function matches that of children) [44]. Festa et al. demonstrated that approximately two-thirds of their adult patients (in a pool of 29 patients) exhibited neurocognitive dysfunction [55]. Moreover, a large proportion performed 2 S.D. below the mean on various tests measuring different cognitive domains (29% in processing speed, 31% in verbal memory, 26% in verbal fluency, 25% in executive function). Manual strength and dexterity were also affected in many patients, with impairment detected in 36–58%. The authors suggested that a mechanism of diffuse small vessel disease, perhaps caused by chronic hypoperfusion, could explain the pattern of deficits. Karzmark et al. evaluated another sample of 20 adult MMD patients and observed 67% of them exhibited small T2 hyperintensities in the cerebral subcortical white matter

on brain MRI but no evidence of grey-matter damage. Significant cognitive impairment, defined as half of the test scores 1 S.D. below the average mean, was present in 7 patients (23%). Executive functioning, mental efficiency, and word- finding were the ability areas most frequently impaired, whereas memory was relatively intact [57]. Comparable cognitive findings were also observed in the subset of 10 patients (33%) with entirely normal static brain MRI, which lead the authors to conclude that cognitive impairment in MMD can occur in the absence of ischemic stroke as manifested on MRI. As the reader will note, executive dysfunction remains a consistent finding between studies, and Mogensen demonstrated that this impaired executive functioning in adults with MMD is most strongly associated with secondary damage to the brain parenchyma in the form of White Matter Disease (WMD) or cortical stroke [63]. They suggested that increases in global WMD burden were a good indicator of cognitive decline. They also showed that patients with higher baseline CBF tend to have better cognitive functioning.

The treatment for MMD usually consists of surgical revascularization techniques, involving dissecting and re-routing a branch of a superficial artery to a distal branch of another. Revascularization surgery augments cerebral blood flow, and such perfusion augmentation may engender cognitive and neurologic improvement even beyond focal regions of established ischemia. The influence of surgical revascularization treatment on the cognitive status of MMD patients is a subject of debate. This approach is favoured over medical management in children in most cases, but limited data are available regarding the effectiveness of an arterial bypass in adults, especially in terms of cognition improvement. Indeed, there are few published cases reporting neuropsychological status pre- and postrevascularization. Jefferson et al. [64] reported the first case of a 48-year old woman who underwent revascularization following a right hemisphere stroke, and showed a clear temporal relationship between the vascular effects of the bypass procedure and an improvement in neurocognitive status. Preoperative performance in tasks involving visuospatial perception, organization, and construction was generally impaired compared to her estimated premorbid abilities, while postoperative visuospatial performance improved to within a normal range. However, nonverbal visuospatial memory did not return to premorbid levels [64]. Some years after this study, a group of 33 adult patients was assessed pre- and post-surgery in Coutinho's report regarding speech, memory and intellectual processes, in which all the patients underwent stabilization or improvement of physiological symptoms together with significant cognitive improvement after surgery [65].

Another study evaluated a larger group of patients (84) in whom postoperative results were dissapointing: 14% showed significant decline and only 11% an improvement. The majority of patients (75%) displayed neither a significant decline nor an improvement in neurocognitive performance after EC-IC bypass surgery, and similar results were obtained when the analysis was confined to those who underwent unilateral or bilateral revascularization [66]. In light of the fact that adult MMD patients can either improve or decline cognitively after revascularization surgery, Yanagihara et al. [67] emphasized that the intervention boosts cerebral blood flow (CBF) and improves cerebral oxygen metabolism. This cerebral hyperperfusion, which is short-term, can induce a significant increase in ipsilateral CBF that greatly exceed the brain's metabolic needs, thus representing a complication. The authors noted that cerebral hyperperfusion can produce widespread, though minimal, injury to the ipsilateral white matter and cortical regions. In their study of 32 patients, neuropsychological assessments demonstrated cognitive improvement in 31%, no change in 25%, and a decline in 44%. Based on brain perfusion SPECT and symptoms, ten patients were considered to have cerebral hyperperfusion syndrome, and all of these patients exhibited a postoperative decline in cognition.

In summary, acute-stage cerebral hyperperfusion after arterial bypass surgery would seem to impair cognitive function.

On the other hand, an increase in CBF in the chronic stage of cerebral hyperperfusion improves cognitive function in adult patients with symptomatic ischemic MMD [67]. In Moyamoya angioplasty, increased apparent diffusion coefficient (ADC) in frontal white matter (WM) with a normal appearance has been associated with frontal hypoperfusion and executive dysfunction.

Multiple burr-hole surgery enables the revascularization of large frontal areas. In this sense, Calviere et al. recently assessed the effect of such surgery on the ADC and cognitive functions in fourteen adults treated with angioplasty before and six months after the intervention [68]. ADC was obtained from regions of interest located in frontal and posterior (temporo-occipital) normal-appearing WM. Ten patients underwent neuropsychological assessment of executive and attentional functions before and after surgery. The authors concluded that, in MMD adults treated with angioplasty, indirect revascularization by means of burr-hole is followed by a decrease of ADC in normal-appearing frontal WM and may improve some executive functions in the flexibility process. Alterations of ADC may reflect an improvement in cerebral perfusion after surgery. Therefore, the measuring of ADC may be a promising tool to explore potentially reversible microstructural WM damage related to hypoperfusion and cognitive change in aMMD.

In non-surgically treated adult MMD patients with onset of ischemia and stable hemodynamics, the cognitive course remains unclear. In the pool of 70 patients in the study by Miyoshi et al. [69] patients without recurrent ischemic events and no hemodynamic compromise displayed intact cognitive functions two years after the last event. Notably, due to controversy surrounding the surgical option, a large proportion of the patients chose conservative treatment, especially those with hemorrhagic MMD [69]. A study by Su et al. employed the MoCA test to assess cognitive function in 26 adult patients with hemorrhagic MMD who received no surgical revascularization, and observed Mild Cognitive Impairment (MCI) after two years in all 26 [70]. These patients obtained significant decreases in all MoCA subscores ($P = 0.000$) regarding delayed recall, visual space and executive function. However, in a longitudinal case series of adults who had suffered stroke secondary to MMD, stroke recovery was good providing the patient was treated transdisciplinary for 3-4 months (as well as being young and healthy and highly functional prior to the stroke) [71]. The functionality of the patients seems to be more critical than supposed. In Araki's [56] study, the ten patients, were divided into those without difficulties maintaining social independence, with higher educational background, better socioeconomic status, no need for public support, and those who had social independence issues and were socioeconomically disadvantaged. The study found subtle impairments in intelligence and working memory in all the sample. However, frontal lobe functions were primarily affected in adult MMD patients with a social independence problem, even if brain imaging techniques did not reveal noticeable abnormalities [56].

All the questions mentioned above were studied in the meta-analysies of cognitive functions performed by Kronenburg et al. [44], and which included 17 studies (11 studies reporting on 281 children, six on 153 adults). Regarding the adult samples, the median percentage with impaired cognition was as high as 31% (range, 0% to 69%), their median I.Q. scores were within the normal range (95; in a range of 94 to 99), and the median z-scores of cognitive domains were between –0.9 and –0.4, with many of them being affected. The highest median percentage of impaired function was detected for domain attention and executive functions. In a previous review, these authors had suggested that cognition is affected more frequently in children than in adults, reporting intelligence to be impaired in children,

and executive functions to be impaired in adults. However, in this systematic review (more detailed and complete), they concluded that the proportion of adult patients with cognitive function impairment is as large as in children. Moreover, the authors could not identify specific determinants of cognitive deficits and deterioration, and urged for further studies to examine such questions, as well as the influence of revascularization treatment on cognitive functioning. The general recommendation for the future was extensive prospective studies using a standardized battery of neuropsychological tests to determine the severity of cognitive impairment and the domains affected, with the inclusion of information on school-level and performance, and on work status, since it reflects functionality rather than deficits [44].

Recent reports (following this metaanalysies) have followed in the same direction regarding the alteration of attention and executive functions. Jia-Bin et al. discovered that, in a sample of 34 MMD patients, one group performed significantly worse than controls in the Symbol Digit Modalities Test ($z = 4.555$, $P < 0.001$) and The Trail-Making Test Part B ($z = 3.953$, $P < 0.001$). An impairment of memory measured through the long-term delayed recall of the Auditory Verbal Learning Test ($P < 0.001$) was also observed [72]. A neurocognitive evaluation case report by Indorewalla et al. [73] showed a lateralized profile and impairments in simple auditory attention, processing speed, working memory, verbal learning, verbal fluency, and speeded fine-motor dexterity.

Importantly, the latest studies about cognition in adult MMD consider other factors, like gender and clinical subtypes [73]. Shi et al. [74] studied a sample of 49 patients divided into 12 hemorrhagic subjects and 37 with ischemia and compared them with healthy controls. All the patients displayed comprehensive cognitive impairment affecting the domain of memory (prospective and retrospective memory), verbal fluency and executive functions (measured with the Stroop test) [74]. They also showed a pattern of attention significantly different from controls (including impairment in the Trail Making Test-A). Interestingly, female patients performed better than male patients, showing significant differences in forward and immediate memory, Stroop and Wisconsin Card Sorting Test. Another intringuing result was that the hemorrhagic patients, fared poorer in the dimension of prospective and retrospective memory than their ischemic counterparts. Besides, prospective and retrospective memory, attention and executive functions were moderately correlated. A recent study exploring the clinical features of MMD sufferers compared 19 patients with a history of cerebral infarction with 21 asymptomatic patients (plus 20 healthy controls matched for age, sex, and years of education). Detailed neuropsychological testing revealed varying degrees of decline in intelligence, spatial imagination, verbal working memory and computational ability (simple and complex subtraction) in asymptomatic patients compared to normal controls. Patients with cerebral infarction showed more severe impairment in complex arithmetic and short-term memory than those without symptoms. In conclusion, the authors suggested that asymptomatic patients can present various cognitive impairments that precedes the onset of clinical signs such as cerebral infarction, which may be a long-term complication of conservative treatment. Future research should address in depth the distinctive profile of MMD patients according to their neurological clinical status, the influence of gender and educational level on their cognition, and the importance of functional independence in their rehabilitation.

Moyamoya disease and atherosclerotic cerebrovascular disease are chronic ischemic diseases with similar consequences in the form of vascular cognitive impairment. The aim of the study conducted by Su et al. [75] was to investigate the patterns of microstructural damage associated with vascular cognitive impairment in the two diseases in a sample of 34 patients with MMD (mean age 43.9),

27 patients with atherosclerotic cerebovascular disease (mean age: 44.6), and 31 normal controls (mean age 43.6) from Huashan Hospital of Fudan University, in China. Cognitive function was assessed using the Mini-Mental State Examination, long-term delayed recall of the Auditory Verbal Learning Test, the Trail-Making Test Part B, and the Symbol Digit Modalities Test. Single-photon emission-computed tomography was used to examine cerebral perfusion. Voxel-based morphometry and tract-based spatial statistics were performed to identify regions of gray matter atrophy and white matter deterioration in patients and controls. The results demonstrated that the severity of cognitive impairment in the two diseases was similar in all the tested domains. Both patients with MMD and those with atherosclerotic cerebrovascular disease exhibited altered supratentorial hemodynamics; gray matter atrophy was evident in the middle cingulate cortex and parts of the frontal gyrus in both groups, but was generally more severe and more diffuse in those with MMD. White matter deterioration was significant in both diseases, in the genu and body of the corpus callosum, the anterior and superior corona radiation, and the posterior thalamic radiation, but was more diffuse and more severe in MMD. Vascular cognitive impairment was associated with regional microstructural damage, with a potential link between gray and white matter damage being highlighted [75].

A last point of interest to mention is that MMD patients sometimes present with cognitive dysfunction and psychiatric or neuropsychiatric symptoms. In 1991, McDade described a rare case of schizophrenia in a 19-years-old boy with MMD [76]. Nagata et al. reported the case of a 50-year-old man who suffered from irritability and agitation that affected his work and relationships after developing a right ipsilateral frontal lobe infarction as a result of MMD [77]. Zalonis et al. described a case of a middle-aged woman who suffered intraventricular haemorrhages due to MMD. Initially, she presented psychiatric symptoms (mood disorder, irritability, or agitation) that did not respond to treatment. Neuropsychological assessment revealed underlying significant cognitive deficits, mostly of complex attention and speed of information processing, visuospatial and constructional abilities, verbal and nonverbal memory, and executive functions. These deficits continued to be present or had improved slightly when follow-up was carried out [78]. Hong et al. [79] described a patient (a 22-year-old, right-handed woman) who presented with transient cortical blindness, anosognosia, and global transitory amnesia associated with MMD. The woman completely denied blindness and recent memory disturbances with confabulation. This case report demonstrated that MMD can manifest itself in transient posterior circulation symptoms in the form of Dide-Botcazo syndrome [55]. Of the 29 adult American MMD patients included in the Festa et al. study, 36% were found to suffer mild depression and 28% to suffer moderate-to-severe depression, as measured by the Beck Depression Inventory (BDI) [55]. In their 2008 study, Karzmak et al. reported five patients with mild depression, and two patients with moderate depression, and later (in their 2012 study) reported clinically significant emotional distress (depression and/or anxiety) in (37% of their cohort) [62]. In summary, although exclusively psychiatric presentations of MMD in adults are exceedingly rare in the literature, complaints of depression or anxiety often do accompany new focal neurological symptoms, and psychosis can indeed occur. In this way, MMD carries with the risk of misdiagnosis as an affective or psychotic disorder. Transient ischemic events may be mistaken for anxiety and panic disorder, and so there is a call for careful screening of precipitating triggers and characterization of symptoms. When a MMD patient shows psychiatric clinical signs, in the absence of a family history (particularly one of psychotic illness), in combination with atypical features (age at onset, visual hallucinations), a neurological investigation is advised, namely MRI or M.R. angiography rather than C.T.

screening. In the cases of new psychiatric symptoms in patients with diagnosed MMD, repeated neuroimaging is called for to rule out further ischemia [80].

Since the main neurovascular alterations of MMD tend to affect fronto-temporal areas, we propose that any neuropsychological evaluation shouldinclude the study of executive functions (working memory, processing speed, sustained and divided attention), intelligence (I.Q., especially in pMMD), verbal memory (including recognition memory) and visual memory. Given the variety of clinical and cognitive symptoms and different forms of presentation and evolution of MMD, we recommend a baseline and neuropsychological follow-up of all patients with a suspected or definitive clinical diagnosis of MMD.

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