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Pediatric Issue

Cognitive Outcome of Pediatric Moyamoya Disease

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Quality of life is the current trend and issue for the most of human diseases. In moyamoya disease (MMD), surgical revascularization has been recognized as the possible assistance to reduce the neurological insult. However, the progressive nature of the disease has been invincible so far. To improve the quality of life of MMD patients not only the protection from the neurological insult but also the maintenance or improvement of cognitive function is inevitable. For pediatric MMD patients, younger age or longer duration of disease is the key factor among the prognostic factors for bad neurological outcomes. Hence, 'the earlier, the better' is the most precious rule for treatment. Protection from neurological insult is very critical and foremost important to improve cognitive outcome. Clinicians need to know the neuropsychological profile of MMD patients for the care of whole person and make an effort to protect the patients from neurological insults to maintain or improve it.

Key Words : Moyamoya disease · Cognitive outcome · Neuropsychological profile · Revascularization.

INTRODUCTION

Pediatric patients with moyamoya disease (MMD) tend to show cognitive impairment, learning disability, and attention deficits as well as neurological abnormalities. The affected area mainly includes the terminal portions of the ICAs and the proximal areas of the anterior or the middle cerebral arteries (ACAs, MCAs)[27], although posterior cerebral arteries (PCAs) might be affected in some cases[12]. Surgical revascularization such as superficial temporal artery to middle cerebral artery (STA-MCA) anastomosis and indirect bypass improves their cerebral hemodynamics and prevents further ischemic attacks[27]. With regard to stroke recurrence and activity of daily living (ADL), postoperative long-term outcome is favorable in both pediatric and adult patients[10,16,20,36]. However, it is also known that intellectual development is impaired in a certain subgroup of pediatric patients[4,29]. Even after surgical revascularization, intellectual impairment has been reported to disturb an independent social life in more than 20% of the patients[14,16,34,36].

The natural course of intellectual outcome is poor in pediatric patients with MMD. Cognitive function is reported to decline within 5–10 years after the onset[13]. The older patients have a more marked reduction of intelligence quotient (IQ). Lower IQ is closely associated with cerebral blood flow reduction[15]. More than one-third of them were poorly educated[4,29]. Kurokawa et al.[29] evaluated the natural course of pediatric patients with MMD and reported that mild intellectual and/or motor impairment was observed in 26% of them, with special school enrollment or care by parents/institutions in teenage years in 11%, and total 24-h care in 7%. Early onset, younger age or longer duration of disease[24,34,35,41], non-transient ischemic attack (TIA) type or completed stroke patients[14,35], major preoperative stroke[20,24,41], PCA involvement[5] have been reported as factors associated with unfavorable social or functional outcomes. However, social outcomes vary in terms of education and employment at adulthood, and a substantial portion of the patients suffer from social adaptation difficulties even after[37,41].

NEUROPSYCHOLOGICAL PROFILE

In pediatric moyamoya disease, in particular, a state of chronic ischemia persists in the developing brain, and the possibility of persistent neurologic findings and progressive intellectual impairment has been recognized. Thus, previous studies have clarified that about 10–30% of the patients had difficulties in social or school life because of intellectual impairment[16,20,34,36]. However, Imaizumi et al.[14] found no significant correlation between age of onset and IQ when the patients were monitored into adulthood. In their later work, Imaizumi et al.[13] further indicated that the intellectual function begins to decrease after the on-

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set of symptoms but eventually stabilize about 10 years later.

Most of the literatures about cognitive ability in pediatric MMD have focused on intellectual function, yet the results have been inconclusive. Neuropsychological impairments are not infrequent in children with MMD despite normal general intellectual functioning. Some revealed a decline in the intellectual functions[9,47], while others found normal results[15,30]. The pattern of cognitive dysfunction is often associated with lesions in frontotemporal areas. Some risk factors of poor intellectual function have been reported, such as younger age[15], younger onset[34], and longer symptom duration[13]. Some also found completed stroke[27] and infarction[28,30] were poor prognostic while the TIA type of symptom presentation usually linked to a better cognitive outcome[13,14]. Hsu et al.[11] reported that single-domain cognitive impairment in 15% of patients and multiple-domain cognitive impairments in 23% of TIA type patients. Selective impairments of episodic memory and processing speed were especially noted in those with younger age of onset and prolonged symptom duration[11,28].

Neuropsychological assessments were preoperatively done on 76 children (boys 31, girls 45, mean of age=8.04 years) with pediatric MMD patients in authors institute. In addition, children with attention-deficit hyperactivity disorder (ADHD) (boys 36, girls 10, mean of age=8.43 years) were selected in clinical control group and thirty-four children (boys 19, girls 10, mean of age=7.85 years) in non-clinical normal control group, who were participating in separate studies that were conducted at the department of clinical psychology, completed the same battery of neuropsychological assessments. On neurocognitive functions, even though the mean of the group on intelligence, memory, executive functions were included within the level of average range, the ratio of belonging to below the average range were 25 to 50%, suggesting declined neurocognitive functions. Among those functions, the decline of performance IQ and memory quotient, and the increased attention and impulsivity problems were remarkable. On emotion and behavioral problems, about 22−25% of children with moyamoya demonstrated significantly increased depression and anxiety, and internalizing problems were reported comparatively much more increased, particularly on social and attention problem. On parenting stress and negative emotion of their mothers, above 30% of mothers of children with moyamoya disease were shown to be experiencing significantly increased parenting stress and depressed mood. On quality of life, children with moyamoya and their mothers reported comparatively low satisfaction on physical, emotion, and academic function (unpublished data).

ROLE OF SURGICAL TREATMENT FOR COGNITIVE OUTCOME

Preoperative symptom duration and the age of onset

Surgical revascularization may improve cognitive function in pediatric patients with MMD. In general younger than 3 years old has been considered as poor prognosis. Matsushima et al.[34] found poor cognitive prognosis for those with an onset younger than 2 years. Even though performance IQ markedly improved after revascularization the degree of reduction in preoperative IQ correlated well to the age of the patients[15]. To the contrary Hsu et al.[11] reported that they did not find a significant correlation between age and intelligence in their patient group. However, longer symptom duration has been reported to be associated with slower processing speed. Younger age or younger age of onset has been associated with poorer new learning ability. These are the crucial findings highlighting the importance of early detection and early intervention in pediatric MMD.

Preoperative clinical status

In Kuroda et al.[28] study, contrary to previous report, age of the onset, preoperative diseased period, and cerebral infarction were not significant factors. However, most of completed stroke-type patients already had hemiparesis or tetraparesis before surgical revascularization, indicating that poor intellectual outcome is closely related to the impairment of motor function[14]. The incidence of completed stroke-type patients is very much higher in a subgroup of patients who develop ischemic attacks in very early childhood (<2 years) or who did not undergo surgical treatment for a long time[3,13,16,29]. In detail, 91% of the patients with cerebral infarction in the deep white matter were classified into a good-outcome group, whereas 67% of the patients with cortical infarction had poor intellectual outcomes[28]. Lee et al.[30] also confirmed this hypothesis recently. The patients who had sustained major infarctions before surgery had significantly lower neurocognitive functions preoperatively. However, even though the intellectual function of patients with major infarctions is poorer preoperatively, further deterioration of their remnant cognitive ability can be prevented through revascularization surgery[30]. Especially the group of patients with borderzone infarction usually do not cause fixed neurological deficits while showed significantly lower preoperative full scale IQ (FSIQ), verbal IQ (VIQ), and performance IQ than no infarctions, but this group showed postoperative improvement or maintenance. This may support the very critical issue of 'the earlier, the better'. Early prevention of completed stroke by early detection and identifying of pediatric patients with MMD and earlier surgical treatment through 'large craniotomy surgery' is essential to improve their intellectual outcome. Lee et al.[30] summarized the neuropsychological outcomes of these patients and reported that performance IQ (PIQ) and visual memory function were improved after surgery. Preoperatively, the children with MMD who had a major infarct showed lower FSIQ, VIQ, and PIQ scores than children without major infarct. However, no interactive effect was found between the presence of major infarctions and their pre- and postoperative neurocognitive profiles. Dominant hemispheric infarcts resulted in lower preoperative FSIQ, VIQ, and PIQ than non-dominant hemispheric infarcts. Nevertheless, patients with over 70 of the preoperative Wechsler test IQ remained stable or improved[35], less than 70 FSIQ resulted in poor intellectual outcome[28]. The postoperative neuropsychological profiles can be similar or better than preoperative scores even though additional postoperative infarct. It is from the improvement of perfusion by the timely revascularization before the progression of the disease[19].

Surgical procedures

It has been suggested that the procedures of surgical revascularization have some influence on intellectual outcome[14,16,20,33]. Recently, Guzman et al.[6] summarized their surgically treated 168 pediatric MMD patients using the direct STA-MCA anastomosis first then indirect procedure. 71.2% of them showed improved quality of life by the upgrading of modified Rankin scale and significant reduction of TIA. Bowen et al.[1] reported gradual improvement of cognitive function after surgical revascularization in two pediatric patients with MMD. Although surgical revascularization is known to resolve TIA and ischemic stroke very effectively, intellectual delay is still serious problem for a certain subgroup of pediatric patients and their families even after surgery. Previously, however, significant predictors of poor intellectual outcome after surgery have not been fully analyzed. Using a univariate analysis model, Matsushima et al.[35] reported that there was no significant factor for intellectual outcome after encephalo-duro-arterio-synangiosis (EDAS). However, their study had some bias in their patient selection, because they excluded the patients with a FSIQ below 70, and they did not perform a multivariate analysis probably because of the small sample size (n=20)[35]. Kuroda et al.[28] assessed significant predictors for poor intellectual outcome in a total of 52 pediatric patients who underwent surgical revascularization, using multivariate analysis. They found that completed stroke and "small craniotomy" surgery were independent predictors of poor intellectual outcome in pediatric patients with MMD[27]. Indirect procedures such as EDAS and encephalo-myo-synangiosis (EMS) are relatively easy, and have been widely performed for patients with MMD[3]. However, one of the disadvantages is the fact that the revascularization area is limited and is confined to the craniotomy field after these procedures[31,43,45], and that blood flow reduction is persistent in the frontal lobe even after EDAS or EMS[43]. Even after the disappearance of ischemic attacks, intellectual outcome was poor in a majority of the patients who underwent these procedures[43]. On the other hand "large craniotomy surgery" along with STA-MCA anastomosis and encephalo-duro-arterio-myo-synangiosis (EDAMS) can normalize regional cerebral bold flow (rCBF) distribution and cerebrovascular reactivity to acetazolamide in the frontal lobe[17,26,45] and can prevent the deterioration of intellectual functions and quality of life (QOL) in pediatric moyamoya patients[38]. Kim et al. developed their novel technique for reinforcing the territory of ACA by bifrontal encephalogaleo (periosteal) synangiosis. Although they showed the improvement of the hemodynamic parameters on frontal area they did not produced the improvement of cognitive function after the procedure[21,23,25,39]. It would be worthy of trying to reinforce this frontal area because the reduction of neurological insult may decrease the further cognitive impairment.

Hallemeier et al.[7] found a reduction of the cumulative 5-year stroke risk from 65% in medically treated hemispheres to 17% in surgically treated hemispheres (p=0.02). Furthermore, it is very critical to further improvement of cognitive function after surgical intervention that the minimization of surgical complication which may potentially be harmful to neurological outcome. Guzman et al.[6] reported overall 6.7% of surgical complication per procedure (1.2% of mortality, 3.0% of ischemic stroke, 2.6% of hemorrhagic stroke). It was relatively lower than previous studies[18,22]. Sakamoto et al.[42] and Scott et al.[44] reported 4% and 3.8% respectively with combined revascularization. Recently Kim et al.[23] reported 0.5% mortality (2/410), 6% of ischemic complication with 81% of favorable outcome (66% of excellent and 15% of good clinical outcome) with indirect revascularization with 410 pediatric MMD patients. Surgical mortality and morbidity may be similar between direct/combined revascularization and indirect revascularization. However, long term neuropsychological outcome should be assessed along with each surgical procedure.

COGNITIVE OUTCOME AFTER SURGERY

It is not surprising that the patients of the TIA type showed better intellectual outcome[11,14]. The pattern of functional difficulty seen in MMD patients may result from vasculopathy due to insufficient blood supply of the ICAs in frontal-temporal circuits under moyamoya pathology[43]. Furthermore these areas are the least revascularized region with either indirect or combined procedures, even though with 'large craniotomy surgery'. There are several features of cognitive functions of MMD patients related to a pathological picture that is consistent to lesions of the frontotemporal regions. First, only free recall but not recognition performances were found defective during memory tests. This contrast of normal acquisition and retention but impaired retrieval ability is commonly seen in patients with subcortical or frontal dysfunction[8,40]. Second, memory impairment combined with a deficit of executive function that could be seen in our patients are usually associated with dysfunction in frontotemporal network[8]. Third, poor performance on the test of psychomotor speed was observed. The slowed processing speed may reflect reduced structural integrity of the white matter associated with frontoparietotemporal systems[46]. This is worthy of educational attention since learning, memory and goal-directed behaviors are important for daily adaptation and essential for academic accomplishment[11]. In authors study (unpublished data) learning ability as well as attention were critically impaired. These are critical factor for school life of pediatric MMD patients. However, fortunately the FSIQ were relatively preserved. A direct survey of real life performance level combined with standardized neuropsychological testing will be still valuable in subsequent studies. Recurrent ischemic strokes may result in neurocognitive dysfunction to be a crucial handicap in learning and social adaptation. School absences and the lack of normal classes during the illness and treatment course can exacerbate this situation[41]. Phi et al.[41] surveyed and reported that compared with the general population, the patients showed a similar rate of attaining a higher education. 80% of patients had entered college or university. Phi et al.[41] also stressed that the presence of neurological deficits on preoperative examination was a negative predictor of entrance into a college or university, as well as employment. Those children with MMD did not have any problems with acquired knowledge, long-term memory, verbal concept formation ability, mathematical ability, vocabulary, social comprehension, or attention span before surgery, and that those abilities were maintained well after surgery. This maintained ability resulted that 48% of patients showed no change of school performance, 15% showed improvement, and 28% reported worsened school performance after surgical treatment[41]. Definitely the cognitive function is an important factor in determining social outcome, especially after school age. Most of the papers about the surgical outcomes for these patient population insisted that appropriate surgical intervention could reduce further ischemic insults and neurological deteriorations[2,31,32,34,35,37]. Conservatively treated pediatric patients showed poor long-term intellectual outcome[13,14,29]. Hence, a role for early active surgery to save the intellectual abilities of children with MMD should be stressed again to reduce the development of neurological deficits, major lobar infarction or hemorrhage[30].

CONCLUSIONS

The prediction of the long term outcome of MMD patients is extremely difficult because of the progressiveness of natural course and bilateral discrepancy of this disease. It is reasonable assumption that less neurological insult will lead to better cognitive outcomes. However, the impact of MMD on cognition is still unclear. Even if the surgical treatment may result in good neurological outcomes the relationship between surgical treatment and cognitive outcome need to be investigated. Further clinical studies should be focused on a wide range of neuropsychological testing and cerebral blood flow and metabolism measurements in large series.

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