Novel insights into symptomatology of moyamoya disease in pediatric patients: survey of symptoms suggestive of orthostatic intolerance

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OBJECTIVE A specific population of young patients with moyamoya disease (MMD) persistently experience physical symptoms not attributable to focal ischemia. These symptoms, highly suggestive of orthostatic intolerance (also termed “orthostatic dysregulation”), were investigated and reported as potential determinants of quality of life in young MMD patients.

METHODS Forty-six patients (6–30 years of age) were selected from a group of 122 patients who were diagnosed with MMD before 18 years of age. The authors administered a structured questionnaire consisting of 11 items based on screening checklists published in the Japanese clinical guidelines for juvenile orthostatic dysregulation in young patients. The results were tabulated, and correlations with clinical data were explored.

RESULTS Thirty-seven (80%) patients (mean age 15.9 years) responded to the questionnaire. Frequent headache, vertigo/dizziness on standing, fatigue, difficulty with getting out of bed, and motion sickness were the top 5 symptoms, resulting in 57% of patients being unable to attend school. Forty-three percent of the patients demonstrated multiple symptoms suggestive of orthostatic intolerance, even as long as 5 years after revascularization surgery. The number of symptoms was inversely associated with the number of years after surgery ($p = 0.028$). The number of symptoms was not associated with a history of surgery, clinical presentations, vascular involvement, cerebral perfusion, brain lesions, or history of transient ischemic attacks.

CONCLUSIONS The present study provided novel insight into the symptomatology of young patients with MMD. Failure to notice nonfocal physical symptoms can significantly impair quality of life in young patients with MMD even years after successful revascularization surgery. These symptoms may serve as independent clinical markers used to assess disease outcome, although the underlying mechanisms of this disease are, as of yet, unclear.

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KEY WORDS hemodynamic compromise; juvenile; moyamoya; orthostatic intolerance; quality of life; vascular disorders

MOYAMOYA disease (MMD) is characterized by steno-occlusive lesions of the intracranial carotid arteries along with the basal collateral arteries, known as moyamoya vessels.⁵ The age at onset has 2 peaks: one at approximately 10 years of age and the other at approximately 40 years. Symptoms associated with hemodynamic compromise are the cardinal signs of MMD.⁴ In addition to focal neurological deficits, nonfocal symptoms, such as headache, dizziness, or faintness, have also been documented. The nonfocal symptoms mimic orthostatic intolerance (also known as “orthostatic dysregulation”),

which is clinically significant because it leads to physical disability, especially in young patients. Nevertheless, these symptoms can often go unnoticed or be overlooked by physicians unless a highly detailed inquiry of patients or their parents is performed. As a result, there is insufficient information with regard to the prevalence of nonfocal symptoms and their clinical significance. Accordingly, we conducted a cross-sectional survey to investigate nonfocal symptoms suggestive of orthostatic intolerance and explored associations with clinical presentations including cerebral perfusion.

ABBREVIATIONS MMD = moyamoya disease; TIA = transient ischemic attack.

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Methods

Patient Population

The present study was approved by the institutional review board of Hokkaido University Hospital (Sapporo, Japan). Records of 122 patients who were younger than 18 years at the time of MMD diagnosis (between 1980 and 2015) were examined. Of these, patients older than 30 years at the time of the survey were excluded to focus on the younger patients. To obtain reliable responses from children, the lower age limit was set at 6 years. As a result, 46 patients ranging in age from 6 to 30 years at the time of the survey were considered to be eligible and were included in the study. Clinical information was collected from a prospective database and included patient demographics (sex, age, disease-onset type, and surgical history), radiographic features (disease laterality, disease stage,³ cerebral perfusion, and brain lesions), and history of recent transient ischemic attack (TIA).

Survey Questionnaire

Self-administered questionnaires were constructed according to a screening checklist established by the Japanese Society of Psychosomatic Pediatrics of orthostatic dysregulation in pediatric patients (Table 1 and Questionnaire).⁷ The questionnaires were mailed to the patients. Patients answered whether they had any of the 11 symptoms in the guidelines at present or at the time of the survey. In the questionnaire, the frequencies of symptom occurrence were defined as more than once a week. Individuals who underwent revascularization surgery were also queried about whether their symptoms were improved after surgery. All patients were then asked whether they had been absent from school due to any of the symptoms. When the pediatric patients could not complete the questionnaire, their parents were allowed to help.

Data Analysis

The patients were divided into 2 groups according to the orthostatic intolerance guidelines: those who had ≥ 3 symptoms and those who had ≤ 2 symptoms.⁷ The aforementioned clinical variables were compared between the groups using the chi-square test or unpaired t-test. Correlations between the period after the surgery and the number of symptoms were explored using Pearson's moment-product coefficient. Furthermore, multivariate logistic regression analysis was performed on factors achieving $p < 0.05$ in the univariate analysis.

Results

Of the 46 eligible patients, 37 (80.4%; 15 males and 22 females; mean age 15.9 years, age range 7–26 years) responded to the questionnaire. The mean age at diagnosis was 8.1 years (range 1–14 years). Of these 37 patients, 31 (84%) underwent revascularization surgery via combined direct/indirect bypass (mean follow-up period 8.1 years after surgery [range 0.7–20.6 years]). Patient demographics are summarized in Table 2.

The 5 most common symptoms were frequent headache, vertigo/dizziness on standing, fatigue, difficulty with

TABLE 1. Prevalence of 11 nonneurological symptoms and improvement rate after surgery

Present Symptoms	Prevalence	Postop Improvement (n = 31)
Frequent headache	67.6	50.0
Susceptibility to vertigo & dizziness on standing	56.8	41.7
Fatigue	45.9	36.4
Difficulty w/ getting out of bed	35.1	41.7
Motion sickness	24.3	28.6
Palpitation &/or dyspnea after mild exercise	18.9	33.3
Tendency for fainting in standing position	13.5	33.3
Anorexia	13.5	28.6
Occasional umbilical colic (severe abdominal pain)	13.5	20.0
Nausea on taking hot bath or encountering unpleasant experiences	10.8	55.6
Pallor	10.8	16.7
Absent from school due to above symptoms	56.8	

Data are presented as percentages.

getting out of bed, and motion sickness, with a combined mean prevalence $> 20\%$ (Table 1). Twenty-one (56.8%) of the 37 patients reported a history of absence from school. Overall, the improvement rate in symptoms after revascularization surgery, with the exception of headache and nausea, was $< 50\%$.

Twenty-two (59%) of 37 patients were clinically diagnosed with probable orthostatic intolerance (≥ 3 symptoms) according to the guidelines. Female sex and a shorter postoperative duration were significantly associated with these symptoms (sex, $p = 0.047$; postoperative duration, $p = 0.014$) (Table 2). The period after surgery showed a significant association with probable orthostatic intolerance after correcting for other variables ($p = 0.028$) (Table 2). None of the other clinical variables was associated with this condition. As shown in Fig. 1, several symptoms were inversely correlated with the number of years after surgery ($r = -0.52$). Of note, however, 9 (43%) of 21 patients who passed the 5-year mark after surgery had ≥ 3 symptoms.

Discussion

Orthostatic intolerance is defined as a disturbance in the physiological adjustment mechanism compensating for physical stresses, such as standing, and causes a variety of symptoms associated with hemodynamic or autonomic nervous system compromise. Circulatory adjustment systems include the circulating blood volume, cardiac output, peripheral blood vessels, cerebral circulation, and the autonomic nervous system.⁷ Although no previous investigation has focused on orthostatic intolerance in MMD,⁷ we believe that symptoms suggestive of orthostatic intoler-

TABLE 2. Univariate and multivariate analysis of factors associated with nonneurological symptoms stratified by the number of symptoms

Characteristic	0–2 Symptoms	≥3 Symptoms	p Value		OR (95% CI)
			Univariate	Multivariate	
No. of patients	15	22			
Female sex	6 (40)	16 (73)	0.047	0.053	
Mean age, yrs	16.7	15.3	0.39		
Underwent op	12 (80)	19 (86)	0.61		
Mean postop duration, yrs	11.0	6.3	0.014	0.028	0.79 (0.65–0.97)
Unilateral disease	2 (13)	5 (23)	0.47		
Disease onset type			0.46		
Infarction	4 (27)	2 (9)			
TIA	9 (60)	15 (68)			
Bleeding	0 (0)	1 (5)			
Other	2 (13)	4 (18)			
Suzuki stage ≥4	10 (77)	13 (59)	0.64		
CBF decrease at Dx	12 (80)	19 (86)	0.61		
Brain infarct lesion	4 (27)	4 (18)	0.54		
TIA w/in 3 mos	2 (13)	2 (9)	0.68		

CBF = cerebral blood flow; Dx = diagnosis.

Values are presented as the number of patients (%) unless stated otherwise.

ance are critical and potentially impact the quality of life of pediatric MMD patients. The present study enhanced our knowledge with regard to symptomatology in MMD and provides relevant information from the perspective of postoperative management as well as long-term patient care.

A national survey reported that 6% of children 10–15 years old suffer from orthostatic intolerance in Japan.⁹ In the screening survey from the present study, 59% of patients had symptoms suggestive of orthostatic intolerance. Although our study is not directly comparable to the aforementioned survey because of the difference in backgrounds of the populations and the effects of revascularization surgery, the prevalence of symptoms appeared to be greater than that in the non-MMD population.⁹ Cerebral hemodynamic impairment likely underlies the symptoms; however, we were not able to attribute the abnormality to the cerebral perfusion measurements. Furthermore, patients who underwent successful revascularization continued to exhibit symptoms years after surgery. Impaired cerebral hemodynamics specific to orthostatic intolerance—suggestive symptoms in MMD may not be detected with sufficient sensitivity using conventional perfusion measurements. Another possible mechanism is that some pediatric MMD patients are carriers of an autonomic dysfunction,^{1,6} which would cause the orthostatic intolerance—suggestive symptoms for years, even without apparent cerebral hemodynamic compromise.

The symptoms of orthostatic intolerance appear to be self-limited and benign in course and therefore explain why nonfocal physical symptoms have not been emphasized in the symptomatology of MMD. Nonetheless, some school-age patients experience physical disability for years, which may result in school absence. This could lead to substandard academic achievement, thereby potentially

reducing the cognitive reserve responsible for maintaining cognitive abilities in the chronically ischemic brain after middle age.² Further investigation is needed to determine the impact on the school life and academic achievement along with activities of daily living.

Several limitations to the present study must be addressed. First, the small number of patients investigated may prevent us from generalizing the results. Furthermore, there may be international differences in the prevalence of symptoms due to environmental or genetic factors.¹⁰ Second, the inclusion of recall bias regarding the improvement of symptoms postsurgery should be con-

FIG. 1. Scatter plot of the number of symptoms versus years after surgery in 31 patients who underwent surgery. A negative linear relationship is apparent.

sidered in the questionnaire, because several years had elapsed since the operation in many patients. Third, the patients were not definitively diagnosed with orthostatic intolerance according to orthostatic tests. Their symptoms were nonspecific and the underlying pathophysiology remains unclear. In patients with MMD with disturbances in cerebral hemodynamic autoregulation leading to orthostatic intolerance—suggestive symptoms, a systemic blood pressure reduction might not be a direct cause.⁸ Further studies describing possible underlying pathophysiology and establishing optimal management strategies for the physical symptoms are warranted.

Conclusions

Results of the present study demonstrated that pediatric MMD patients may exhibit nonfocal physical symptoms, which might affect the normal activities of daily living. The study emphasizes the clinical significance of nonfocal physical symptoms being overlooked and encourages further investigation.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Uchino, Kazumata, Nakayama. Acquisition of data: Uchino, Ito. Analysis and interpretation of data: Uchino. Drafting the article: Uchino. Critically revising the article: Uchino. Reviewed submitted version of manuscript: Uchino. Approved the final version of the manuscript on behalf of all authors: Uchino. Statistical analysis: Uchino. Study supervision: Kazumata, Nakayama, Houkin.

Supplemental Information

Online-Only Content

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