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Original article

The etiologic relation between disequilibrium and orthostatic intolerance in patients with myalgic encephalomyelitis (chronic fatigue syndrome)

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ABSTRACT

Background: Orthostatic intolerance (OI) causes a marked reduction in the activities of daily living in patients with myalgic encephalomyelitis (ME) or chronic fatigue syndrome. Most symptoms of OI are thought to be related to cerebral hypo-perfusion and sympathetic activation. Because postural stability is an essential element of orthostatic tolerance, disequilibrium may be involved in the etiology of OI.
Methods and results: The study comprised 44 patients with ME (men, 11 and women, 33; mean age, 37 ± 9 years), who underwent neurological examinations and 10-min standing and sitting tests. Symptoms of OI were detected in 40 (91%) patients and those of sitting intolerance were detected in 30 (68%). Among the 40 patients with OI, disequilibrium with instability on standing with their feet together and eyes shut, was detected in 13 (32.5%) patients and hemodynamic dysfunction during the standing test was detected in 19 (47.5%); both of these were detected in 7 (17.5%) patients. Compared with 31 patients without disequilibrium, 13 (30%) patients with disequilibrium more prevalently reported symptoms during both standing (100% vs. 87%, $p = 0.43$) and sitting (92% vs. 58%, $p = 0.06$) tests. Several (46% vs. 3%, $p < 0.01$) patients failed to complete the 10-min standing test, and some (15% vs. 0%, $p = 0.15$) failed to complete the 10-min sitting test. Among the seven patients with both hemodynamic dysfunction during the standing test and disequilibrium, three (43%) failed to complete the standing test. Among the 6 patients with disequilibrium only, 3 (50%) failed while among the 12 patients with hemodynamic dysfunction only, including 8 patients with postural orthostatic tachycardia, none (0%, $p = 0.02$) failed.
Conclusions: Patients with ME and disequilibrium reported not only OI but also sitting intolerance. Disequilibrium should be recognized as an important cause of OI and appears to be a more influential cause for OI than postural orthostatic tachycardia in patients with ME.

Introduction

Chronic fatigue syndrome (CFS) is characterized by severe disabling fatigue and post-exertional malaise, not resolved by rest, and that causes a marked reduction in the activities of daily living, and impairs the quality of life [1–3]. The dysfunction of the central nervous system associated with myalgic encephalomyelitis (ME) has been postulated as the main cause of CFS [4].

Most patients with ME/CFS have orthostatic intolerance (OI) which is the primary factor restricting the daily functional capacity [5–10]. OI is characterized by the inability to remain upright without severe signs and symptoms, such as hypotension, palpitation, lightheadedness, pallor, fatigue, weakness, dizziness, diminished concentration, tremulousness, and nausea [7–9]. Most symptoms of OI are related to reduced cerebral blood flow with or without impaired cerebral circulatory autoregulation [11], and compensatory activation of the sympathetic nervous system. OI has been classified as an important cardiovascular symptom in the diagnostic criteria for both ME and systemic exertion intolerance disease [12]. Indeed, several patients have been reported to have postural orthostatic tachycardia, delayed orthostatic hypotension, and neurally-mediated hypotension

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[5,9–13]. Furthermore, many patients also have low cardiac output in association with a small left ventricle [14–18]. Both the renin–aldosterone and anti-diuretic hormone systems that regulate circulatory blood volume were reported to be down-regulated [19]. With further progression of the disease, patients may even have sitting intolerance and finally become bedridden.

Static balance is an essential element for performing daily activities as well as for postural stability. Komaroff [20] estimated that approximately 30–50% of patients with CFS suffer from some degree of disequilibrium, whereas Merry [21] suggested the incidence could be as high as 70% of all patients. Our recent report suggested that disequilibrium may be involved in the induction of OI [22]. In the present study, the etiologic relation between disequilibrium and OI was investigated in patients with ME using neurological examinations and both conventional active standing and sitting tests.

Methods

Study patients

A total of 44 consecutive patients who visited our clinic, diagnosed with ME, could stand up and walk, and gave informed consent to participate, were included in the present study. ME was diagnosed according to the International Consensus Criteria proposed in 2011 [4]. Of the total 44 study patients, 11 were men and 33 women with a mean age of 37 ± 9 (range, 18–55) years. The study was approved by ethics committees of our institutes.

Neurological examinations

All patients underwent intensive neurological physical examinations including tandem gait, standing on one leg and diadochokinesis tests, as well as the Romberg test, which involves making the patients stand with their feet together and eyes shut.

Performance status grading

Performance status (PS) was graded as below, according to symptom severity as reported previously [23] just before the active standing test.

PS 0: The patient can perform the usual activities of daily living and social activities without malaise.
PS 1: The patient often feels fatigue.
PS 2: The patient often needs to rest because of general malaise or fatigue.
PS 3: The patient cannot work or perform usual activities for a few days in a month.
PS 4: The patient cannot work or perform usual activities for a few days in a week.
PS 5: The patient cannot work or perform usual activities but can perform light work.
PS 6: The patient needs daily rest but can perform light work on a “good day”.
PS 7: The patient can take care of himself/herself but cannot perform usual duties.
PS 8: The patient needs help to take care of himself/herself.
PS 9: The patient needs to rest the whole day and cannot take care of himself/herself without help.

Standing test

The 10-min active standing test was performed as reported previously [23]. Medications were unremarkable before the test. Either adrenergic β-receptor blocking agents or vasopressors were discontinued before the standing or sitting test, although nutritional supplements or multi-enzyme tablets were not discontinued. Postural orthostatic tachycardia was diagnosed as an increase in the heart rate of ≥30 and/or ≥120 beats/min during the test. Instantaneous or delayed orthostatic hypotension was diagnosed as a decrease in the systolic blood pressure of ≥20 and/or ≤90 mmHg or diastolic blood pressure of ≥10 mmHg.

Sitting test

The 10-min active sitting test was separately performed within 2 months after the standing test. Patients were asked to keep the sitting position on the center of a side of a bed without cushions for 10 min after lying in the recumbent position for 5 min. Postural sitting tachycardia was diagnosed as an increase in the heart rate of ≥20 and/or ≥90 beats/min during the sitting test. Sitting hypotension was diagnosed as a decrease in the systolic blood pressure of ≥20 and/or ≤90 mmHg or diastolic blood pressure of ≥10 mmHg.

Statistical analysis

Continuous variables are presented as mean ± standard deviation. Student's *t*-test was used to compare continuous variables. Proportional data were analyzed using the Fisher's exact test. Mann–Whitney's *U* test was used to compare median PS scores between the groups. Statistical significance was set at $p < 0.05$.

Results

The disequilibrium test was performed by making the patients stand with their feet together and eyes shut. When the instability was markedly worsened, thereby producing wide oscillations and possibly a fall, disequilibrium was positive. Disequilibrium was detected in 13 (30%) patients; among these, 6 (46%) had some instability on standing with their feet together and eyes open, which further markedly worsened with eyes shut and the other 7 (54%) had a positive Romberg test in which the stability on standing with their feet together and eyes open was lost with eyes shut.

During the 10-min active standing test, 40 (91%) patients reported the symptoms of OI, and during the 10-min active sitting test, 30 (69%) had sitting intolerance. Among the 40 patients with symptoms of OI, hemodynamic dysfunction was detected in 19 (47.5%) during the standing test and disequilibrium was detected in 13 (32.5%) during the neurological examination. In further classification, the 40 patients were divided into 4 categories: 12 (30%) patients with hemodynamic dysfunction only, 6 (15%) with disequilibrium only, 7 (17.5%) with both, and 15 patients (37.5%) with neither.

Comparative data between patients with and without disequilibrium are summarized in Tables 1 and 2. Women were more predominant (92% vs. 68%, $p = 0.18$) in patients with disequilibrium (Table 1). Age and disease history length were not significantly different between patients with and without disequilibrium. A significantly higher rate of unstable standing on one leg (100% vs. 3%, $p < 0.01$) as well as abnormal tandem gait (100% vs. 6%, $p < 0.01$) was noted in patients with disequilibrium than those without disequilibrium. Unstable standing on one leg was observed in a total of 14 (32%) patients and abnormal tandem gait in a total of 15 (34%) out of all the study patients.

Compared with patients without disequilibrium, patients with disequilibrium more prevalently reported various symptoms including faintness, dizziness, nausea, dyspnea, and palpitation (100% vs. 87%, $p = 0.43$), had postural sway (92% vs. 16%, $p < 0.01$)

Table 1
Comparison of physical neurological findings between patients with myalgic encephalomyelitis with and without disequilibrium.

	Disequilibrium		
	Positive	Negative	*p* value
Number of patients	13 (30%)	31 (70%)	
Male/female	1/12	10/21	0.18
Age (years)	36 ± 10	37 ± 9	0.94
Disease history length (years)	6.8 ± 8.5	6.5 ± 7.6	0.91
Performance status score	4–8	3–7	<0.01
Median score	6	4	<0.01
Neurologic examinations			
Standing on one leg, unstable	13 (100%)	1 (3%)	<0.01
Tandem gait: abnormal	13 (100%)	2 (6%)	<0.01

Values are presented as mean ± standard deviation.

Table 2
Comparison of results of both 10-min active standing and sitting tests between patients with myalgic encephalomyelitis with and without disequilibrium.

	Disequilibrium		
	Positive	Negative	*p* value
Number of patients	13 (30%)	31 (70%)	
Standing test			
Symptoms (+)	13 (100%)	27 (87%)	0.43
Postural sway	12 (92%)	5 (16%)	<0.01
Failure to complete 10-min standing test	6 (46%)	1 (3%)	<0.01
Abnormal hemodynamics	7 (54%)	12 (39%)	0.55
Postural orthostatic tachycardia[a]	4 (31%)	9 (29%)	0.57
Sitting test			
Symptoms (+)	12 (92%)	18 (58%)	0.06
Postural sway	5 (38%)	2 (6%)	0.03
Failure to complete 10-min sitting test	2 (15%)	0 (0%)	0.15
Abnormal hemodynamics	5 (38%)	10 (32%)	0.96
Postural sitting tachycardia[b]	3 (23%)	9(29%)	0.97

[a] Heart rate ↑ ≥30 and/or ≥120 beats/min.
[b] Heart rate ↑ ≥20 and/or ≥90 beats/min.
Values are presented mean ± standard deviation.

during the standing test, and failed to complete the 10-min standing test (46% vs. 3%, $p < 0.01$) (Table 2). Among the total 7 patients who failed to complete the test, 5 (71%) had both hemodynamic dysfunction during the standing test and disequilibrium, one (14%) disequilibrium only and the other one (14%) neither. Among the 7 patients with both hemodynamic dysfunction during the standing test and disequilibrium, 3 (43%) failed to complete the test, and among the 15 patients with neither, 1 (7%) failed. Among the 6 patients with disequilibrium only, 3 (50%) failed while among the 12 patients with hemodynamic dysfunction only, including 8 patients with postural orthostatic tachycardia, none (0%, $p = 0.02$) failed.

During the sitting test, patients with disequilibrium reported various symptoms including faintness, nausea, dyspnea, palpitation, and severe fatigue (92% vs. 58%, $p = 0.06$) and had postural sway (38% vs. 6%, $p = 0.03$) more prevalently than those without disequilibrium. Some (15%) patients with disequilibrium were unable to complete the 10-min sitting test, whereas none (0%) of the patients without disequilibrium failed to complete it. Postural sitting tachycardia (heart rate ≥ 90/min) was noted in 3 (23%) patients with disequilibrium and in 9 (29%) without disequilibrium ($p = 0.97$).

Patients with disequilibrium had higher PS scores on the activities of daily living (range, 4–8), suggesting more severely restricted activities of daily living in them (Fig. 1). The median PS score (6) was significantly higher ($p < 0.01$) in patients with disequilibrium than that (5) in those without disequilibrium

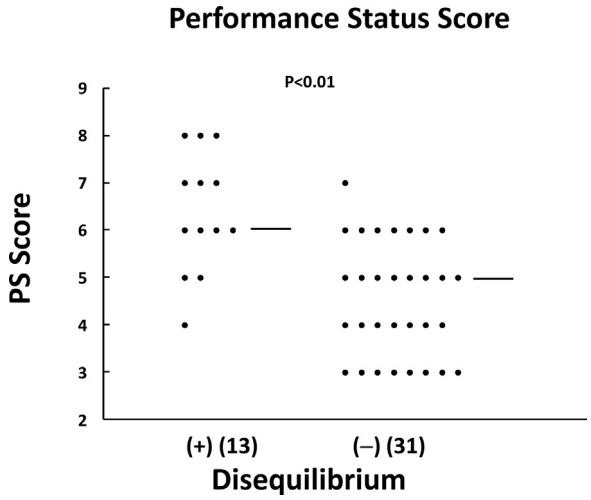

Fig. 1. Comparison of performance status (PS) scores between patients with myalgic encephalomyelitis with and without disequilibrium. The parentheses show the number of patients per group. —: median.

(range, 3–7). No patients in either group had dysdiadochokinesis or abnormal finger-to-nose, finger-to-finger, and heal-shin tests.

Discussion

In the present study, the standard neurological examination demonstrated abnormal results such as disequilibrium on standing with their feet together, impaired one-leg standing, and unstable tandem gait, suggesting disequilibrium or truncal ataxia in a considerable number of patients with ME. Almost all patients with disequilibrium had intolerance with postural sway in the orthostatic position and some even in the sitting position, being clearly differentiated from those without disequilibrium. The dysfunction of postural reflex in association with truncal or static ataxia appears to play an important role in the etiology of postural intolerance. Disequilibrium is a useful sign of advanced disease. Half of the 6 patients with disequilibrium only failed to complete the 10-min standing test, while none of the 8 patients with postural orthostatic tachycardia failed, suggesting that disequilibrium is a more influential cause of OI than is postural orthostatic tachycardia. In addition, patients with disequilibrium had higher PS scores than those without disequilibrium, suggesting more severely restricted activities of daily living. Contradictory results have been reported concerning disequilibrium in patients with CFS. Some studies have previously demonstrated balance problems in patients with CFS [24,25]. In contrast, Paul et al. [26] revealed that there was no significant difference in postural stability between CFS and control subjects as evidenced by differences in dispersion under eyes open and shut conditions measuring postural sway, as a measure of balance. The present study revealed that 30% of the patients with ME had disequilibrium.

The exact cause of the observed disequilibrium in patients with ME remains unknown. Because a positive Romberg test suggests a significant visual sensory compensation for truncal ataxia and limb ataxia was not observed in the patients, the main cause of the ataxia appears to be not of cerebellar origin. It appears to be of central type of vestibular origin, which is consistent with the previously revealed results of vestibular function tests in patients with CFS that have been shown previously [24]. The pathogenesis of the observed neurologic defect of disequilibrium is also unknown; it may be caused by either neurologic inflammation [27] or degeneration, or by a transient local cerebral circulatory impairment or hypoperfusion during orthostatic position. Whether disequilibrium is related to possible cerebral hypoperfusion

during orthostatic position in the study patients with ME remains to be elucidated. This is the limitation of the present study. Further investigation will be required to clarify the exact cause and mechanism of the disequilibrium observed in several patients with ME.

The present study demonstrated that disequilibrium revealed by neurological physical examinations was present in 32.5% of patients with OI and circulatory impairment during the active standing test was present in 47.5% of them, whereas in 17.5% both abnormalities were present. It is possible that patients with disequilibrium require an increased effort to maintain the orthostatic position, resulting in an exaggerated sympathetic activation with circulatory impairment. However, in 37.5% of patients with OI, neither of the abnormalities was noticed, suggesting an unknown cause for OI, which may be the cerebrovascular circulatory impairment of autoregulation in the orthostatic position or minimum disequilibrium undetected by the neurological physical examination employed in the present study.

In conclusion, patients with ME and disequilibrium predominantly report not only OI but also sitting intolerance. Postural reflex dysfunction in association with disequilibrium appears to play an important role in the induction of postural intolerance. Disequilibrium should be recognized as an important cause of OI and appears to be a more influential cause of OI than postural orthostatic tachycardia in patients with ME. Thus, disequilibrium is a useful sign for advanced disease.

Conflict of interest

The authors declare that there is no conflict of interest.

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