Research Paper

Paradigm shift to disequilibrium in the genesis of orthostatic intolerance in patients with myalgic encephalomyelitis and chronic fatigue syndrome

Kunihisa Miwa [a,1,*], Yukichi Inoue [b,1]

[a] Department of Internal Medicine, Miwa Naika Clinic, Toyama, Japan
[b] Department of Neurology, Toyama Prefectural Rehabilitation Hospital & Support Center for Children with Disabilities, Toyama, Japan

ABSTRACT

Background: Orthostatic intolerance (OI) markedly impairs activities of daily living in patients with myalgic encephalomyelitis (ME) or chronic fatigue syndrome. OI is surmised to be a cardiovascular symptom correlated with cerebral hypo-perfusion and exaggerated sympathetic activation. Postural instability or disequilibrium may be part of the etiology of OI.
Methods: The study comprised 72 patients with ME (18 men, 54 women; mean age, 37 ± 10 years) who underwent neurological examinations and the 10 min standing test. We quantified disequilibrium (instability upon standing with feet together and eyes shut), ability to complete the 10 min standing test, and postural orthostatic tachycardia (POT) during the test.
Results: Disequilibrium was detected in 23/72 (32%) patients and POT in 16 (22%). Nineteen (26%) patients failed to complete the 10 min standing test; disequilibrium was significantly more common in the 19- patient subgroup than in the 53-patient test-completing subgroup (89% vs. 11%, $p < 0.01$). However, the rate of POT was not different between the groups (21% vs. 23%, $p = 1.00$). Compared with the 49 (68%) patients without disequilibrium, the 23 (32%) patients with disequilibrium were significantly more likely to have failed to complete the test (74% vs. 4%, $p < 0.01$). The rate of POT was comparable between the groups (23% vs. 22%, $p = 1.00$). Among patients with disequilibrium who failed to complete the 10 min standing test and had a previous record, 6/8 had completed the test 6–24 months earlier when all six had reported no disequilibrium.
Conclusion: Disequilibrium should be recognized as an important cause of OI in patients with ME.

1. Introduction

Chronic fatigue syndrome (CFS), characterized by severe disabling fatigue, prolonged post-exertional malaise and unrefreshing sleep, causes a marked reduction in activities of daily living and impairs quality of life [1–3]. Central nervous system dysfunction associated with myalgic encephalomyelitis (ME) has been postulated as the main cause of CFS [4].

Most patients with ME or CFS also present with orthostatic intolerance (OI), which is the primary factor restricting daily functional capacity [5–9]. OI is characterized by the inability to remain upright without severe signs and symptoms, including hypotension, palpitation, light-headedness, pallor, fatigue, weakness, dizziness, diminished concentration, tremulousness and nausea [5,6]. With further progression of OI, patients may become intolerant to sitting and become bedridden. Most symptoms of OI are believed to be cardiovascular and related to

cerebral blood flow reduction and compensatory activation of the sympathetic nervous system [10]. Indeed, postural orthostatic tachycardia (POT), delayed orthostatic hypotension, and neurally mediated hypotension have been observed during OI in several patients [5,9–12]. Many such patients also have a small left ventricle and associated low cardiac output [13–18]. In addition, both the renin−aldosterone and anti-diuretic hormone systems that regulate circulatory blood volume were reported to be down-regulated [19].

Postural stability is often necessary to allow the static balance critical for performing many daily activities. Recently, we reported that postural instability or disequilibrium possibly related to central vestibular dysfunction should be considered to be involved in the pathogenesis of OI in patients with ME or CFS [20–23].

In the present study, we tried to clarify the importance of disequilibrium in the development of severe OI. We tested patients with ME

---

using a conventional active standing test and quantified the associations between disequilibrium and failure to complete the 10 min test.

2. Methods

2.1. Patients

We included 72 consecutive patients who were seen at our clinic between May 2016 and July 2018. ME was diagnosed according to the 2011 International Consensus Criteria [4]. Briefly, symptoms related to neuroimmune exhaustion, such as marked, rapid physical and/or cognitive fatigability in response to exertion, prolonged recovery period and low threshold of physical and mental fatigability, were compulsory for the diagnosis of ME. In addition, at least one symptom from 3 of the 4 symptom categories related to neurological impairments, including neurocognitive impairments, pain, sleep disturbance and neurosensory, perceptual and motor disturbances, and at least one symptom from 3 of the 5 symptom categories related to immune, gastro-intestinal and genitourinary impairments, including recurrent or chronic flu-like symptoms, susceptibility to viral infections, gastro-intestinal tract symptoms, genitourinary symptoms and sensitivities to food, medications, odors or chemicals, were required. Also at least one symptom of the symptoms related to energy metabolism/ion transportation impairments, including cardiovascular symptoms such as orthostatic intolerance, respiratory symptoms, loss of thermostatic stability and intolerance of extremes of temperature, was required.

All the patients could stand up and walk, and gave informed consent to participate. Patients complicated with any significant disease unrelated to ME had been excluded. Also, pregnant or lactating women were not included in this study. Of the 72-patient cohort, 18 were men and 54 were women, and the mean age was 37 ± 10 (range, 18–55) years. Thirty-eight of the patients were being seen for an initial visit, whereas the other 34 were being seen for a second examination and had recorded scores of their previous standing tests and neurological examinations for disequilibrium. The study was approved by the Toyama Prefectural Medical Association Ethics Committee (Approval#: 2016-010) and performed in accordance with the Declaration of Helsinki.

2.2. Neurological examination

All patients underwent comprehensive neurological examinations that included the standing-on-one-leg test and tandem gait test, as well as the Romberg test (standing with feet together and eyes shut).

2.3. Performance status (PS) grading

Subjective symptom severity was reported by patients just prior to the active standing test as described previously [24], On the basis of the patient report, PS was graded on a 10-point scale as follows:

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 or herself but cannot perform usual duties.

PS 8: The patient needs help to take care of himself or herself.

PS 9: The patient needs to rest the whole day and cannot take care of himself or herself without help.

2.4. Active standing test

The conventional active 10 min standing test was performed as reported previously [24]. The patients were asked to stand and keep standing without changing their foot positioning. Medications were unremarkable before the test; however, patients were required to discontinue adrenergic β-receptor blocking agents and vasopressors (if any), but not nutritional supplements or multi-enzyme tablets, before the standing test. POT was diagnosed as either an increase in heart rate of ≥30 bpm or an actual heart rate of ≥120 bpm, during the test. Instantaneous or delayed orthostatic hypotension was diagnosed as a decrease in systolic blood pressure of ≥20 mmHg or diastolic pressure of ≥10 mm Hg and/or systolic pressure of ≤90 mmHg during the test. Neurally mediated hypotension was diagnosed as orthostatic hypotension with a decrease in heart rate of ≥20 beats/min during the test.

2.5. Statistical methods

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

3. Results

3.1. Detection of disequilibrium

The Romberg test was used to diagnose disequilibrium; a positive diagnosis was scored when postural instability markedly worsened while standing, thereby producing wide oscillations and possibly a fall. Disequilibrium was detected in 23/72 (32%) patients. Among these, 7 (30%) had some instability on standing with their feet together and eyes open that worsened further upon closing the eyes; the remaining 16 (70%) had a positive Romberg test in which they were stable in the eyes open condition, and the stability was lost in the eyes shut condition. Instability in the standing-on-one- leg test was observed in 25/72 (35%) patients and abnormal tandem gait identified in 26/72 (36%) patients.

Table 1

Clinical data and neurological findings in patients with myalgic encephalomyelitis who failed to complete and who completed the active 10 min standing test.

	10 min Standings		p value
	Failed	Completed	
Number of patients	19 (26%)	53 (74%)	
Male/female	2/17	16/37	0.13
Age (years)	39 ± 12	36 ± 10	0.49
Disease history length (years)	7.8 ± 9.1	4.3 ± 5.5	0.14
Performance status score	4–8	3–8	<0.01
Median score	6	5	<0.01
Neurologic examinations			
Romberg standing, unstable	17 (89%)	6 (11%)	<0.01
Standing on one leg, unstable	16 (84%)	9 (17%)	<0.01
Tandem gait: abnormal	16 (84%)	11 (21%)	<0.01
Active 10-min standing test			
Body sway	17 (89%)	12 (23%)	<0.01
Postural orthostatic tachycardia	4 (21%)	12 (23%)	1.00
Orthostatic hypotension	2 (11%)	2 (4%)	–
Neurally mediated hypotension	2 (11%)	0 (0%)	–
Serum cortisol (μg/dl)	10.2 ± 9.0	8.7 ± 4.1	0.32
Plasma renin activity (ng/ml/h)	1.6 ± 1.4	1.8 ± 1.3	0.68
Plasma aldosterone concentration (pg/ml)	142 ± 102	147 ± 94	0.88

Values are presented as mean ± standard deviation.

Table 2

Clinical data, neurological findings and 10 min standing test results in patients with myalgic encephalomyelitis with and without disequilibrium.

	Disequilibrium		p value
	Positive	Negative	
Number of patients	23 (32%)	49 (68%)	
Male/female	3/20	15/34	0.15
Age (years)	37 ± 12	37 ± 10	0.98
Disease history length (years)	5.3 ± 7.1	5.2 ± 6.6	0.95
Performance status score	3–8	3–7	
Median score	7	5	<0.01
Neurologic examinations			
Standing on one leg, unstable	22 (96%)	3 (6%)	<0.01
Tandem gait: abnormal	21 (91%)	6 (12%)	<0.01
Active 10-min standing test			
Failed to complete	17 (74%)	2 (4%)	<0.01
Body sway	23 (100%)	6 (12%)	<0.01
Postural orthostatic tachycardia	5 (23%)	11 (22%)	1.00
Orthostatic hypotension	1 (4%)	3 (6%)	–
Neurally mediated hypotension	2 (9%)	0 (0%)	–

Disequilibrium: instability upon standing with feet together and eyes shut.
Values are presented as mean ± standard deviation.

3.2. Failure to complete the 10 min standing test

During the active 10 min standing test, 19 (26%) patients gave up standing after reporting symptoms of OI before completion. The average standing duration among these patients was 5.9 ± 1.6 min. Comparative data between patients who failed to complete and those who completed the 10 min standing test are summarized in Table 1. Disease history was generally longer in non-completing patients. PS scores were significantly higher in non-completing patients than completing patients, suggesting more restriction of activities of daily living in the former. Significantly higher rates of disequilibrium (89% vs. 11%, $p < 0.01$), unstable standing on one leg (84% vs. 17%, $p < 0.01$), and abnormal tandem gait (79% vs. 11%, $p < 0.01$) were found in the non-completing patient group. Body sway during the 10 min standing test was significantly more prevalent in the non-completing patients than in the completing patients (89% vs. 23%, $p < 0.01$); however, the rate of POT was not significantly different between the groups (21% vs. 23%, $p = 1.00$). Orthostatic hypotension and neurally mediated hypotension were rare during the test. The mean serum cortisol levels, the mean plasma renin activity levels and the mean plasma aldosterone concentrations were not significantly different between the groups.

3.3. Patients with disequilibrium

Comparative data between patients with and without disequilibrium are summarized in Table 2. Age and disease history length were not significantly different between patients with and without disequilibrium; however, the median PS score was significantly higher in patients with disequilibrium than in those without it. Also, the patients with disequilibrium demonstrated significantly higher rates of unstable standing on one leg (96% vs. 6%, $p < 0.01$) and abnormal tandem gait (91% vs. 12%,

$p < 0.01$) than those without it. Compared with the patients without disequilibrium, patients with disequilibrium failed to complete the 10 min standing test significantly more often (74% vs. 4%, $p < 0.01$) (Table 2). Body sway during the 10-min standing test was significantly more prevalent in the patients with disequilibrium than in those without it (100% vs. 12%, $p < 0.01$); notably the rate of POT was comparable between the groups (23% vs. 22%, $p = 1.00$). Delayed orthostatic hypotension was noted in one (4%) and neurally mediated hypotension in two (9%) patients with disequilibrium who failed to complete the 10 min standing test.

No patients were found to have dysdiadochokinesis; abnormal finger-to-nose, finger-to-finger, and heal-shin tests; or proprioceptive sensory disturbances.

3.4. Review of the previous records

Upon reviewing the initial visit records of the 34-patient subgroup being seen a second time, we noted that on the tests performed 6–24 months prior to the second visit, 5/34 patients had failed to complete the 10 min standing test. Among them orthostatic hypotension was reported in one and POT in a second. Two others had reported diagnosis of disequilibrium. Among the 8/34 total patients with disequilibrium who failed to complete the 10 min standing test, 2/8 were reported to have pre-test disequilibrium, and the remaining six were reported to develop disequilibrium during the follow-up. All of the six patients who failed to complete the current test and had disequilibrium, were reported to have no disequilibrium and completed it at the first test (Table 3).

4. Discussion

4.1. Disequilibrium as an important cause of OI

In the present study using the conventional active 10 min standing test and neurological examinations, most of the patients with diagnosed ME who could not complete the test had disequilibrium, as demonstrated by their difficulty with Romberg test. Also, when disequilibrium was present, it was significantly more likely that the patient would fail to complete the standing test, while not completing the test was extremely rare in those without disequilibrium. This suggests that disequilibrium could have a causal or etiologic role in OI. Indeed, body sway during the test was significantly more frequent in the patients with disequilibrium than in those without it. Moreover, the review of the records of the 34-patient subgroup at their second visit revealed that some of the patients with disequilibrium who could not complete the test had completed the test and were without disequilibrium at their first visit, suggesting that OI and disequilibrium had developed together during the interim time course. The dysfunction of postural reflex or disequilibrium play an important role in the etiology of OI, although the extent of causality in this association is still not clear. On the other hand, POT was not associated with OI to an appreciable extent. The incidence of POT observed was rather low in the study patients irrespective of the

Table 3

Time course of appearance of disequilibrium and failure to complete the 10 min standing test in 6 patients with myalgic encephalomyelitis.

Patient #	Age/Sex	History (years)	Interval (months)	Disequilibrium			10-min standing test			PS score		
				before		after	before		after	before		after
1	25/F	2.5	11	(−)	→	(+)	complete Symptom free, POT	→	9′30″ Fainting POT	4	→	6
2	34/F	3	12	(−)	→	(+)	complete Dyspnea, POT	→	8′40″ Light-headedness	3	→	6
3	32/F	7	12	(−)	→	(+)	complete Weakness	→	5′ Dizziness	3	→	6
4	39/F	10	6	(−)	→	(+)	complete Dyspnea, POT	→	7′10″ Nausea, Dyspnea, POT	5	→	7
5	29/F	9	10	(−)	→	(+)	complete Light-headedness	→	6′20″ Fainting, POT	3	→	4
6	34/F	10	24	(−)	→	(+)	complete Light-headedness, DOH	→	2′ Nausea	7	→	8

PS: performance status; POT: postural orthostatic tachycardia; DOH: delayed orthostatic hypotension; See text for details.

completion or the failure of the 10 min standing. We have reported [24] that the failure of 10 min standing was often observed with the apparent normal hemodynamics without POT in patients with ME/CFS who had completed the 10 min standing in association with POT previously, suggesting the development of impaired sympathetic activation during the progression of disease severity.

We also noted that patients with disequilibrium had higher PS scores than those without it, suggesting they had more severely restricted activities of daily living. It is possible the increased effort needed to maintain a standing position persistently increases fatigue and exaggerates sympathetic activation, amplifying the fatigue or exhaustion.

4.2. The cause of disequilibrium

The exact cause of the observed disequilibrium in patients with ME or CFS remains unknown. Because a positive Romberg test suggests a significant visual sensory compensation for the apparent truncal ataxia and limb ataxia was not observed in the patients, a cerebellar substrate seems unlikely. Rather, it appears to be of central vestibular origin, which is consistent with the previously described results of vestibular function tests in patients with CFS [22,23]. However, it is possible that those patients who could not stand stably even with their eyes open may have some cerebellar dysfunction. The pathogenesis of neurological deficit causing disequilibrium is also unknown. It may be neurologic inflammation [25] or degeneration. Also whether disequilibrium is related to possible cerebral hypoperfusion while standing upright in the study patients with ME remains to be elucidated.

Kakuda et al. [26] reported a therapeutic effect on fatigue in several patients with CFS after applying high-frequency repetitive transcranial magnetic stimulation (rTMS); they believed the effect was mediated by activation of the dorsolateral prefrontal cortex (DLPFC) of the patient's dominant hemisphere. Whether rTMS of the DLPFC would improve both OI and disequilibrium needs to be elucidated.

4.3. Study limitations

The present study had several limitations. First, the direct evidence showing the causal role of disequilibrium for OI is still lacking. Second, whether the therapeutic recovery from disequilibrium leads to OI free in the patients is still unknown. Third, the precise pathognomonic mechanism, by which the disequilibrium develops in some of the patients with ME or CFS, remains to be elucidated. The mechanism may vary among the patients. Indeed, the results of the neurological examinations, including the Romberg test, standing-on-one-leg test, and tandem gait test, were not identical among the patients with disequilibrium. Some differences were observed among the patients for each neurological test. Disequilibrium may be due to the deficit of the central vestibular system, cerebellar impairment, or a malfunction of DLPFC that is an important part of the neural network possibly involved in regulating the vestibular or cerebellar function.

5. Conclusions

Disequilibrium in association with postural reflex dysfunction appears to be strongly associated with the expression of OI. Our results indicate that disequilibrium or postural reflex dysfunction are in fact causal for OI and are more related to OI than POT in patients with ME or CFS.

CRediT author statement

Kunihisa Miwa: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, data collection, Writing - original draft preparation, Writing - review & editing, Visualization,

Project administration. **Yukichi Inoue**: Supervision.

Conflicts of interest

The authors have no, financial relationships, or conflicts of interest to disclose.

References

[1] S.D. Shafran, The chronic fatigue syndrome, Am. J. Med. 90 (1991) 730–739.
[2] K. Fukuda, S.E. Straus, I. Hickle, M.C. Sharpe, J.G. Dobbins, A. Komaroff, International Chronic Fatigue Syndrome Study Group. The chronic fatigue syndrome: a comprehensive approach to its definition and study, Ann. Intern. Med. 121 (1994) 953–959.
[3] N. Afari, D. Buchwald, Chronic fatigue syndrome: a review, Am. J. Psychiatr. 160 (2003) 221–236.
[4] B.M. Carruthers, M.I. van de Sande, K.L. DeMeirleir, et al., Myalgic encephalomyelitis: international Consensus criteria, J. Intern. Med. 270 (2011) 327–338.
[5] R. Schondorf, R. Freeman, The importance of orthostatic intolerance in the chronic fatigue syndrome, Am. J. Med. Sci. 317 (1999) 117–123.
[6] R. Schondorf, J. Benoit, T. Wein, D. Phaneuf, Orthostatic intolerance in the chronic fatigue syndrome, J. Auton. Nerv. Syst. 75 (1999) 192–201.
[7] K. Miwa, M. Fujita, Small heart with low cardiac output for orthostatic intolerance in patients with chronic fatigue syndrome, Clin. Cardiol. 34 (2011) 782–786.
[8] K. Miwa, Cardiac dysfunction and orthostatic intolerance in patients with myalgic encephalomyelitis and a small left ventricle, Heart Ves. 30 (2015) 484–489.
[9] A. Costigan, C. Elliott, C. McDonald, J.L. Newton, Orthostatic symptoms predict functional capacity in chronic fatigue syndrome: implications for management, QJM 103 (2010) 589–595.
[10] H. Tanaka, R. Matsushima, H. Tamai, Y. Kajimoto, Impaired postural cerebral hemodynamics in young patients with chronic fatigue with and without orthostatic intolerance, J. Pediatr. 140 (2002) 412–417.
[11] IOM (Institute of Medicine), Beyond Myalgic Encephalomyelitis/chronic Fatigue Syndrome: Redefining an Illness, The National Academies (Abstract), Washington DC, 2015.
[12] P.C. Rowe, I. Bou-Holaigah, J.S. Kan, H. Calkins, Is neutrally mediated hypotension an unrecognised cause of chronic fatigue? Lancet 345 (1995) 623–624.
[13] K. Miwa, M. Fujita, "Small heart syndrome" in patients with chronic fatigue syndrome, Clin. Cardiol. 31 (2008) 328–333.
[14] K. Miwa, M. Fujita, Cardiac function fluctuates during exacerbation and remission in young adults with chronic fatigue syndrome and "small heart", J. Cardiol. 54 (2009) 29–35.
[15] K. Miwa, M. Fujita, Cardiovascular dysfunction with low cardiac output due to small heart in patients with chronic fatigue syndrome, Intern. Med. 48 (2009) 1849–1854.
[16] B.E. Hurwitz, V.T. Coryell, M. Parker, et al., Chronic fatigue syndrome: illness severity, sedentary lifestyle, blood volume and evidence of diminished cardiac function, Clin. Sci. (Lond.) 118 (2010) 125–135.
[17] Q. Fu, T.B. VanGundy, M. Galbreath, et al., Cardiac origins of the postural orthostatic tachycardia syndrome, J. Am. Coll. Cardiol. 55 (2010) 2858–2868.
[18] K. Miwa, M. Fujita, Renin–aldosterone paradox in patients with myalgic encephalomyelitis and orthostatic intolerance, Int. J. Cardiol. 172 (2014) 514–515.
[19] K. Miwa, Down-regulation of renin–aldosterone and antidiuretic hormone systems in patients with myalgic encephalomyelitis/chronic fatigue syndrome, J. Cardiol. 69 (2017) 684–688.
[20] K. Miwa, Y. Inoue, Truncal ataxia or disequilibrium is unrecognised cause of orthostatic intolerance in patients with myalgic encephalomyelitis, Int. J. Clin. Pract. (2017), https://doi.org/10.1111/ijcp.12967.
[21] K. Miwa, Y. Inoue, The etiologic relation between disequilibrium and orthostatic intolerance in patients with myalgic encephalomyelitis (chronic fatigue syndrome), J. Cardiol. 72 (2018) 261–264.
[22] K. Miwa, Variability of postural orthostatic tachycardia in patients with myalgic encephalomyelitis and orthostatic tachycardia, Heart Ves. 31 (2016) 1522–1528.
[23] J.M.R. Furman, Testing of vestibular function: an adjunct in the assessment of chronic fatigue syndrome, Rev. Infect. Dis. 13 (11 Suppl) (1991) S109–S111.
[24] R. Ash-Bernal, C. Wall, A.L. Komaroff, et al., Vestibular function test abnormalities in patients with chronic fatigue syndrome, Acta Otolaryngol. 115 (1995) 9–17.
[25] Y. Nakatomi, K. Mizuno, A. Ishii, et al., Neuroinflammation in patients with chronic fatigue syndrome/myalgic encephalomyelitis: an ^{11}C-(R)-PK11195 PET study, J. Nucl. Med. 55 (2014) 945–950.
[26] W. Kakuda, R. Momosaki, N. Yamada, M. Abo, High-frequency rTMS for the treatment of chronic fatigue syndrome; a case series, Intern. Med. 55 (2016) 3515–3519. Shafran SD. The chronic fatigue syndrome. Am J Med 1992;90:730-739.