Cardiovascular Dysfunction with Low Cardiac Output Due to a Small Heart in Patients with Chronic Fatigue Syndrome

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Abstract

Objective Little attention has been paid to possible cardiovascular involvement in patients with chronic fatigue syndrome (CFS), although many of their symptoms and signs suggest cardiovascular dysfunction. Possible cardiovascular symptoms and cardiac function were investigated in CFS patients.

Methods Cardiovascular symptoms were intensively investigated and cardiac function was evaluated echocardiographically.

Patients Fifty-three patients (23 men and 30 women, mean age: 31±7 years) with CFS under 50 years were studied.

Results Slender build (body mass index <20 kg/m²) was common (47%). Possible cardiovascular symptoms including shortness of breath (32%), dyspnea on effort (28%), rapid heartbeat (38%), chest pain (43%), fainting (43%), orthostatic dizziness (45%) and coldness of feet (42%), were all frequent complaints. Hypotension (28%) was occasionally noted. Electrocardiograms frequently revealed right axis deviation (21%) and severe sinus arrhythmia (34%) suggesting accentuated parasympathetic nervous activity. Small heart shadow (cardiothoracic ratio ≤42%) was noted on the chest roentgenogram in 32 patients (60%). Echocardiographic examination demonstrated low cardiac indexes (<2 L/min/m²) with low stroke volume indexes (<30 mL/m²) due to a small left ventricular chamber in 19 (36%, p<0.05 vs. 8% in 36 controls). None had reduced left ventricular ejection fraction.

Conclusion Cardiovascular symptoms are common in CFS patients. Cardiac dysfunction with low cardiac output due to small left ventricular chamber may contribute to the development of chronic fatigue as a constitutional factor in a considerable number of CFS patients.

Key words: chronic fatigue syndrome, low cardiac output, small heart, cardiothoracic ratio, cardiac function

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Introduction

The chronic fatigue syndrome affects many young people in today's modern, stressful society; it is characterized by persistent or relapsing, severe disabling fatigue, not resolved by rest, causing a marked reduction of working activity (1-5). Although the fatigue is often accompanied by multiple unexplained symptoms including headache, sore throat, self-reported impairment in concentration and short-term mem-

ory, sleep disturbances, and musculoskeletal pain (1-5), the etiology of chronic fatigue syndrome remains unclear. Various factors have been implicated in this peculiar syndrome (1, 3-6). However, unreasonably the symptoms and signs have rarely been related to cardiovascular impairment or dysfunction.

Small heart syndrome has previously been reported by Master (7) as so-called "neurocirculatory asthenia" in young adults associated with a small heart shadow on the chest roentgenogram. The most frequent complaints are fatigue or

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weakness, rapid heart, chest pain, shortness of breath, nervousness, trembling, sweating and fainting. These symptoms are also common in patients with chronic fatigue syndrome. Recently, we reported that a small heart shadow on the chest roentgenogram is common in patients with chronic fatigue syndrome (8). Echocardiographic evaluation demonstrated that cardiac function was actually impaired with low cardiac output due to a small heart in many of the patients with chronic fatigue syndrome. In addition, the cardiac function fluctuated during the exacerbation and remission phases directly related to the severity of their symptoms (9).

In the present study, possible cardiovascular symptoms were intensively investigated and cardiac function was evaluated echocardiographically to clarify how prevalent cardiovascular impairment or dysfunction is in young adults with chronic fatigue syndrome.

Methods

Study population

After alternative medical and psychiatric causes of chronic fatigue-inducing illness had been excluded, chronic fatigue syndrome was diagnosed according to the revised case definition of Fukuda et al (10) as follows. Chronic fatigue syndrome was defined by the presence of the following: 1) self-reported, unexplained, persistent or relapsing fatigue lasting six or more consecutive months; is not substantially alleviated by rest; and results in marked reduction in previous levels of occupational, educational, social, or personal activities; and 2) the concurrent occurrence of four or more of the following eight symptoms: self-reported impairment in short-term memory or concentration severe enough to cause substantial reduction in previous levels of occupational, educational, social, or personal activities; sore throat; tender cervical or axillary lymph nodes; muscle pain; multi-joint pain without joint swelling or redness; headaches of a new type, pattern, or severity; unrefreshing sleep; and postexertional malaise lasting more than 24 hours.

The study population comprised 53 Japanese patients (23 men and 30 women: mean age 31 ± 7 years) with chronic fatigue syndrome who were younger than 50 years old. None of them had muscle atrophy detectable by the physical examination.

Symptoms and physical examination

All of the study patients underwent a thorough history taking at the first visit to our institute or when the diagnosis of chronic fatigue syndrome was established. The presence or absence of cardiovascular complaints including shortness of breath, dyspnea on effort, dyspnea at rest, rapid heartbeat, chest pain, orthostatic dizziness, coldness of feet, fainting and weakness was determined. They also underwent an intensive physical examination. In particular, abnormalities in heart sounds, such as murmurs and extrasounds, coldness of feet and presence of pretibial pitting edema and epigastric

splash sound were monitored. Bimanual palpability of the right kidney was also determined. The body mass index was calculated as body weight (kg)/body height (m)².

Chest roentgenograms

Cardiothoracic ratio (CTR) was calculated as the transverse diameter of the cardiac shadow divided by the transverse diameter of the thoracic cage at the level of diaphragm in the postero-anterior projection on the chest roentgenogram. In the present study, a $CTR \leq 42\%$ was defined as a small heart (8, 10, 11). Also, the presence or absence of narrow chest findings including flat chest and straight back was determined. Narrow chest was diagnosed when the anteroposterior diameter of the thoracic cage at the level of the 8th thoracic vertebra estimated in the right-to-left projection of the lateral view on the chest roentgenogram was less than 40% of the transverse diameter of the thoracic cage estimated in the postero-anterior projection.

Electrocardiographic examination

All of the study patients underwent a 3-min electrocardiographic recording following at least a 10-min rest in the morning. RR50 (%) was calculated as the number of differences >50 ms between two successive R-R intervals divided by total heartbeats.

Echocardiographic examination

All individuals underwent standard M-mode and two-dimensional echocardiography. The left ventricular (LV) dimensions were measured according to the recommendations of the American Society of Echocardiography (12). LV volume was calculated by the Teichholz' formula (13), and an ejection fraction was determined by the conventional method. Mitral valve prolapse was diagnosed according to the criteria of Gilbert et al (14) with Yoshikawa's modification (15). Echocardiographic parameters were compared between the patients and 36 age- and sex-matched healthy control subjects (15 males and 21 females with a mean age of 33 ± 8 years).

All studied patients gave informed consent, and the study protocol was approved by the ethics committee of our institution.

Statistical analysis

Values are presented as the mean $\pm$ standard deviation. Comparisons of echocardiographic parameters between the study patients and the controls were performed with Student unpaired t-test. Proportional data were analyzed by the chi-square test, with Yates' correction. The value of significance was set at $p < 0.05$.

Results

The results are summarized in Tables 1, 2 and also in Fig. 1. As shown in Table 1, minor criteria symptoms by the revised case definition (10) were often found. In addition,

Table 1. Clinical Profiles and Cardiovascular Complaints and Symptoms in 53 Study Chronic Fatigue Syndrome Patients

Minor criteria symptoms		
Difficulty concentrating	41 (77%)	
Forgetfulness	36 (68%)	
Sore throat	22 (42%)	
Neck or axillary tenderness	17 (32%)	
Myalgia	26 (49%)	
Arthralgia	16 (30%)	
Headache	32 (62%)	
Sleep disturbance or unrefreshing sleep	39 (74%)	
Postexertional malaise	38 (72%)	
Possible cardiovascular symptoms		
Shortness of breath	17 (32%)	
Dyspnea on effort	15 (28%)	
Rapid heartbeat	20 (38%)	
Chest pain	23 (43%)	
Orthostatic dizziness	24 (45%)	
Coldness of feet	22 (42%)	
Fainting	23 (43%)	
Weakness	25 (47%)	
Other symptoms		
Anorexia	19 (36%)	
Abdominal pain	16 (30%)	
Nausea	21 (40%)	
Diarrhea	15 (28%)	

possible cardiovascular symptoms including shortness of breath (32%), dyspnea on effort (28%), rapid heartbeat (38%), chest pain (43%), orthostatic dizziness (45%), coldness of feet (42%), fainting (43%) and weakness (47%) were found to be common in the study chronic fatigue syndrome patients. Also, gastrointestinal symptoms including anorexia (36%), abdominal pain (30%), nausea (40%) and diarrhea (28%) were frequent.

As shown in Table 2, hypotension was occasionally found (28%). Pretibial pitting edema (25%), cold feet (40%), epigastric splash sound (19%) and right kidney palpability (37%) were frequently noted on physical examination. Lymph node enlargement was relatively rare (23%). Mitral

valve prolapse was suggested in some of the patients by auscultatory findings including late systolic murmur (21%) and midsystolic click (7%). Slender built (body mass index $<20 \text{ kg/m}^2$) was frequently (47%) noted, whereas obesity (body mass index $>25 \text{ kg/m}^2$) was rare (13%). Chest roentgenographic examination revealed that small heart was prevalent (60%) in the study patients, as was narrow chest (43%). Figure 1 shows the chest roentgenogram of a typical case with chronic fatigue syndrome and small heart.

Both right axis deviation including vertical axis (electrical axis $\geq 90^\circ$) (21%), and severe sinus arrhythmia (RR50 $> 20\%$ of total beats during the 3-min electrocardiogram) (34%) were frequently noted in the electrocardiographic examination. Echocardiographic examination revealed that the mean values of LV end-diastolic and end-systolic dimensions, stroke volume indexes and cardiac indexes were all rather lower in the study CFS patients than in the control subjects, although the difference was not statistically significant. However, small values of LV end-diastolic dimensions ($<41 \text{ mm}$: 34%, $p<0.05$ vs. 11% in controls), stroke volume indexes ($<30 \text{ mL/m}^2$: 36%, $p<0.05$ vs. 8% in controls) and cardiac indexes ($<2 \text{ L/mL/m}^2$: 36%, $p<0.05$ vs. 8% in controls) were significantly more prevalent in the study patients as compared with those in the controls (Table 2). Mitral valve prolapse was noted in 8 (15%) of the study patients. No patient had a reduced ($<60\%$) left ventricular ejection fraction.

Discussion

It has been known that patients with chronic fatigue syndrome have various unexplained symptoms including headache, sore throat, self-reported impairments in concentration and short-term memory, sleep disturbances, and musculoskeletal pain. Several symptoms and physical findings are known to be prevalent among chronic fatigue syndrome patients, although none of them are specific for the diagnosis of the syndrome (10, 16). The subjects in the present study also had a variety of possible cardiovascular complaints, including chest pain, palpitation, dyspnea or shortness of breath, coldness of feet, dizziness and fainting, although all of these symptoms are not necessarily attributable to cardiovascular dysfunction. Frequently noted physical examination findings such as epigastric splash sound, right kidney palpability, cold feet and pretibial pitting edema, may be related to visceral ptosis with slender build, and peripheral circulatory impairment. Weakness, rapid heartbeat and orthostatic dizziness may be related to hypotension and orthostatic dysregulation. Auscultatory findings suggested typical mitral valve prolapse in some of the patients. In addition, chest roentgenographic, electrocardiographic and, echocardiographic examinations revealed several distinct findings in the present young adult patients. Specifically, a small heart shadow was often observed on the chest roentgenogram in these patients. Both small LV chamber size and poor cardiac function with low stroke volume and cardiac indexes were

Table 2. Physical, Chest Roentgenographic, Electrocardiographic and Echocardiographic Findings of 53 Study Chronic Fatigue Syndrome Patients

Physical findings				
Body temperature (°C)				36.4±0.3
Heart rate (beats/min)				73±13
Blood pressure (systolic/diastolic)				112±12/75±7
Hypotension (Systolic blood pressure <100mmHg)				15 (28%)
Lymphnode swelling				12 (23%)
Late systolic murmur				11 (21%)
Midsystolic click				4 (7%)
Cold feet				21 (40%)
Pretibial pitting edema				13 (25%)
Epigastric splash sound				10 (19%)
Right kidney palpability				20 (37%)
Obesity (body mass index >25)				7 (13%)
Slender built (body mass index <20)				25 (47%)
Chest roentgenographic findings				
Cardiothoracic ratio ≤42%				32 (60%)
Narrow chest				23 (43%)
Electrocardiographic findings				
Heart rate (beats/min)	>100			1 (2%)
	<60			9 (17%)
Right axis deviation (axis ≥90°)				11 (21%)
Clockwise rotation				9 (17%)
Severe sinus arrhythmia (RR50>20%)				18 (34%)
Supraventricular arrhythmia				4 (8%)
Ventricular arrhythmia				2 (4%)
Echocardiographic findings				
			Controls	
Left ventricular end-diastolic dimension (mm)		43±6	NS	45±4
	<41	18 (34%)	p<0.05	4 (11%)
Left ventricular end-systolic dimension (mm)		26±5	NS	27±1
	<26	19 (36%)	NS	6 (17%)
Stroke volume index (mL/m ²)		35±8	NS	39±7
	<30	19 (36%)	p<0.05	3 (8%)
Cardiac index (L/min/m ²)		2.5±0.6	NS	2.8±0.6
	<2	19 (36%)	p<0.05	3 (8%)
Ejection fraction (%)		69±6	NS	70±6
	<60	0 (0%)	NS	0 (0%)
Mitral valve prolapse		8 (15%)	NS	1 (3%)

NS: not significant

documented echocardiographically. Reduced LV ejection fraction was not observed in any of the patients. Electrocardiograms showed severe sinus arrhythmia and vertical or right axis deviation in a considerable number of the patients, suggesting parasympathetic predominance and vertical heart position.

Recently, we have reported that “small heart” is commonly noted in chronic fatigue syndrome patients, suggesting that small heart syndrome in association with a small LV cavity and poor LV function may be related to the genesis in these patients as a predisposing factor to fatigue (8). Moreover, repeated echocardiographic examinations also revealed that hemodynamic abnormalities including smaller LV chamber size, and diminished stroke volume and cardiac output during the exacerbation phase significantly improved during the remission phase, suggesting a direct relation between the severity of chronic fatigue and impaired cardiac function in chronic fatigue syndrome patients with a small

heart (9).

In 1944, Master (7) reported several young adult cases with both “small heart shadow” and “neurocirculatory asthenia” and hypothesized that the symptoms might be caused by diminished venous return, diminished cardiac output, anoxic heart muscle and decreased oxygen saturation of the blood as a result of constitutionally small heart. Similarly, DaCosta (17) described “irritable heart” in 1871, a peculiar form of functional disorder of the heart found in the military population during the American Civil War. The disorder frequently presented after an episode of diarrhea. Fatigue was an almost universal complaint in DaCosta’s syndrome, although symptoms included palpitation, cardiac pain, headache and dimness (17, 18). The present study showed evidence of a small heart chamber and impaired cardiac function in patients with both chronic fatigue syndrome and small heart. Diarrhea, sweating and loss of appetite may lead to dehydration and reduce venous return or preload, re-

Figure 1. The chest roentgenogram of a 34-year-old female chronic fatigue syndrome patient with a “small heart” [cardiothoracic ratio (CTR): 33%]. She had suffered from relapsing severe general malaise and easy fatigability for several years. She also frequently developed orthostatic dizziness. She frequently became unable to work as a housewife due to severe malaise and headache. The symptoms were exacerbated every summer. The upper arrow line indicates the cardiac transverse diameter, and the lower line, the thoracic transverse diameter.

sulting in further decreases in both stroke volume and cardiac output, thereby exacerbating symptoms in young chronic fatigue syndrome patients with small heart. Komaroff et al (16), based on analysis of the experiences from one large center, reported that gastrointestinal symptoms including anorexia and nausea, discriminated chronic fatigue syndrome patients from the control and the patients with other conditions. Preload reduction due to dehydration may

contribute to the development and exacerbation of symptoms via further lowering cardiac output in many of these patients.

Patients with small heart are known to have slender physiques with low body mass indexes, frequently visceral ptosis with wandering kidney, asthenia, nervousness as well as foot coldness, suggesting physical, autonomic nervous and psychological irritability or lack of relaxation (6, 9, 17). Autonomic nervous dysfunction with accentuated basal parasympathetic tone may be associated with these symptoms through inhibiting compensatory sympathetic activation which otherwise contributes to preserve cardiac function.

Although muscle atrophy was not evident in the study patients, it is possible that total muscle volume has been reduced due to immobility in the patients as compared with the controls. It cannot be excluded that low cardiac output is attributable in part to the decreased demand by the loss of muscle volume. Further investigation is needed to clarify the causal relationship between the low cardiac output observed in the patients and the symptoms of chronic fatigue syndrome.

In conclusion, possible cardiovascular symptoms including dyspnea on effort, palpitation, chest pain, fainting, orthostatic dizziness and coldness of feet, are often complaints of young adult chronic fatigue syndrome patients. Electrocardiograms frequently showed severe sinus arrhythmia, suggesting exaggerated parasympathetic nervous function. Echocardiographic examination demonstrated poor LV function resulting from a small LV chamber in a considerable number of these patients. Thus, impaired cardiac function with low output appears to contribute to the development of chronic fatigue as a constitutional factor in a considerable number of patients with chronic fatigue syndrome.

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