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Chronic fatigue syndrome: physical and cardiovascular deconditioning

F. DE LORENZO, H. XIAO, M. MUKHERJEE, J. HARCUP, S. SULEIMAN, Z. KADZIOLA and V.V. KAKKAR

From the Thrombosis Research Institute, London, UK

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Summary

We investigated whether chronic fatigue syndrome (CFS) patients have physical and/or cardiovascular de-conditioning, in 273 CFS patients and 72 healthy controls. We used laboratory tests to assess haematological, biochemical, endocrinological and immunological systems. The cardiovascular system was assessed by echocardiography and carotid echography. Body composition was determined by dual energy X-ray absorptiometry (DEXA). CFS patients had smaller left ventricular end systolic ($p<0.001$) and diastolic ($p=0.008$) dimensions but thinner posterior walls ($p=0.02$) than corresponding values in healthy controls. Left ventricular mass was also reduced in CFS patients ($p=0.006$). Both maximum ($p<0.001$) and minimum ($p<0.008$) diameter of the carotid artery were smaller in CFS patients. The laboratory screening tests showed significant differences in serum albumin ($p=0.05$), phosphate ($p=0.02$), HDL-cholesterol ($p=0.03$), HDL:total cholesterol ratio ($p=0.01$), triglycerides ($p=0.02$), neutrophils ($p=0.01$) and thyroid-stimulating hormone ($p=0.04$) between CFS patients and controls. Male CFS patients had an increased percentage of fat mass compared with healthy male subjects ($p=0.02$). This large group of CFS patients had evidence of physical and cardiovascular de-conditioning, suggesting that in these patients a graded exercise programme could lead to physical reconditioning and could increase their ability to perform physical activities.

Introduction

Chronic fatigue syndrome (CFS) is an illness of unknown cause, characterized by unexplained, disabling fatigue lasting more than 6 months, chronic and recurrent low-grade fever, pharingitis, adenopathy, arthralgia and neuropsychological symptoms.[1,2]

The Centers for Disease Controls (CDC) have produced a working case definition for such a heterogeneous disease which relies on two major criteria that must be met: (i) new onset of severe fatigue for a period of 6 months; and (ii) exclusion of other clinical conditions that may produce similar symptoms. The CDC case definition also includes 11 symptom-related criteria and three based on the findings of physical examination criteria.[1,2]

Multiple abnormal immunological, hematological, virological and neuroendocrine laboratory findings have been reported in CFS,[3–6] suggesting the possible presence of different biological processes that may contribute to the symptoms.

A variety of immunological studies have detected abnormalities in immunoglobulin levels, cytokine production, and in markers of immune activation in a varying proportion of CFS patients.[7,8]

In a variable proportion of CFS patients the presence of leukocytosis or leukopenia,[9,10] lymphocytosis or lymphopenia,[11,12] monocytosis[13] and elevated sedimentation[11,13] rates has been observed, also mild elevations in hepatic transaminase levels,[12] but their rates were too low to be useful for diagnosis.

More recently, delayed orthostatic hypotension associated with decreased or increased heart rate has been found in 30% of CFS patients.[14,15] An

Address correspondence to Dr F. De Lorenzo, Thrombosis Research Institute, Emmanuel Kaye Building, 1 Manresa Road, London SW3 6LR

altered sympathetic-parasympathetic balance has been proposed as the possible cause of orthostatic symptoms in CFS patients.[14] Some suggested mechanisms of orthostatic intolerance could be due to cardiovascular de-conditioning.[16] Furthermore, phosphate diabetes has been found in 14% of patients with CFS.[17] One reason why CFS patients might have a decrease in oxidative metabolism could be related to a metabolic defect that is secondary to a state of chronic underutilization of skeletal muscle.[17] If the 'de-conditioning' of skeletal muscle is a clinical reality, CFS patients may be subject in some degree, to its metabolic effects.[17] On the other hand, physical de-conditioning has been excluded as the principal pathogenetic mechanism of CFS.[18]

Therefore, in the last few years it has been suggested that an appropriate CFS screening test should also include erythrocyte sedimentation rate, renal and liver function, thyroid-stimulating hormone, electrolytes, glucose, chemistry tests of minerals and skeletal muscle assessment.[3]

The aims of this prospective study were to investigate the hypothesis of physical de-conditioning as a possible cause of reduced ability to perform physical activities by the assessment of the cardiovascular system with the use of electrocardiography, echocardiography and carotid echography; and to evaluate the skeletal muscle mass by dual energy X-ray absorptiometry (DEXA).

Methods

CFS-CDC case definition

This definition[1] includes two major criteria that must be met: (i) the new onset of persistent or relapsing, debilitating fatigue, or easy fatiguability in a person who has no previous history of similar symptoms, that does not resolve with bedrest and that is severe enough to reduce or impair average daily activity below 50% of the patient's premorbid activity level for a period of at least 6 months; and (ii) exclusion of other clinical conditions that may produce similar symptoms by thorough evaluation, based on history, physical examination and appropriate laboratory findings. It also includes 14 minor criteria: 11 symptom criteria, and three physical examination criteria. To meet the case definition, patients must meet both major criteria, and either eight of 11 symptom criteria or six of 11 symptom criteria and two of three physical examination criteria.

Patient population

The Thrombosis Research Institute received filled-in questionnaires from 2000 patients with chronic fatigue, who were invited for several investigations to confirm the diagnosis of CFS. The large number of patients with CFS included in this study is related to the media coverage of our research projects.

Of the 2000 responders, 273 fulfilled the CDC criteria for the working case definition of CFS.[1] They were observed and had clinical and laboratory evaluations. Patients completed a 40-item symptom checklist, simply answering 'yes' or 'no' to whether they suffered from a wide range of symptoms.

Patients whose questionnaire, interview, examination or medical record revealed medical conditions associated with chronic fatigue such as chronic infections, parasitic infection, neuromuscular diseases, connective tissue disorders were excluded, as were patients with other auto-immune diseases, cardiovascular diseases, malignancies, severe gastrointestinal disorders, endocrine diseases, haematological and renal diseases and psychiatric disorders.

Selection of controls

Controls were 72 volunteers reporting no history of chronic illness on a questionnaire, who were attending the Research Institute as part of a health screening programme. All underwent physical examination and a laboratory work-up to assess their healthy condition, and reported that they had not experienced a period of fatigue or unexplained malaise lasting more than 1 week in the 6 months preceding immunological assessment.

Ethics approval

The study was approved by local ethical review committee and written consent was obtained from all participants.

Clinical data

Standardized historical and physical examination data were obtained at both sites according to a protocol. The symptom checklist enquired about 40 symptoms commonly seen in CFS, including mild fever or chills; sore throat; unexplained, generalized muscle weakness, myalgia, prolonged generalized fatigue, headaches, arthralgia, insomnia, hypersomnia, photophobia, confusion, inability to concentrate, difficulty with thinking.

The following measurements were taken for all subjects: height, weight, tympanic temperature, pulse rate, peripheral oxygen saturation and blood pressure. Body mass index was calculated as weight divided by height squared.

Electrocardiography

Standard 12-lead electrocardiograms were recorded at rest. Heart rate, PR interval, QRS duration, QT

and corrected QT intervals, axes of P, QRS and T waves were determined and printed out by built-in software.[19]

Doppler and echocardiography

Cross-sectional image-guided M-mode echocardiograms of the left ventricle were recorded at the tip level of the mitral leaflets, with a 2.25 MHz transducer. Records were made simultaneously with lead II electrocardiograms on a magnetic video tape. Left ventricular end diastolic dimension (LVEDD), anterior (TH_{ant}) and posterior (TH_{post}) wall thickness were taken at the onset of the QRS complex on the ECG. The minimum diameter of the left ventricle was taken as end systolic dimension. Left ventricular (LV) mass was calculated as:[20]

$$\text{LV mass (g)} = 1.04 \times (\text{LVEDD} + TH_{ant} + TH_{post})^3 - \text{LVEDD}^3 - 14$$

Pulsed-wave Doppler was used to record mitral, tricuspid and aortic flow velocities, again with simultaneous ECGs. The following measurements were made: (i) peak velocity of aortic flow, ejection time from the onset to its end of aortic flow and acceleration time from the onset to its peak; (ii) peak velocities of mitral E and A waves; (iii) peak velocities of tricuspid E and A waves.

Carotid echography

A 10 or 5 MHz linear transducer was used to record cross-sectional image-guided M-mode echograms of the left common carotid artery, at the level of approximately one centimetre below the bifurcation. From the M-mode records, the maximum and minimum diameters of the carotid artery were determined on-line. Carotid distensibility was defined as the difference between maximum and minimum diameters divided by arterial pulse pressure. Pulsed-wave Doppler signals of carotid flow were obtained, and carotid pulsatility index was calculated by a built-in software.

Laboratory testing

For CFS patients and controls, tests were performed in the same laboratories by technicians blinded to the source of the specimens. All CFS patients and healthy subjects were examined in a fasting state. The haematological, biochemical, endocrinological and immunological specimens were processed immediately.

Biochemistry and haematology testing

Sodium and potassium were measured using ion-selective electrodes and creatinine, calcium, phosphate, alkaline phosphatase, aspartate transaminase, total bilirubin, glucose, total protein, albumin, gamma glutamyltransferase, cholesterol and triglycerides by spectrophometric methods on the Technicon DAX 48 analyser (Bayer Diagnostic). HDL cholesterol was measured by precipitation of other cholesterol fractions with magnesium carbonate, followed by assay of remaining cholesterol on the DAX 48. LDL cholesterol was calculated using the Friedwald equation. A Coulter S-Plus STKR automated haematology analyser was used to produce a full blood count.

Immunology testing

Immunoglobulins were quantified by an immunonephelometric technique. The instrument used was the Behring nephelometric analyzer. Calibration was achieved with standard serum SPS–01 (UK Protein Reference Unit). T-cell analysis used anti-CD3/4 and anti-CD3/8 monoclonal antibodies (Becton Dickinson). A whole-blood lysis method was used, and cells were counted in a FACScan flow cytometer using standard software.

Endocrinology testing

Thyroid-stimulating hormone, free thyroxin and cortisol were assayed by enzyme-immunometric methods on the Immuno 1 immunochemistry analyzer (Bayer Diagnostics). Testosterone was assayed by radioimmunoassay (Biomerieux Limited).

Dual energy X-ray absorptiometry (DEXA)

Total body composition scan was performed using a Lunar DPX dual energy X-ray absorptiometer (Lunar Corp, w1: software version 3.6). The patient lay on the scan table and the DPX scanner performed a series of transverse scans from head to toe with 1-cm intervals at a medium speed mode using a constant X-ray source with effective energies of 38 and 70 keV. The scan took about 20 min to complete, and the radiation dose was less than 0.05 mrad. The precision (co-efficient of variation of duplicate total body scans in five normal subjects, with repositioning between scans) was 0.4% for total bone mineral density (TBMD), 1.4% for total percentage fat and 0.8% for total lean mass.

Statistical analysis

The statistical analysis was done using SAS software. Not all the variables were normally distributed, consequently results are expressed as median with 1st and 3rd quartiles, and non-parametric tests were used for between-group comparisons.

Univariate analysis

Fisher's exact test and Wilcoxon's rank-sum test were used for between-group comparisons.

Multivariate analysis

For each analysed variable, the influence of age and body mass index was estimated with the aid of multivariate linear regression (separately for each group). This estimated effect was used to compute adjusted values:

$$\text{Adjusted value} = \text{value} - A \times (\text{age} - \text{age}_{\text{median}}) - B \times (\text{BMI} - \text{BMI}_{\text{median}})$$

where 'value' is the original value of the analysed variable; $\text{age}_{\text{median}}$ and $\text{BMI}_{\text{median}}$ are the medians for the whole sample (both groups together), and A and B are the linear regression coefficients.

Such adjusted values were compared using Wilcoxon's rank-sum test.

Results

We analysed data from 273 CFS patients and 72 healthy subjects. Table 1 shows the anthropometric parameters and electrocardiogram findings in both groups.

Healthy subjects were significantly older ($p = 0.001$) and fewer were female (NS) than among CFS patients, while tympanic temperature ($p < 0.001$) and heart rate ($p < 0.001$) were significantly higher in CFS patients.

The analysis of the electrocardiograms showed that the QT interval was significantly shorter in CFS patients than in healthy subjects ($p < 0.001$), but this difference disappeared when corrected for by the difference in heart rate.

A statistical difference between groups ($p < 0.05$) was seen for the incidence of all the systemic (sore throat, fever), muscular (myalgia, muscle weakness) and neuropsychological (confusion, sleep disorders, photophobia, amnesia) parameters considered in the initial questionnaire (data not shown).

The biochemistry results in CFS patients showed significantly lower phosphate ($p = 0.02$) serum levels than in healthy subjects. On the other hand albumin serum levels were higher in CFS patients ($p = 0.05$).

Patients with CFS also presented with higher triglycerides ($p = 0.02$) and lower HDL cholesterol ($p = 0.03$) serum levels compared with healthy subjects.

Moreover, the HDL/total cholesterol ratio ($p = 0.01$) was lower in CFS patients. The haematological tests showed a significantly higher neutrophil count in CFS patients ($p = 0.01$).

Basal cortisol serum level was higher in CFS patients than in healthy subjects (379 mg/dl vs. 367.8 mg/dl), as was thyroid-stimulating hormone ($p = 0.04$). No significant differences between CFS patients and healthy subjects were observed regarding immune system activity.

In patients with CFS, left ventricular end systolic ($p < 0.001$) and diastolic ($p = 0.008$) dimensions were smaller, and the posterior wall was thinner ($p = 0.002$), than in healthy controls (Table 2). Left ventricular mass was reduced in CFS patients ($p = 0.006$). All other measurements from Doppler from aortic, mitral and tricuspid flows did not differ between groups (data not shown). Both maximum ($p < 0.001$) and minimum ($p = 0.008$) diameters of the carotid artery were significantly smaller in CFS patients compared with healthy subjects (Table 2).

Total body composition determined by DEXA showed an increased percentage of tissue fat in both legs in CFS male patients ($p = 0.02$) (Table 3**a**) whereas total percentage of tissue fat was increased, but not significantly, in both CFS men and women as compared with healthy controls (Table 3**a** and **b**).

Discussion

The objective of this study was to investigate the possible presence of physical de-conditioning in CFS

Table 1 Clinical details

	Healthy ($n = 72$)	CFS ($n = 273$)	p
Female	40 (56%)	175 (61%)	0.22
Age (years)	47.3 (38.3–56.4)	41.3 (32.4–49.7)	0.001
Body mass index (kg/m^2)	23.3 (21.1–26.2)	22.8 (20.9–26.0)	0.48
Temperature (°C)	36.7 (36.3–37.0)	36.9 (36.5–37.2)	<0.001
Systolic blood pressure [mmHg]	120 (110–140)	120 (110–130)	0.41
Diastolic blood pressure (mmHg)	80.0 (70.0–82.5)	80.0 (70.0–80.0)	0.61
Heart rate:ECG (bpm)	62.0 (54.5–67.0)	67.0 (61.0–74.0)	<0.001
QT:ECG (ms)	389.5 (371.0–404.5)	374.0 (355.0–391.0)	<0.001
Smoker	8 (11%)	39 (14%)	0.57

Data are medians (1st –3rd quartiles) or numbers (percentage).

Table 2 Echocardiogram and carotid arterial ultrasound findings

	Healthy ($n=72$)	CFS ($n=273$)	p	
			Unadjusted	Adjusted for BMI and age
Left ventricle measurements				
End systolic dimension (cm)	3.2 (2.8–3.5)	2.9 (2.6–3.2)	0.003	<0.001
End diastolic dimension (cm)	4.7 (4.3–5.1)	4.6 (4.3–4.9)	0.05	0.008
Posterior wall thickness (cm)	0.9 (0.7–1.0)	0.8 (0.7–0.9)	0.03	0.002
Ventricular mass (g)	155.8 (133.6–227.5)	145.3 (120.8–183.0)	0.008	0.006
Carotid artery measurements				
Minimum diameter (mm)	6.5 (6.0–7.1)	6.2 (5.6–6.7)	0.02	0.008
Maximum diameter (mm)	5.8 (5.1–6.3)	5.4 (4.9–5.9)	0.004	<0.001

Data are medians (1st –3rd quartile).

Table 3a DEXA measurements: men

	Healthy ($n=32$)	CFS ($n=98$)	p	
			Unadjusted	Adjusted for BMI and age
Total % tissue fat	22.9 (17.0–26.8)	24.0 (19.0–28.7)	0.16	0.19
Upper body % tissue fat	0.23 (0.17–0.29)	0.24 (0.18–0.29)	0.35	0.07
Lower body % tissue fat	20.1 (16.2–23.5)	23.3 (17.6–27.9)	0.02	0.02

Data are medians (1st –3rd quartile).

Table 3b DEXA measurements: women

	Healthy ($n=40$)	CFS ($n=175$)	p	
			Unadjusted	Adjusted for BMI and age
Total % tissue fat	32.2 (27.6–43.8)	34.6 (29.7–40.4)	0.53	0.58
Upper body % tissue fat	0.31 (0.24–0.41)	0.33 (0.26–0.38)	0.55	0.17
Lower body % tissue fat	35.3 (31.7–46.3)	38.7 (33.3–43.4)	0.52	0.56

Data are medians (1st – 3rd quartile).

and to compare the results of readily available laboratory studies, and clinical and anthropometric data, for patients with CFS versus those for healthy subjects. Ours is the first study of total body composition and cardiovascular function in a large number of patients with CFS.

Among systemic signs and symptoms, we found increased body temperature, pulse, and heart rate in CFS patients, as has been previously reported.[3] These findings are consistent with those seen in patients with altered sympathetic-parasympathetic balance and/or physical deconditioning.[3,16]

All the symptoms previously associated with CFS[1,2] were more frequently reported by patients than healthy subjects.

Until a few years ago, routine laboratory blood test results were usually considered normal in CFS patients.[3] However, more recent studies[4–6] suggested that objective clinical laboratory test results could support the presence of a biological process that may contribute to, or be responsible for, the symptoms of CFS.

Although there is at present no one specific test for CFS, in our study an appropriate screening test was performed on the basis of specific guidelines.[3]

Several studies[11–13] have reported a variable proportion of patients with CFS to have leukocytosis, lymphocytosis and monocytosis. However, our analysis of the complete blood cell count with a differential count showed an higher neutrophil count in CFS patients than in healthy subjects.

Increased lymphocyte count in CFS patients has been explained as a possible sign of chronic viral infections,[11,12] but to our knowledge higher neutrophil count in CFS patients, as a possible evidence of chronic bacterial infections, has not been previously reported. A pathogenically significant imbalance of the immune system in CFS patients has been postu-

lated by several authors,[7,8] but we did not observe any significant difference between CFS patients and healthy subjects.

Of interest, chronic fatigue, myalgia and depression have also been reported in patients with hypophosphataemia due to an idiopathic phosphaturia[22] and in patients with idiopathic phosphate diabetes.[23,24] In our study, CFS patients presented with lower phosphate serum levels compared with healthy subjects. This finding is probably related to the presence of phosphate diabetes in 14% of patients with CFS.[17] Other studies are needed to establish the prevalence and incidence of hypophosphataemia due to renal disorders in CFS patients by an analysis of a rate for renal tubular reabsorption of phosphate and phosphate clearance.

The raised serum albumin level in CFS patients could indicate a mild degree of dehydration. In one previous report, an erratic arginine-vasopressin production in CFS patients was observed that caused a significant decreased urine osmolality and abnormal water metabolism.[25]

Furthermore, CFS patients had higher serum triglyceride levels and lower serum HDL-cholesterol levels. Body fat distribution has been demonstrated to be an independent predictor of triglycerides and HDL-cholesterol serum levels.[26] In our group of CFS patients, as compared with healthy subjects, there was an increased percentage of fat, although body mass index was not different between these two groups. The direction of change in muscle mass and fat tissue in CFS patients, although they were younger, is expected to happen with age. This can be explained to certain extent, by the reduced ability of patients with CFS to perform physical activities, but we could not exclude the possibility that an as yet undefined systemic process could play a role in the different body composition of such patients. Giada *et al.*[27] studied the effect of physical conditioning and de-conditioning on blood lipids and body composition. They concluded that after physical de-conditioning, body fat mass increases in parallel with LDL cholesterol and fibrinogen. These changes were reversed after a period of reconditioning due to physical training.[27]

On the other hand, the possible role of physical de-conditioning as a cause of reduced ability to perform physical activity in CFS patients has been excluded by Montague *et al.*[18] by a graded exercise test. In this study CFS patients had a significantly lower rise in their heart rates with exercise when compared with control subjects.

In our patients with CFS, left ventricular end systolic and diastolic dimension and posterior wall thickness values were smaller than those seen in healthy controls, as were the minimum and maximum diameters of the carotid artery. This resulted in calculated left ventricular mass being lower than normal. The combination of fast heart rate and a small left ventricular dimension in CFS might suggest that the cardiovascular system in CFS was in a state of de-conditioning. A decreased ventricular mass is further evidence of this. The finding that de-conditioning may be associated with a considerable reduction in wall thickness is confirmed by the observations of Maron *et al.*[28]

Although, fatigue often leads to inactivity, de-conditioning, and more fatigue, it has to be investigated if the cause of this clinical state is only related with physical inactivity or with an altered sympathetic-parasympathetic balance as previously reported.[14,15,29] Freeman *et al.*[16] have shown that de-conditioning and a postviral idiopathic autonomic neuropathy may possibly contribute to autonomic dysfunction in CFS patients. Orthostatic hypotension as an effect or cause of cardiovascular de-conditioning may cause several CFS symptoms, such as lightheadedness, headache and fatigue.[16]

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