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Autonomic function and serum erythropoietin levels in chronic fatigue syndrome

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Abstract

Objective: Given previous findings, we wished to investigate whether there was evidence of autonomic dysfunction in patients with chronic fatigue syndrome, and whether this could be related to reduced erythropoietin levels and altered red blood cell indices. **Methods:** We assessed autonomic function and analysed blood parameters (including erythropoietin) in 22 patients with chronic fatigue syndrome who were medication-free and without comorbid depression or anxiety. Results were compared to 23 iron-deficiency anaemia patients and 18 healthy individuals. **Results:** Autonomic testing in patients with chronic fatigue syndrome yielded a significantly greater increase in heart rate together with a more pronounced systolic blood pressure fall on standing compared to healthy individuals. Heart rate beat-to-beat variation on deep breathing and responses to the Valsalva manoeuvre were normal. Two of 22 patients with chronic fatigue had mild normochromic normocytic anaemia with normal ferritin, vitamin B12 and folate levels. Serum erythropoietin levels were within reference range. **Conclusion:** Some autonomic dysfunction is present in chronic fatigue syndrome (CFS) patients; the explanation remains uncertain, but could relate to cardiovascular deconditioning. There were no major haematological, biochemical or immunological abnormalities in these patients.

Keywords: Chronic fatigue syndrome; Erythropoietin; Autonomic dysfunction; Anaemia

Introduction

Chronic fatigue syndrome (CFS) has been reported to be associated with autonomic dysfunction, including delayed orthostatic hypotension, vagal dysfunction and postural tachycardia [1–3]. Specifically, delayed orthostatic hypotension (hypotension beyond 10 min of standing) may coexist with feeling fatigued, whereas more acute orthostatic hypotension may relate to lightheadedness [4]. Recent studies of CFS patients with delayed orthostatic hypotension have found significantly decreased red cell mass [1] and impaired sympathetic innervation of foot veins; such changes might, if more widespread, contribute both to the blood pressure drop and symptoms of fatigue [5].

Erythropoietin (EPO), produced by the renal peritubular fibroblasts, stimulates the proliferation and differentiation of erythroid cells in the bone marrow and thus regulates the red blood count. EPO deficiency can lead to a normochromic normocytic anaemia; of relevance here is that EPO production is modulated by the sympathetic nervous system activity, most likely through β-adrenergic receptors [6], and that EPO-deficient anaemia can occur in autonomic neuropathy [7].

We have investigated, therefore, whether there is evidence of autonomic dysfunction or EPO deficiency in CFS. We hypothesised that CFS patients may suffer from

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altered autonomic function, including renal sympathetic denervation, which may lead to low EPO levels and subsequent anaemia.

Methods

Subjects

Twenty-two patients with CFS (representing approximately one in five attenders due to our exclusion criteria) were recruited from our tertiary referral CFS clinic; 23 Haematology Clinic patients with laboratory-defined iron deficiency anaemia and 18 healthy, non-anaemic subjects acted as controls. CFS patients were independently interviewed using a semistructured format [8] by two psychiatrists: CFS was diagnosed according to the Centres for Disease Control and Prevention (CDC) [9], while patients with comorbid depression or anxiety [10] were excluded. Healthy subjects were recruited from members of staff; medical screening excluded CFS, anaemia and a significant past medical or psychiatric history. All subjects were medication free except for intermittent paracetamol/ibuprofen in six CFS patients. A full clinical examination was performed in all patients. The study received Ethics Committee approval; written informed consent was obtained from all subjects.

Procedures

Questionnaires

Each patient completed our routine questionnaires assessing fatigue [11], psychiatric symptoms (GHQ-28 [12]) and disability (SF-36 [13]).

Autonomic function tests

We obtained the following measures:

a. Heart rate beat-to-beat variation on deep breathing, determined by measuring the R–R interval electrocardiographically during six breathing cycles [14].
b. Heart rate response to the Valsalva manoeuvre during and after breathing against a resistance of 40 mm Hg, and the Valsalva ratio [14].
c. Heart rate increase on standing at 15 s [15].
d. Blood pressure readings after remaining supine for at least 10 min and upon standing at 1-min intervals for 5 min. Using the lowest standing value, orthostatic hypotension was defined as a fall in systolic blood pressure of at least 20 mm Hg [16]. Symptoms on standing, such as lightheadedness and dizziness, were recorded.

Except for the Valsalva ratio, the obtained results were compared to those of healthy individuals.

Blood and urine analysis

A full blood count, serum EPO and creatinine concentration were obtained in all the patients. CFS patients were tested additionally for reticulocytes, serum ferritin, B12, folate, C-reactive protein, electrolytes and ESR. Furthermore, the urinary albumin/creatinine ratio was established from random midstream urine samples to detect microalbuminuria as an indicator for renal impairment. The WHO defines anaemia as a Hb < 13 g/dl in males and a Hb < 12 g/dl in females. As the majority of our patients were female, we opted for a cut-off of 12 g/dl.

EPO assay

Serum EPO levels were measured by a two-site chemiluminescence immunoassay automated for use on a Nicols Advantage analyser (Nicols Institute Diagnostics; San Juan Capistrano, USA). Within- and between-assay coefficients of variation were 2.7% and 5.3% at 17.7 mU/ml.

Statistical analysis

Values are given as mean ± S.D. We used a one-way ANOVA for three group comparisons and independent *t* tests (two-tailed) for two group comparisons. Correlations were calculated using Pearson's product-moment correlation coefficients.

Results

Gender distribution and ages of subjects are shown in Table 2. The average length of CFS was 5.8 ± 4.9 years; mean fatigue scores were 21.6 ± 6.2, mean GHQ-28 was

Table 1
Results of autonomic function tests in CFS patients compared to healthy individuals

	CFS patients	Healthy individuals	Reference values	*P* values
HR at rest (beats/min)	66.9 ± 13.1	70.8 ± 14.4	60–80	.43
HR variation (deep breathing, beats/min)	16.9 ± 7.3	21.2 ± 7.2	>12	.14
Valsalva ratio	1.6 ± 0.2	–	>1.2	–
HR change (standing, beats/min)	19.9 ± 7.4	15.4 ± 4.8	>15	.03
Systolic BP drop (standing, mm Hg)	8.1 ± 7.8	1.1 ± 3.6	≥20	<.001

Results are represented as mean ± S.D.
The quoted reference values represent normative data that were established in our laboratory with healthy individuals of similar age to that of our patients with CFS.

Table 2
Clinical, haematological and biochemical data

	CFS patients	Iron-deficiency anaemia patients	Healthy individuals	Reference ranges
Gender (M/F)	11:11	7:16	3:15	–
Age (year)	41.4 ± 8.1	46.5 ± 14.2	41.1 ± 10.8	–
Hb (g/dl)	13.7 ± 1.2	9.8 ± 1.4	13.5 ± 0.8	12.0–15.5
MCV (fl)	90.0 ± 3.9	73.1 ± 6.6	91.7 ± 2.8	79–96
MCH (pg)	29.6 ± 1.5	22.5 ± 2.7	31.1 ± 1.5	27–32
EPO (mU/ml)	12.9 ± 7.4	64.1 ± 41.2	9.6 ± 10.1	5–25
Creatinine (μmol/l)	81.6 ± 13.8	75.9 ± 24.9	85.3 ± 20.6	45–120

31.3 ± 14.5, and mean SF-36 physical function was 47.1 ± 17.9.

Table 1 shows autonomic function test results. Although mean resting heart rate did not differ, eight patients had a resting heart rate of 60 beats/min or below compared to only two control subjects. However, heart rate on standing was significantly increased in CFS patients compared to the healthy individuals: 10 patients showed an increase of >20 beats/min on standing compared to only 1 control subject. Two patients with CFS showed an increase in heart rate of >30 beats/min (32 and 37 beats/min), which was symptomatic in one patient. Patients also showed a larger systolic blood pressure drop on standing compared to the healthy individuals: 10 patients had a systolic blood pressure drop of 10 mm Hg or more, 9 of whom were symptomatic with dizziness and lightheadedness. None of the control subjects showed a systolic blood pressure drop of more than 10 mm Hg. Only two CFS patients had clinically symptomatic significant orthostatic hypotension of 20 and 25 mm Hg according to the consensus definition [33]. None of the measures correlated with fatigue, age or illness; however, heart rate increase on standing and GHQ scores were positively correlated, i.e., higher heart rate increases were associated with more psychological symptomatology ($r = .5$, $P = .02$).

Blood parameters are shown in Table 2. Although the mean Hb was within the normal range, two CFS patients, both females, were mildly anaemic (11.8 and 11.9 g/dl), with a normochromic normocytic picture and normal serum ferritin, vitamin B12 and folate. However, reticulocyte counts were decreased in both (46.7 and 46.1×10^9/l, respectively; normal range $50–150 \times 10^9$/l), indicating hypoproliferative anaemia. Four non-anaemic CFS patients (Hb levels 12.4–15.5 g/dl and normal red blood cell indices) had decreased ferritin (6 and 7 μg/l; reference range: 15–200 μg/l), B12 (152 ng/l; reference range: 180–1100 ng/l) and/or folate levels (2.9 and 2.9 μg/l; reference range: 3–13 μg/l).

EPO levels in CFS patients were not significantly different from those of healthy, non-anaemic individuals, but were significantly different from iron-deficiency anaemia patients ($P < .001$; Table 2). Renal damage, which may impair EPO production, was excluded since both serum creatinine and urinary albumin/creatinine ratios were all within the reference range. Interestingly, ESR was elevated in six (13–42 mm/h) and CRP in three CFS patients (7.3–13.7 mg/dl), one of whom with both elevated ESR (42 mm/h) and CRP (13.7 mg/dl) was mildly anaemic (11.8 g/dl). There was no obvious clinical reason for these increased parameters.

Discussion

In this study, we found autonomic dysfunction in a proportion of patients with CFS. Previous studies of autonomic function in CFS have been inconclusive, some finding no abnormalities at all [17,18]. We found evidence of greater heart rate increases and larger drops in systolic blood pressure on standing, with orthostatic dizziness in some patients. We could not confirm previous findings [2,19] of reductions in the heart rate variation on deep breathing, a parasympathetic measure; normal Valsalva ratios provide further evidence against obvious damage of the autonomic nervous system. This isolated increase in the heart rate on standing with some orthostatic intolerance is consistent with cardiovascular deconditioning, possibly representing an alteration of the sympathetic/parasympathetic balance; this is further supported by a correlation of physical activity and autonomic function found in a previous study [19]. On the other hand, undetected hyperventilation, anxiety states or depression are potential causes for the autonomic dysfunction [20–22]; the positive correlation between the heart rate increase on standing and the GHQ score provides some support for this.

Othostatic hypotension was significant in two patients only, a much smaller proportion than has been reported after 1 h standing [1,5]. Orthostatic hypotension in our patients may have been more pronounced if the period of upright standing had been longer.

Only two of our patients satisfied the definition of the postural tachycardia syndrome (POTS) [23]. We determined the heart rate increase at 15 s standing [15], dependent on both parasympathetic and sympathetic nervous systems, whereas other studies measured heart rate after 1 min, representing mainly sympathetic systems. Therefore, our

results may indicate an increased activity of both the sympathetic and parasympathetic nervous systems.

Serum EPO levels were normal, failing to confirm our hypothesis of potential effects of renal sympathetic denervation. Two of the CFS patients were mildly anaemic for no detectable reason; all CFS patients had normal physical findings, and no evidence of increased plasma volume. Furthermore, all renal parameters were normal. We suggest that the slightly decreased Hb in 2 of 22 CFS patients should be interpreted as normal variance within the sample. This is in disagreement with a previous study that found significantly reduced red cell mass in 12 of 15 patients with CFS [1].

Interestingly, seven CFS patients had increased ESR and/or CRP values, consistent with previous findings [24]. Amongst four non-anaemic patients, there was slightly low ferritin, B12 and/or folate. Again, much of this could be expected by chance in a sample size of 22 patients. Alternatively, it could be related to dietary changes in CFS patients. Nevertheless, vitamin deficiencies have been implicated in CFS [25], although controlled trials have yielded controversial results [26,27].

Potential limitations of our study include the relatively small sample size; the different gender ratios in the samples; the selected nature of the patients (whilst chosen to be more homogeneous, they may not generalise to CFS subjects in the community) and the possibility that our control group of staff may not be representative of the general population.

We conclude that some autonomic dysfunction is present in CFS patients, the most likely explanation being physical inactivity. Testing patients before and after physical activity is restored, such as with graded exercise therapy or cognitive behaviour therapy, could help confirm this suggestion. We were unable to demonstrate any major haematological, biochemical or immunological abnormalities in patients with CFS, although a small number of patients may have parameters outside the reference range, the significance of which remains unclear.

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