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Clinical characteristics of a novel subgroup of chronic fatigue syndrome patients with postural orthostatic tachycardia syndrome

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Abstract. Lewis I, Pairman J, Spickett G, Newton JL (Newcastle University, Newcastle; Newcastle Hospitals NHS Foundation Trust, Newcastle; Newcastle University, Newcastle). Clinical characteristics of a novel subgroup of chronic fatigue syndrome patients with postural orthostatic tachycardia syndrome. *J Intern Med* 2013; **273**: 501–510.

Objectives. A significant proportion of patients with chronic fatigue syndrome (CFS) also have postural orthostatic tachycardia syndrome (POTS). We aimed to characterize these patients and differentiate them from CFS patients without POTS in terms of clinical and autonomic features.

Methods. A total of 179 patients with CFS (1994 Centers for Disease Control and Prevention criteria) attending one of the largest Department of Health-funded CFS clinical services were included in this study. Outcome measures were as follows: (i) symptom assessment tools including the fatigue impact scale, Chalder fatigue scale, Epworth sleepiness scale (ESS), orthostatic grading scale (OGS) and hospital anxiety and depression scale (HADS-A and -D, respectively), (ii) autonomic function analysis including heart rate variability and (iii) haemodynamic responses including left ventricular ejection time and systolic blood pressure drop upon standing.

Results. CFS patients with POTS (13%, $n = 24$) were younger (29 ± 12 vs. 42 ± 13 years, $P < 0.0001$), less fatigued (Chalder fatigue scale, 8 ± 4 vs. 10 ± 2, $P = 0.002$), less depressed (HADS-D, 6 ± 4 vs. 9 ± 4, $P = 0.01$) and had reduced daytime hypersomnolence (ESS, 7 ± 6 vs. 10 ± 5, $P = 0.02$), compared with patients without POTS. In addition, they exhibited greater orthostatic intolerance (OGS, 11 ± 5; $P < 0.0001$) and autonomic dysfunction. A combined clinical assessment tool of ESS ≤ 9 and OGS ≥ 9 identifies accurately CFS patients with POTS with 100% positive and negative predictive values.

Conclusions. The presence of POTS marks a distinct clinical group of CFS patents, with phenotypic features differentiating them from those without POTS. A combination of validated clinical assessment tools can determine which CFS patients have POTS with a high degree of accuracy, and thus potentially identify those who require further investigation and consideration for therapy to control heart rate.

Keywords: autonomic dysfunction, chronic fatigue syndrome, dysautonomia, postural orthostatic tachycardia syndrome.

Introduction

Chronic fatigue syndrome (CFS) has a prevalence of 0.2%–4% in the UK [1], and is characterized by persistent/recurrent postexertional fatigue for longer than 6 months that cannot be explained by other conditions [2, 3]. CFS affects individuals of all ages, and can greatly reduce the ability to function on a daily basis, work or attend school. Despite its impact on patients, the cause of CFS remains unknown [4].

Abnormalities of the vascular system and its regulation by the autonomic nervous system (particularly in response to standing) are commonly found in patients with CFS [5–20] resulting in a high association between CFS and dysautonomia. Postural orthostatic tachycardia syndrome (POTS), a form of dysautonomia, is found in 29% of CFS patients [21], whereas fatigue is experienced by almost 50% of those with POTS [22].

POTS is diagnosed when symptoms of orthostatic intolerance are associated with an increase in heart

rate from the supine to upright position [22].The results of previous studies have suggested that POTS underlies the orthostatic intolerance observed in the majority of those with CFS [20]. It is currently unclear whether POTS is a separate clinical entity distinct from CFS, or whether patients with POTS form a subset of those with CFS with a specific group of particularly marked symptoms.

In the current study, subjects with CFS underwent clinical assessment including a number of symptom assessment tools, autonomic function analysis and measures of haemodynamic response to standing. The primary aim of this study was to determine whether CFS patients with and without POTS can be differentiated based on symptoms, heart rate variability (HRV) and left ventricular ejection time (LVET). Combining the results of these assessments may lead to the identification of a distinct clinical subtype of CFS. A secondary aim was to identify a clinical tool to aid the prediction of POTS in CFS patients, which could improve the management of patients with both conditions.

Methods

Recruitment of participants

A total of 179 consecutive patients who had attended the Northern Regional Department of Health-funded CFS Clinical Service (Newcastle upon Tyne, UK) between November 2008 and June 2011 with a diagnosis of CFS according to the 1994 Centers for Disease Control and Prevention (CDC) criteria [3] were included in this study. All patients with secondary causes of fatigue (such as hypothyroidism or diabetes) or who fulfilled the 1994 CDC exclusion criteria were excluded from the study (n = 23). The 1994 CDC criteria are the most widely used benchmark in research and clinical practice for diagnosing CFS.

In addition to a full clinical evaluation, subjects underwent assessment of symptoms and autonomic nervous system function. Subjects were divided into two groups according to the presence of POTS; defined as symptoms of orthostatic intolerance associated with an increase in heart rate from the supine to upright position of >30 beats per min (beat to beat) or to a heart rate of >120 beats per min on immediate standing or during 2 min of standing [22].

A small proportion of subjects failed to return any symptom assessment questionnaires (with POTS, 3/24; without POTS, 8/155). Therefore, analyses of the questionnaires were based on only 21 CFS patients with and 147 without POTS.

The study was approved by the Newcastle and North Tyneside local research ethics committee and all subjects provided written informed consent. The symptom assessment questionnaires have been used in previous studies. HRV analysis was undertaken by a specialist trained nurse experienced in the use of the Task-force™ monitor (CNSystems, Graz, Austria), and able to offer constant reassurance to put the patient at ease.

Outcome measures

Symptom assessment tools

The following symptom assessment tools were used to evaluate all participants.

Fatigue impact scale (*FIS*). The FIS [23] is a 40-item generic scale of fatigue impact which is used to assess fatigue severity. This scale has previously been validated and extensively used in CFS patients. Possible scores range from 0 to 160 with higher scores representing increased fatigue.

Cognitive failures questionnaire (*CFQ*). The CFQ measures self-reported failures in perception, memory and motor function [24]. The questionnaire consists of 25 items, each graded on a scale of 0–4; adding the scores for the individual items creates a total score.

Hospital anxiety and depression scale (HADS). The HADS [25] is a 14-item measure of current anxiety (HADS-A) and depression (HADS-D). Caseness for anxiety or depression is revealed by subscores greater than 11.

Short-form health survey. The 36-item Short Form (SF-36) is a generic scale of functional impairment in eight areas [26]. Scores in each area reflect function and well-being, and lower values indicate more impairment.

Self-efficacy. The self-efficacy scale assesses the ability to cope with daily stresses [27]. The scale consists of 10 items, each graded on a scale of 1–4, giving a total score range 10–40.

Chalder fatigue scale. The Chalder fatigue scale measures self-reported fatigue. It consists of 14 items which can be separated into two subdomains; the

Chalder Fatigue mental and physical scales, which measure mental and physical fatigue, respectively.

Pain rating. Widespread muscle and joint pain occur in CFS and we therefore asked each subject to rate their pain on a visual analogue scale. Subjects were asked to mark a position on a 10-cm line to indicate how much pain they were feeling at that time, from 'No pain' to 'Worst pain ever'.

Epworth sleepiness scale (ESS). In view of the recently identified association between excessive daytime sleepiness and fatigue, all subjects completed the ESS questionnaire (possible score range 0–24) [28]. This fully validated tool assesses daytime hypersomnolence, with a score ≥ 10 being indicative of significant hypersomnolence during the day.

Orthostatic grading scale (OGS). Subjects completed the OGS, a fully validated self-reported tool to assess the symptoms of orthostatic intolerance due to orthostatic hypotension (e.g. severity, frequency and interference with daily activities) [29]. The OGS consists of five items, each graded on a scale of 0–4; adding the scores for the individual items creates a total score of 0–20.

Haemodynamic and autonomic parameters

Autonomic function was assessed using HRV, baroreflex sensitivity and the baroreceptor effectiveness index (which quantifies the number of times the baroreflex is effective in driving the sinus node) [30–32]. Detailed methods have previously been described [33]. All haemodynamic measurements were performed following a 10-min period of supine rest for stabilization; during this period electrocardiography was performed and noninvasive beat-to-beat blood pressure was monitored continuously using a vascular unloading device (Task-force™).

LVET is the time interval from the opening to the closing of the aortic valve (mechanical systole). Heart rate and blood pressure response to standing was assessed in all subjects [30]. Subjects were asked to stand in the supine position within 3 s with assistance if required. Continuous beat-to-beat heart rate and blood pressure measurements were recorded for 2 min whilst standing [3]. Systolic blood pressure (SBP) drop upon standing was calculated by subtracting the lowest SBP upon standing for 3 min (nadir SBP) from the mean SBP over 20 cardiac beats prior to standing.

Statistical analysis

All statistical analyses were performed using GraphPad Prism version 5.00 (Windows, GraphPad Software, San Diego, CA, USA). All data were normally distributed. Comparisons were, therefore, made between proportions in each group using Fisher's exact test and between continuous variables using the independent two-tailed Student's *t*-test. The level of significance was set at $P < 0.05$. All values are expressed as mean $\pm$ SD unless otherwise stated. The Pearson R correlation was used to determine the correlation between variables. The positive predictive value was calculated by dividing the number of true positives by the sum of the true and false positives. Conversely, the negative predictive value was calculated by dividing the number of true negatives by the sum of the false and true negatives.

Results

Overall, 179 consecutive CFS patients from the Newcastle CFS Clinical Service were included in the study and underwent a series of demographic, symptom assessment and autonomic function tests. There was a wide variation in age amongst subjects: 26% were aged ≤ 30 years, 45% were 31–49 years and 29% were ≥ 50 years. In total 18% ($n = 33$) were men and the mean $\pm$ SD length of history of CFS and body mass index (BMI) were 87 $\pm$ 79 months and 25 $\pm$ 5 kg m^{-2} respectively. Table 1 summarizes the characteristics of the CFS cohort. As expected, the level of fatigue was high throughout the study population measured using both the FIS and the Chalder fatigue scale. The rates of anxiety and depression were 32% ($n = 58$) and 30% ($n = 54$) respectively. There was a high prevalence of daytime sleepiness and orthostatic symptoms such as feelings of 'light-headedness' within the cohort. The degree of functional impairment was high, as was cognitive impairment. The mean pain rating scores were low, although they varied over a wide range.

Characteristics of the subgroup with POTS

The CFS cohort was separated into two subgroups based on the concomitant presence of POTS: 13% ($n = 24$) with (POTS-CFS group) and 87% ($n = 155$) without POTS (non-POTS-CFS group; Table 1). Patients in the POTS group were significantly younger (29 $\pm$ 12 vs. 42 $\pm$ 13 years, $P \leq 0.0001$), with a greater proportion under the

Table 1 *Characteristics of the total CFS cohort and patients with and without POTS based on symptom assessment tools*

	Cohort	POTS	Non-POTS	*P*
Total subjects (*n*)	179	24	155	ns
Male (*n*,%)	33 (18%)	5 (21%)	28 (18%)	0.8[a]
Age (years)	40 ± 13	29 ± 12	42 ± 13	<0.0001
Length of history (months)	87 ± 79	73 ± 66	89 ± 81	0.4
BMI (kg m^{-2})	25 ± 5	25 ± 6	25 ± 5	0.5
POTS (*n*,%)	24 (13%)	-	-	-
FIS	98 ± 30	101 ± 34	98 ± 30	0.7
Chalder Fatigue (% max)	9 ± 3	8 ± 4	10 ± 2	<0.01
Physical (% max)	6 ± 2	5 ± 3	6 ± 1.6	<0.01
Mental (% max)	3 ± 1	3 ± 2	3 ± 1	<0.01
CFQ	61 ± 20	56 ± 30	62 ± 18	0.3
HADS total	18 ± 7	15 ± 7	18 ± 7	0.04
HADS-A	9 ± 5	8 ± 5	9 ± 4.5	0.5
Normal (%)[b]	69 ± 3 (39%)	10 ± 2 (48%)	59 ± 3 (41%)	0.7
Borderline (%)[b]	39 ± 4 (22%)	4 ± 1 (19%)	35 ± 4 (24%)	0.5
Abnormal (%)[b]	58 ± 5 (32%)	7 ± 3 (33%)	51 ± 5 (35%)	0.6
HADS-D	9 ± 4	6 ± 4	9 ± 4	0.01
Normal (%)[b]	69 ± 2 (39%)	12 ± 2 (57%)	57 ± 2 (39%)	0.03
Borderline (%)[b]	45 ± 1 (25%)	6 ± 1 (29%)	39 ± 1 (27%)	0.6
Abnormal (%)[b]	54 ± 2 (30%)	3 ± 1 (14%)	51 ± 2 (35%)	0.05
SF-36	18 ± 5	17 ± 5	18 ± 5	0.3
Self-efficacy	26 ± 14	25 ± 16	26 ± 13	0.7
Pain rating	4 ± 3	4 ± 3	4 ± 3	0.9
ESS	10 ± 6	7 ± 6	10 ± 5	0.02
Score ≥ 10	53%	33%	56%	-
OGS	7 ± 5	11 ± 5	6 ± 4	<0.0001
Score ≥ 4	74%	95%	71%	-
Score ≥ 9	56%	67%	29%	-

BMI, body mass index; CFS, chronic fatigue syndrome; CFQ, cognitive failures questionnaire; ESS, Epworth sleepiness scores; FIS, fatigue impact scores; HADS, hospital anxiety and depression scale (A, anxiety; D, depression); OGS, orthostatic grading scale; POTS, postural orthostatic tachycardia syndrome; SF-36, short-form (36-item) health survey. [a]Fisher's exact test. [b]Percentage of subjects with subscores included in the category for caseness for anxiety (A) or depression (D). Normal = score 0–7; borderline = 8–10; abnormal = 11–21.
Values are given as mean ± SD unless stated otherwise. *P* values calculated from two-tailed Student's *t*-test with $P < 0.05$ considered statistically significant.

age of 30 years (54% vs. 22%) and considerably fewer aged above 50 years (4% vs. 30%). There were no differences in the proportion of men, length of CFS history, weight or BMI between the two groups.

Table 1 shows the results of the symptom assessment tools for the two subgroups. Amongst the POTS-CFS subgroup, there were fewer subjects with depression (14%, $n = 3$ vs. 35%, $n = 51$; $P = 0.05$). There was no difference in the anxiety domain of the HADS test between these two groups. Patients in the POTS-CFS subgroup were significantly less fatigued according to the Chalder fatigue scale in both the physical and mental domains, and also reported significantly lower levels of daytime sleepiness (Fig. 1a). The presence of orthostatic symptoms was significantly more

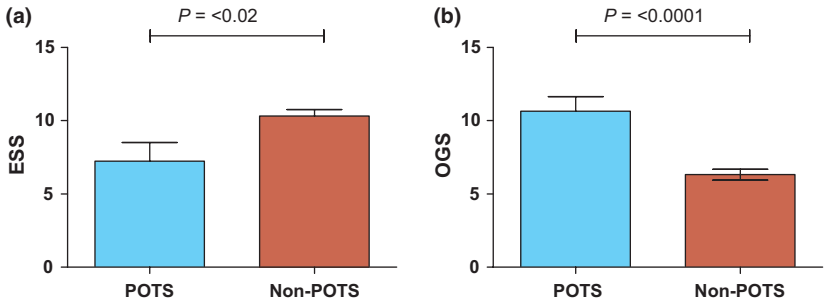

Fig. 1 *Comparison of CFS-POTS and non-CFS-POTS subgroups with regard to (a) Epworth sleepiness scale, where ≥ 10 is considered abnormal daytime sleepiness that severely impacts on quality of life, and (b) orthostatic grading scale (OGS), a measure of the prevalence of orthostatic symptoms. Statistics calculated using the two-tailed Student's t-test with P ≤ 0.05 considered statistically significant.*

likely in the POTS-CFS group, with two thirds (n = 8) of patients scoring >9 on the OGS (Fig. 1b). Finally, there were no differences in functional domains (SF-36 and self-efficacy), cognitive impairment (CFQ) and pain ratings between the two subgroups.

We found no significant difference in FIS scores between the two groups. Whereas there was a wide range of FIS scores, there appeared to be a 'low ceiling effect' with the Chalder fatigue scale (Fig. 2a), in which due to the low range of scores on the Chalder fatigue scale, a high proportion of subjects demonstrated maximum fatigue scores, yet demonstrating highly varied FIS scores. There was a correlation between the two fatigue measuring tools (r = 0.1; r^2 = 0.03; P = 0.01); however, 62.5% (n = 105) of subjects scored the maximum score of 7 on the Chalder fatigue scale (physical), whereas the same subjects reported fatigue on the FIS in the range from 44 to 156 (Fig. 2b). Similar results were found for both total and the mental domain of the Chalder fatigue scale.

Autonomic function in the POTS-CFS subgroup

Due to the high prevalence of autonomic dysfunction in CFS patients, next we assessed the differences in autonomic dysfunction between the POTS-CFS and non-POTS-CFS groups. The two groups underwent HRV analysis during a 10-min supine rest (Table 2). Compared with subjects in the non-POTS-CFS group, those in the POTS-CFS group had significantly lower, (i) low-frequency HRV (LF; predominantly sympathetic), (ii) high-frequency HRV (HF, predominantly parasympathetic) and (iii) very low-frequency HRV (VLF) (Fig. 3).

The capacity of the left ventricle to respond to orthostasis was markedly reduced in patients in the POTS-CFS group (LVET), although these patients had a higher resting heart rate (Table 2).

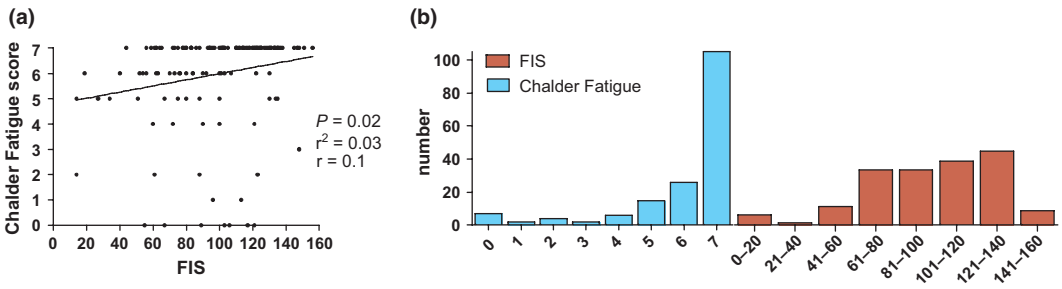

Fig. 2 *Comparison of the Chalder fatigue (physical) scale and the fatigue impact scale (FIS). (a) The relationship between the two fatigue scales. (b) Whereas the majority (n = 105) of subjects scored the maximum possible score on the Chalder fatigue (physical) scale, there was a broader range of FIS scores. Both scales were split into eight categories.*

Table 2 *Autonomic function of the total CFS cohort and patients with and without POTS*

	Cohort	POTS	non-POTS	*P*
HR (beats per min)	75 ± 12	88.9 ± 15.3	72.5 ± 9.9	<0.0001
Systolic BP (mmHg)	120 ± 18	120 ± 11.5	119.9 ± 17.7	0.7
Diastolic BP (mmHg)	79 ± 13	79.2 ± 12.2	78.3 ± 13.2	0.8
Mean BP (mmHg)	92 ± 14	93.4 ± 11.5	92.1 ± 14.3	0.7
LVET (ms)	281 ± 14	266.1 ± 16.8	283.3 ± 11.6	<0.0001
Total HRV (ms^2)	1193 ± 1663	883.9 ± 1504.8	1221.6 ± 1672.2	0.6
LF-HRV (ms^2)	410 ± 524	247.4 ± 187.5	430.5 ± 547.5	<0.01
HF-HRV(ms^2)	464 ± 963	181.5 ± 218.4	488.9 ± 1002.7	<0.001
VLF-HRV(ms^2)	318 ± 708	137.5 ± 138.2	302.3 ± 526.3	<0.001
LF/HF	3 ± 4	2.0 ± 1.4	1.9 ± 2.4	0.1
BRS (ms $mmHg^{-1}$)	14 ± 11	12 ± 6.6	14.4 ± 11.0	0.5
BEI (%)	69 ± 16	66.3 ± 22.8	69.7 ± 15.4	0.4
Systolic BP drop on active standing (mmHg)	15 ± 11	20 ± 12	14 ± 10	0.01

BEI, baroreflex effectiveness index; BP, blood pressure; BRS, baroreflex sensitivity; HF, high frequency; HR, heart rate; HRV, heart rate variability; LF, low frequency; LVET, left ventricular ejection time; VLF, very low frequency.
Values are given as mean ± SD. *P* values calculated from two-tailed Student's *t*-test with $P < 0.05$ considered statistically significant.

Baseline measures of systolic, diastolic and mean blood pressures did not differ between the two groups, and neither did baroreflex sensitivity or the baroreflex effective index.

There was a high level of antidepressant use amongst all CFS subjects, regardless of the presence of depression (Table 3). In addition, there was no significant difference in autonomic function between CFS patients taking and not taking antidepressants.

During the 3-min period of active standing, the POTS-CFS subgroup had a significantly greater drop in systolic blood pressure compared with the non-POTS-CFS subgroup (Fig. 4). Furthermore, the POTS-CFS subgroup had significantly lower RR 30:15 ratios, a measure of dynamic, parasympathetic activity during active standing, than the subgroup without POTS (with smaller ratios considered abnormal).

Based on the present findings, we have proposed a clinical diagnostic tool for the prediction of CFS patients with POTS (Table 4). We found that an OGS score ≥ 9 combined with an ESS score ≤ 9 provides both positive and negative predictive values of 100% for POTS.

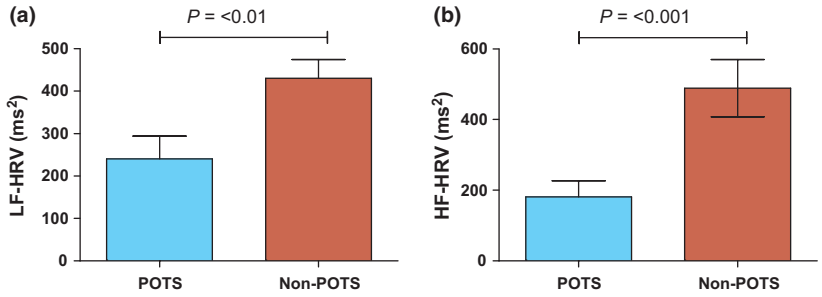

Fig. 3 *Comparison of CFS-POTS and non-CFS-POTS subgroups with regard to autonomic nervous system function: (a) low-frequency heart rate variability (LF-HRV; predominantly sympathetic) and (b) high-frequency heart rate variability (HF-HRV; predominantly parasympathetic). Statistics calculated using the two-tailed Student's t-test with $P \leq 0.05$ considered statistically significant.*

Table 3 *Depression in CFS patients according to the HADS-D and use of antidepressant medication*

	POTS	Non-POTS
Normal (*n*,%)	2/12 (17%)	17/57 (30%)
Borderline (*n*,%)	1/6 (17%)	10/40 (25%)
Abnormal (*n*,%)	2/3 (67%)	19/50 (38%)
Total	5/21 (24%)	46/147 (31%)

Subscores for caseness for depression on the HADS-D in POTS-CFS and non-POTS-CFS subgroups. Normal = score 0–7; borderline = 8–10; abnormal = 11–21. Percentages show number of patients receiving antidepressants out of the total number of patients in each HADS-D category.

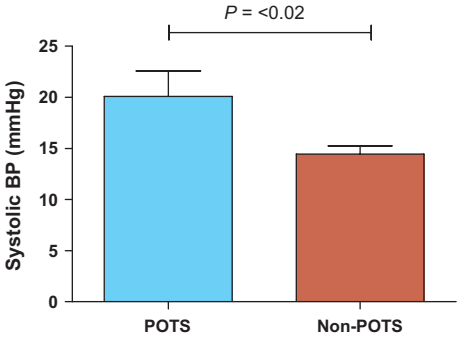

Fig. 4 *Comparison of CFS-POTS and non-CFS-POTS subgroups with regard to systolic blood pressure drop upon standing. Statistics calculated using the two-tailed Student's t-test with $P \leq 0.05$ considered statistically significant.*

Discussion

In a large cohort of well-characterized CFS patients, 13% were found to have POTS. There are number of novel findings presented here. First, we describe a distinct clinical subgroup of CFS patients with POTS who are younger, report reduced depression and daytime sleepiness, and have significantly more orthostatic symptoms and a reduced capacity of the left ventricle to respond to such orthostasis, coupled with a much greater systolic blood pressure drop upon standing, compared with the total cohort. In terms of underlying autonomic differences, the POTS-CFS group had reduced sympathetic and parasympathetic function. Secondly, due to its 'low ceiling effect', the Chalder fatigue scale is not a good indicator of change in fatigue levels in patients with CFS. Thirdly, a combination of validated clinical assessment tools such as heart rate response to standing and OGS and ESS scores can be used to predict with high accuracy CFS patients with POTS, and thus potentially identify those who may require further investigation and consideration for therapies that target heart rate control.

Patients in the POTS-CFS subgroup were significantly younger. This is in contrast to a previous study in which no such difference in age was found between CFS patients with and without POTS [21]. However, fewer subjects were included in the previous study (63 vs. 179) and the mean age was higher (47 ± 12 vs. 40 ± 13 years). Therefore, based on our results from this large CFS cohort, we believe that CFS patients with POTS are likely to be younger than those without POTS. The POTS-CFS subgroup had a lower level of depression, with higher rates in the older, non-POTS-CFS subgroup. In addition, there was a high rate of use of antidepressant medication amongst all CFS subjects, regardless of the presence of depression (according to the HADS). This may reflect a poor sensitivity of the test or unwarranted belief amongst the wider medical community that

Table 4 *Clinical diagnostic tools for the prediction of POTS in patients with CFS based on symptom assessment tools (ESS and OGS)*

	POTS		non-POTS			
	Reach criteria	Fail to reach criteria	Reach criteria	Fail to reach criteria	PPV	NPV
ESS $\leq$ 9	14	7	64	82	18%	92%
OGS $\geq$ 4	20	1	103	41	16%	98%
OGS $\geq$ 9	14	7	43	101	25%	94%
OGS $\geq$ 4 and ESS $\leq$ 9	13	0	23	0	36%	NA
OGS $\geq$ 9 and ESS $\leq$ 9	7	0	0	37	100%	100%

ESS, Epworth sleepiness scale; NA, not applicable; NPV, negative predictive value; OGS, orthostatic grading scale; PPV, positive predictive value.

antidepressants are an effective treatment option for fatigue and CFS.

We found high rates of daytime sleepiness amongst the cohort of CFS patients. This is in agreement with the findings of three previous studies of high mean scores on the ESS in CFS patients (10.5, 8.8 and 10.5, respectively [34–36]). Whereas the non-POTS-CFS group in the present study demonstrated levels of daytime sleepiness typical of CFS patients, the POTS-CFS group reported much reduced levels. However, only scores of 10–24 on the ESS reflect significant daytime sleepiness [29], therefore our findings support previous conclusions that CFS is not primarily a disease of hypersomnolence.

Patients in the POTS-CFS subgroup demonstrated greater autonomic dysfunction than those in the non-POTS-CFS group, with reduced levels of LF-HRV, HF-HRV, VLF-HRV and RR 30:15 (a marker of parasympathetic function). Greater autonomic dysfunction is consistent with our findings of a higher burden of orthostatic symptoms in the same patients, with greater orthostatic symptoms correlating with reduced LF-HRV and HF-HRV.

Greater autonomic dysfunction in the POTS-CFS subgroup supports the notion that CFS is a disorder of the central nervous system, with hypersensitivity in the form of central sensitization being evident in CFS [37–45]. Central sensitization in CFS may explain some of the symptoms of this condition, including postexertional malaise, whereby the autonomic nervous system is unable to respond appropriately to the physical stressors of exercise [46–48].

In addition to greater autonomic dysfunction, we observed more severe cardiovascular dysfunction in patients with POTS, with greater reductions in systolic blood pressure upon standing and significantly reduced left ventricular performance (LVET). These findings are consistent with previous evidence of impaired cardiac function and reduced mass and blood pool volumes [49–54] in CFS patients.

The observed 'low ceiling effect' with the Chalder fatigue scale in this study was consistent with previous findings [55–57]. Goudsmit *et al.* noted that 50% of CFS patients scored the highest possible score on this scale, whereas 77% scored the two highest possible scores. The authors noted a marked overlap between patients who rated themselves as moderately or severely ill, yet scored the highest possible score on the Chalder fatigue scale.

We demonstrated here that although there is some correlation between the Chalder fatigue scale and the FIS, there remains a marked discrepancy between what individuals report using the two scales in terms of fatigue. Subjects who reported the maximum possible Chalder fatigue score of 7 also scored a range of FIS scores from 44 to 156. Further research is needed to examine this effect of the Chalder fatigue scale. However in the meantime problems may arise in the clinical setting as those with a maximum score at baseline will not be able to record a change in fatigue during or following treatment and will therefore appear to be unresponsive to therapy.

This study has some limitations. Due to the small size of the POTS-CFS subgroup (n = 24), comparisons between these patients and non-POTS-CFS remained difficult and thus, studies to confirm our findings in other centres are needed. In addition, we used a number of questionnaires, and as such their accurate completion is affected by the motivation of the patient. However the questionnaires were short and have been used in numerous previous studies. In addition, in our experience, CFS patients tend to be more cooperative and willing to help in research studies than patients with other illnesses, partly due to the widespread negative impression of CFS. However, this may in turn introduce a degree of selection bias as more symptomatic patients such as those with concurrent POTS may report increased symptoms. This reinforces the need to reproduce our findings at other centres.

We aimed to determine whether CFS patients with/without POTS could be differentiated based on clinical and autonomic features to identify whether the presence of POTS reflects a distinct subgroup of these patients. Utilizing a large, well-characterized cohort of CFS patients, we have characterized for the first time a subgroup with POTS.

In conclusion, CFS patients with POTS reflect a distinct subgroup of those with CFS; they are younger, predominantly female and report reduced daytime hypersomnolence and depression. Furthermore, patients with POTS show greater orthostatic intolerance and symptoms that affect their quality of life. We propose that this is due to a greater underlying autonomic dysfunction,

treatment of which will improve functional impairment and quality of life in this subgroup of patients.

Conflict of interest statement

No conflict of interest to declare.

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