

---

# Symptoms of autonomic dysfunction in chronic fatigue syndrome

J.L. NEWTON, O. OKONKWO, K. SUTCLIFFE, A. SETH, J. SHIN and D.E.J. JONES

*From the Fatigue Interest group and Liver Research Group, Institute for Cellular Medicine, University of Newcastle, Newcastle, UK*

*Received 5 March 2007 and in revised form 24 April 2007*

---

## Summary

**Background:** Chronic fatigue syndrome (CFS) is common and its cause is unknown.

**Aim:** To study the prevalence of autonomic dysfunction in CFS, and to develop diagnostic criteria.

**Design:** Cross-sectional study with independent derivation and validation phases.

**Methods:** Symptoms of autonomic dysfunction were assessed using the Composite Autonomic Symptom Scale (COMPASS). Fatigue was assessed using the Fatigue Impact Scale (FIS). Subjects were studied in two groups: phase 1 (derivation phase), 40 CFS patients and 40 age- and sex-matched controls; phase 2 (validation phase), 30 CFS patients, 37 normal controls and 60 patients with primary biliary cirrhosis.

**Results:** Symptoms of autonomic dysfunction were strongly and reproducibly associated with the

presence of CFS or primary biliary cirrhosis (PBC), and correlated with severity of fatigue. Total COMPASS score >32.5 was identified in phase 1 as a diagnostic criterion for autonomic dysfunction in CFS patients, and was shown in phase 2 to have a positive predictive value of 0.96 (95%CI 0.86–0.99) and a negative predictive value of 0.84 (0.70–0.93) for the diagnosis of CFS.

**Discussion:** Autonomic dysfunction is strongly associated with fatigue in some, but not all, CFS and PBC patients. We postulate the existence of a ‘cross-cutting’ aetiological process of dysautonomia-associated fatigue (DAF). COMPASS >32.5 is a valid diagnostic criterion for autonomic dysfunction in CFS and PBC, and can be used to identify patients for targeted intervention studies.

---

## Introduction

Chronic Fatigue Syndrome (CFS) is a common condition (up to 2% of the USA/UK population is affected) characterized by profound and persistent fatigue. CFS affects people of all ages, and can greatly reduce a sufferer’s ability to function on a daily basis, work or attend school. Despite its impact on the population, the cause of CFS remains unknown.<sup>1</sup> One of the problems that limits study of the pathogenesis of CFS and the development of therapies is the lack of objective diagnostic/disease quantification tools. In the absence of such tools, it is even unclear whether CFS patients are a homogenous disease group, or whether different

pathological processes contribute to a common end result of fatigue.

Several strands of research point to abnormalities of the vascular system and its regulation by the autonomic nervous system (particularly in response to standing) as common in CFS,<sup>2–16</sup> although the literature in this area is complex and contradictory, with a number of studies failing to identify such links.<sup>17,18</sup> The apparent association between clinical features of autonomic dysfunction and CFS mirrors emerging findings in a number of other, unrelated disease settings, including multiple sclerosis, Parkinson’s disease and primary biliary cirrhosis

---

*Address correspondence to Dr J.L. Newton, Fatigue Interest Group, Institute for Cellular Medicine, Newcastle University, Newcastle NE2 4HH. e-mail: julia.newton@nuth.nhs.uk*

(PBC), where similar associations between dysfunction of the autonomic nervous system and fatigue have been noted.<sup>19–23</sup> One interpretation of these observations in CFS and other fatigue-associated conditions is that abnormalities in autonomic nervous system regulation could provide an overarching pathogenic mechanism (albeit one induced by different pathogenic processes in the individual diseases) that leads to the result of fatigue. If correct, this model would have profound implications for the treatment of fatigue in these conditions.

A major limitation of the existing studies of autonomic dysfunction in CFS (and a potential explanation for why findings of autonomic dysfunction have yet to translate into new therapies) is the lack of sensitivity of the assessment modalities. A further limitation has been the tendency in the field to carry out small-scale observational studies with limited control groups. We set out to comprehensively assess the prevalence, degree and associations of symptoms of autonomic dysfunction in a large and well characterized group of CFS patients matched to normal controls, and patients with PBC (a patient group with a well characterized association between autonomic dysfunction and fatigue) using the comprehensive and highly sensitive Composite Autonomic Symptom Scale (COMPASS). The COMPASS has been validated against a laboratory-based haemodynamic autonomic function test,<sup>24</sup> and has been used effectively to identify autonomic dysfunction in a wide variety of conditions, including Parkinson's disease and diabetes.<sup>24–28</sup>

## Methods

### Study design

In Phase 1, symptoms of fatigue and autonomic dysfunction were assessed and compared in CFS patients and fully age- and sex-matched population controls, and COMPASS data from the normal population were used to define a diagnostic criterion for the presence of significant autonomic dysfunction. In Phase 2, we attempted to replicate and confirm the symptom association data in a mixed CFS population control population, to test the validity of the diagnostic criterion, and to study its applicability to PBC patients.

### Subjects

Patients with CFS were recruited via the Northern CFS network, and through the local patient support

group, ME North East. All fulfilled the Fukuda clinical diagnostic criteria for CFS, and all major potential secondary causes for fatigue had been excluded, as per the standard CFS service protocol.<sup>29</sup> Normal controls were recruited from the local population through advertisements inviting people to participate in research into the autonomic nervous system (no selection was made on the basis of presence or absence of fatigue). Patients with PBC were recruited through the local patient support group. All PBC subjects had early-stage liver disease and all had normal liver synthetic function at the time of the study. Subjects were excluded from all study groups if they had potential secondary causes for fatigue, and/or autonomic dysfunction such as diabetes mellitus or hypothyroidism, or were taking medications that could lead to fatigue or symptoms suggestive of autonomic dysfunction. All subjects returned questionnaires anonymously, and local research ethics committee approval ruled that return of the questionnaire implied consent, as it allowed the subject to 'opt in'.

### Assessing severity of fatigue

All participants completed the Fatigue Impact scale (FIS). This tool has been validated for self-completion in primary biliary cirrhosis<sup>30</sup> and has also been used in both normal populations and in those with CFS.

### Assessing symptoms of autonomic dysfunction

The population frequency and severity of symptoms of autonomic dysfunction were assessed using the COMPASS,<sup>24</sup> which consists of 73 questions that assess symptoms, grouped into domains relating to individual aspects of the autonomic nervous system. Each domain is scored on the basis of presence, severity, distribution, frequency and progression of symptoms. The eight domains relate to: (i) Orthostatic Intolerance (generalized adrenergic) (maximum score 40); (ii) Vasomotor (peripheral adrenergic) (max. 10); (iii) Secretomotor (cholinergic) (max. 20); (iv) Gastrointestinal (max. 10) (including Autonomic Diarrhoea (max. 20) and Constipation (max. 10) sub-domains); (v) Bladder (max. 20); (vi) Pupil Responses (max. 5); (vii) Sleep disorder (max. 15); and (viii) Syncope (max. 20). The measure also includes a male erectile dysfunction domain, which was not included in this study. The individual domain scores are then weighted according to clinical relevance, as described in the original derivation and validation of the questionnaire.<sup>24</sup> Individual scores are then summed to

provide an indicator of total overall symptom burden (total COMPASS score). Two further scales (Understatement and Psychosomatic scales) are incorporated into the assessment tool, and are scored independently from the COMPASS score itself. These scales are aimed at detecting over- or under-reporting of symptoms between individuals; an example of an understatement question is, 'Have you ever in your adult life had difficulty keeping your mind on your job?'. These validity scales allow assessment of whether the subject has actively engaged in completion of the questionnaire. In all scales, higher scores indicate a greater symptom load, with the highest total possible score (excluding the erectile dysfunction domain) being 170.

### Validation of COMPASS against objective measurement of autonomic function in CFS

To test the validity of COMPASS for the study of symptoms of autonomic dysfunction in CFS, it was compared with objective measures of autonomic function for use in CFS in 15 representative CFS patients. All assessments were performed at the same time of day, in a quiet room with constant ambient temperature, in a dedicated Cardiovascular Investigation Unit. All subjects were asked to refrain from caffeine or smoking for the 12 h prior to the study, and had a light breakfast prior to assessment. The integrity of the autonomic nervous system was measured over 10 min using continuous digital photo-plethysmography (Taskforce, CNSystems) to obtain resting baroreflex sensitivity and heart rate variability (HRV), and using spectral analysis<sup>31</sup> to derive total power (power spectral density), low frequency heart rate variability (LF, predominantly sympathetic), high frequency heart rate variability (HF, predominantly parasympathetic) and very low frequency heart rate variability (VLF). The LF/HF ratio was considered an indicator of the balance between the sympathetic and parasympathetic nervous systems. Autonomic parameters were correlated against total COMPASS scores for each individual.

### Statistical analysis

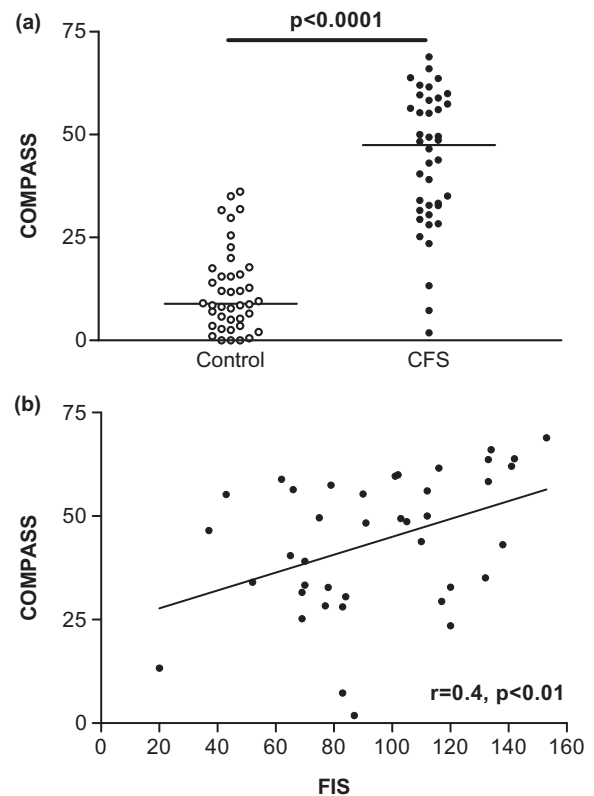
All COMPASS domain and total scores were normally distributed, and comparisons were therefore made between groups using parametric tests. The Understatement and Psychosomatic scales were found to be skewed, and therefore comparisons were made using non-parametric analyses. Correction for multiple testing using multi-domain measures used the Bonferroni correction.

## Results

### Phase 1 (derivation phase)

In phase 1 of the study, COMPASS and FIS scores were assessed in 40 CFS/ME and 40 fully age- and sex-matched population controls (9 males and 31 females in each group, mean  $\pm$  SD ages  $45.5 \pm 16.8$  and  $45.5 \pm 17.8$ , respectively). As expected, the CFS patients were significantly more fatigued than the normal controls (mean  $\pm$  SD FIS  $94 \pm 32$  vs.  $14 \pm 13$ ,  $p < 0.0001$ ). Total COMPASS score was significantly higher in CFS patients than in controls (Figure 1a), and was correlated with FIS (Figure 1b). The upper limit for a normal COMPASS score was defined as the mean  $+2$ SD for the normal population cohort scores (32.5). By this definition, 30/40 (75%) of CFS patients had COMPASS scores suggesting autonomic dysfunction.

When the individual domains of the COMPASS were assessed, significant differences were seen between the CFS patient and the population control groups (after correction for multiple testing) for the Orthostatic Tolerance, Vasomotor, Secretomotor, Gastrointestinal (total and Autonomic Diarrhoea



**Figure 1.** **a** Individual total COMPASS scores in CFS patients and in case-matched normal controls, in phase 1. **b** Correlation between degree of symptoms of dysautonomia as assessed by COMPASS and severity of fatigue (as assessed by FIS), in phase 1.

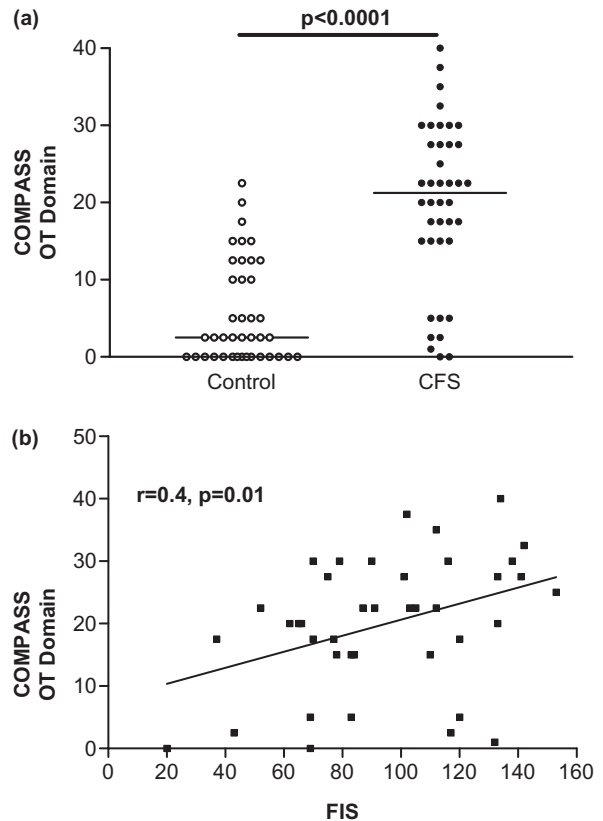
**Table 1** COMPASS domain scores in CFS/ME patients and age- and sex-matched normal controls (mean±SD) in phase 1 of the study

COMPASS domain	Normal controls (n=40)	CFS/ME patients (n=40)	p
<i>Orthostatic Tolerance</i>	5.6 ± 6.6	19.9 ± 10.7	<0.0001*
<i>Vasomotor</i>	0.1 ± 0.7	3.6 ± 2.5	<0.0001*
<i>Secretomotor</i>	1.5 ± 2.0	6.0 ± 3.9	<0.0001*
<i>Gastrointestinal (Diarrhoea)</i>	0.2 ± 0.5	1.9 ± 2.1	0.0001*
<i>(Constipation)</i>	1.1 ± 2.6	3.7 ± 3.9	<0.005*
<i>Bladder</i>	0.8 ± 1.8	1.7 ± 2.1	>0.05
<i>Pupillomotor</i>	1.6 ± 2.4	2.7 ± 3.3	>0.05
<i>Sleep</i>	0.3 ± 0.5	1.1 ± 1.1	<0.0001*
<i>Syncope</i>	0.6 ± 1.3	2.4 ± 2.2	<0.0001*
<i>Syncope</i>	0.2 ± 0.9	0.6 ± 1.4	>0.05
<i>Total score</i>	12.1 ± 10.2	43.7 ± 16.6	<0.0001*

The cut-off for significance was  $p < 0.005$ , following correction for multiple testing. \*Significant differences using this cut-off.

sub-domain), Pupil Response and Sleep disorder domains of the COMPASS, but not for the Bladder and Syncopal domains and the Gastrointestinal Constipation subdomain (Table 1). These findings suggest that CFS is associated with a substantial, and broadly-based (but not universal), burden of symptoms relating to autonomic dysfunction. In keeping with previous literature describing abnormal haemodynamic responses to standing, one of the dominating differences between CFS patients and population controls is with regard to the Orthostatic Tolerance (OT) domain, where CFS patients had mean scores almost four-fold higher than controls (Figure 2a). Moreover, the OT domain was the only COMPASS domain for which scores showed a significant correlation with fatigue severity (Figure 2a).

The COMPASS includes sub-scales (potential range 0–10) that assess understatement of symptom severity and psychosomatic symptomatology. Interestingly, the CFS patients were actually marginally more likely to understate their symptoms (as assessed in this way) than population controls, though not significantly so (CFS  $2.1 \pm 2.9$  vs. controls  $1.8 \pm 2.4$ ,  $p = \text{NS}$ ). Psychosomatic symptoms were greater in CFS patients than in controls, but scores were below 1 in both groups, indicating low overall impact from psychosomatic symptoms (CFS  $0.8 \pm 1.2$  vs. controls  $0.1 \pm 0.4$ ,  $p < 0.05$ ). There was no significant relationship between increasing fatigue and the Understatement scale or the Psychosomatic scale in the CFS group,

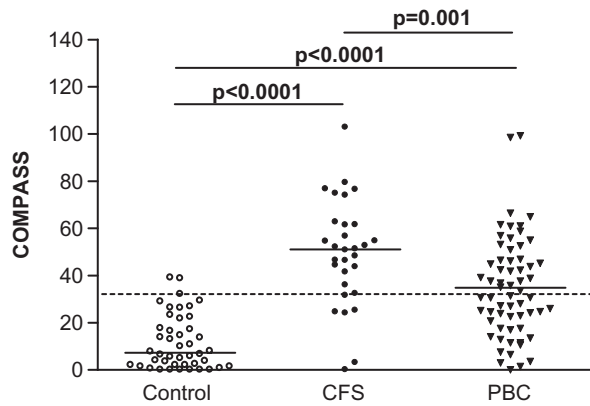


**Figure 2.** **a** Individual COMPASS orthostatic tolerance (OT) domain scores in CFS patients and in case-matched normal controls, in phase 1. **b** Correlation between degree of symptoms of cardiovascular dysautonomia as assessed by COMPASS OT domain and severity of fatigue (as assessed by FIS) in phase 1.

suggesting that increasing fatigue was not associated with increased over- or under-recognition of autonomic symptoms. To determine whether autonomic symptom burden was related to length of disease, CFS patients were also invited to self-report the number of years over which they had experienced fatigue. There was no significant relationship between length of history of fatigue and either total COMPASS score or any individual domain score (data not shown).

### Phase 2 (validation phase)

In the second phase of the study we set out to; (i) confirm our phase 1 findings of a strong association between fatigue and autonomic dysfunction in CFS; (ii) to validate our diagnostic criterion for the presence of fatigue-associated autonomic dysfunction (COMPASS  $> 32.5$ ) in 30 CFS patients (23 females, mean age  $53.5 \pm 8.1$  years) and 37 controls (29 females, mean age  $50.2 \pm 14.5$  years); and (iii) to explore the utility of this diagnostic criterion in a second condition in



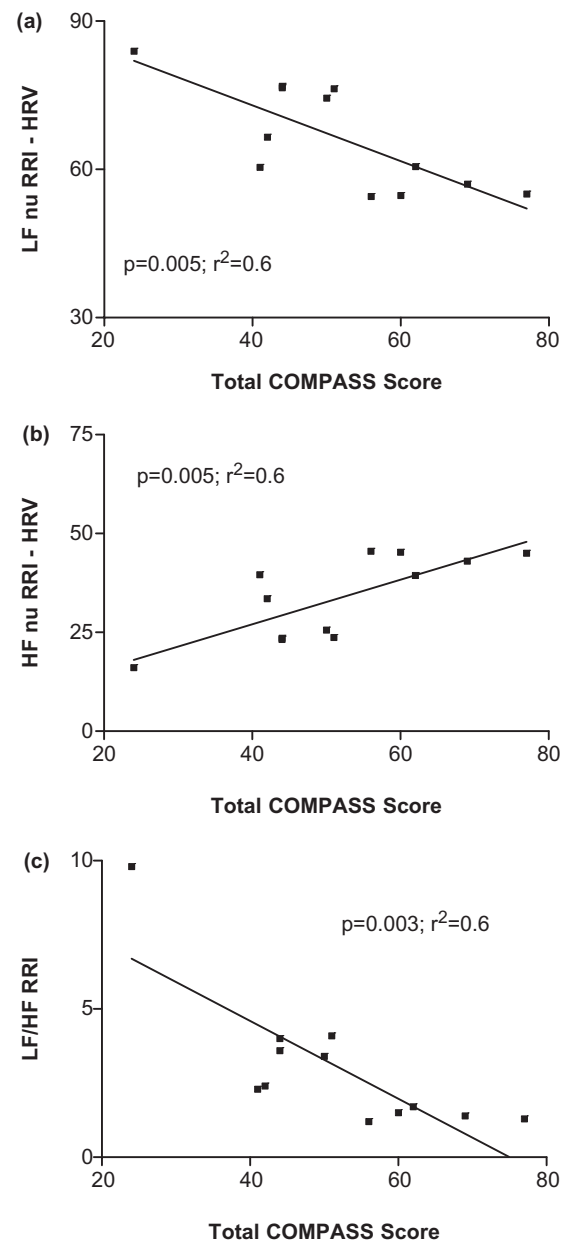
**Figure 3.** Individual total COMPASS scores in CFS patients, normal controls and PBC patients in phase 2.

which autonomic dysfunction has been linked to the expression of fatigue (primary biliary cirrhosis, 60 patients, all female, mean age  $58.7 \pm 12.3$ ).

Our previous observation of significantly higher COMPASS scores in CFS patients than in normal controls was confirmed in the validation group (Figure 3). COMPASS scores were also significantly higher in PBC patients than in normal controls, confirming previous observations suggesting a strong association between PBC and autonomic dysfunction. COMPASS scores were in fact significantly higher in CFS patients than in patients with PBC, a disease in which there is strong evidence of a causal link between fatigue and autonomic dysfunction.

Next we used the phase 2 groups to validate the diagnostic criterion for significant autonomic dysfunction of COMPASS >32.5 identified in phase 1 of the study. For the mixed group of CFS patients and population controls ( $n=67$ ), COMPASS >32.5 had a positive predictive value for the presence of CFS of 0.96 (95%CI 0.86–0.99) and a negative predictive value of 0.84 (0.70–0.93) ( $\chi^2 = 40.5$ ,  $p < 0.0001$ ).

Finally, given autonomic dysfunction was present in our PBC, as well as our CFS patients, we addressed the broader question of the value of COMPASS >32.5 as a diagnostic criterion for the presence of significant fatigue-associated disease. For the purposes of this study, significant fatigue was defined as FIS >40.0 (based on mean FIS score +2SD for the normal control population in phase 1 of the study), which was applied to the whole phase 2 population of 127 CFS patients, PBC patients, and normal controls. In this mixed group, COMPASS >32.5 had a positive predictive value for the presence of significant fatigue of 0.89 (0.78–0.96) and a negative predictive value of 0.74 (0.62–0.84) ( $\chi^2 = 50.1$ ,  $p < 0.0001$ ).



**Figure 4.** Correlation between total COMPASS Score and: **a** low-frequency heart rate variability (LF) (normalized units: nu) (predominantly sympathetic function); **b** high-frequency (HF) (predominantly parasympathetic function); **c** LF/HF ratio (balance between sympathetic and parasympathetic autonomic nervous system function).

### Relationship between total COMPASS scores and heart rate variability

Strong significant correlations were seen between heart rate variability, measured during 10 min rest, and both the orthostatic tolerance domain (data not shown) and the total COMPASS score. There was an increasingly impaired sympathetic function (LF HRV) with higher COMPASS score (Figure 4a), while parasympathetic function (HF HRV) was

higher with higher scores (Figure 4b). Taken together there, was a change in the sympatho-vagal balance with higher COMPASS scores (Figure 4c).

## Discussion

Our data show a clear and significant association between CFS (identified using the established Fukuda criteria)<sup>30</sup> and the symptoms of autonomic dysfunction (identified using the COMPASS score). Interestingly, autonomic symptoms were not universal in those diagnosed with CFS, which may go some way towards explaining the conflicting literature in this area. Also, although broadly-based, the association did not cover the full range of autonomic symptoms. A particularly strong association was seen with symptoms of orthostatic intolerance, suggesting that abnormality of dynamic blood pressure regulation is particularly associated with fatigue severity in CFS/ME. In the first phase of the study, we defined a diagnostic criterion for significant abnormality of the COMPASS score (COMPASS >32.5). In the second phase of the study we confirmed our observations on the association between CFS and COMPASS scores, and validated this diagnostic criterion using a mixed CFS and normal population group, with a positive predicted value of 96% and a negative predicted value of 84%.

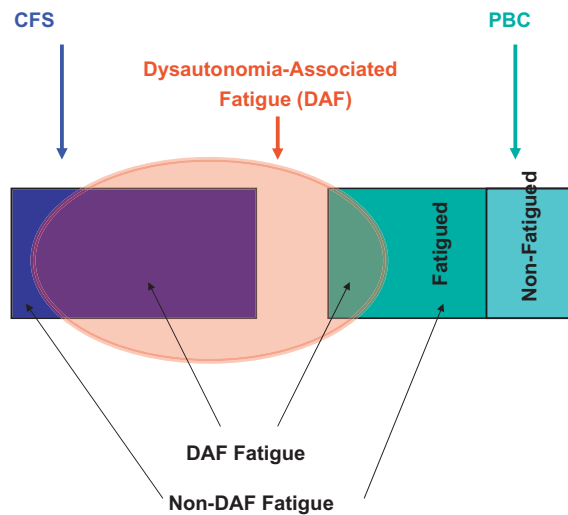
Three conclusions can be drawn from this component of the study. First, autonomic dysfunction (as identified by the COMPASS score) is a frequent feature of patients with CFS (75% of this CFS patient group). Second, the finding of a significantly elevated COMPASS was highly specific to patients with CFS, in a mixed group of CFS patient and normal controls. Third, COMPASS >32.5 appears to be a robust, reproducible and objective diagnostic tool for identifying a significant CFS sub-population in whom autonomic dysfunction is a prominent disease feature.

The contrast between the findings of this study and earlier studies that failed to identify a link between autonomic dysfunction and CFS may well reflect the robust diagnostic criteria for CFS in this study, and the favourable psychometric properties of the COMPASS, although the routes we used for patient recruitment, including through local patient support groups, may have contributed to identifying a particularly symptomatic CFS patient group. The strong relationship seen in the validation element of the study between COMPASS scores and heart rate variability (an objective measure of autonomic function) strongly suggests that the COMPASS is indeed identifying autonomic dysfunction.

Although the majority of CFS patients in both our study cohorts had significantly elevated COMPASS scores, a minority of patients did not. Severity of fatigue was similar in patients with high and with low COMPASS scores, suggesting that we may have identified subgroups of CFS with potentially different aetiological mechanisms. Interestingly, this division into dysautonomia-associated and non-dysautonomia-associated fatigue has recently been observed in primary biliary cirrhosis, where 60% of patients have significant fatigue.<sup>19,20,23</sup> We therefore applied our diagnostic criterion to a group of mixed PBC patients. In this group of 60 patients, of whom 37 had significant fatigue, our COMPASS score diagnostic criterion had a positive predictive value for presence of fatigue of 83% and a negative predictive value of 60%. Of the 37 fatigued patients, 25 (67%) met our COMPASS diagnostic criterion for significant autonomic dysfunction.

These findings appear to confirm that dysautonomia is a feature of some, but not all, fatigued PBC patients, and also show that our COMPASS diagnostic criterion is about equally good at identifying fatigue-associated dysautonomia in PBC and in CFS patients. Our findings thus have implications for the broader context of autonomic dysfunction and disease. Further studies are needed to elucidate the multiple mechanisms responsible for the expression of fatigue in complex disease settings, but our findings support the hypothesis that autonomic dysfunction is a common pathway to the development of fatigue that can be triggered by a number of seemingly disparate disease processes. Further research is also needed to explore whether autonomic dysfunction arises as a primary defect, or secondary to abnormalities such as volume depletion. Previous research approaches have tended to look at single diseases in isolation, which may have contributed to important 'cross-cutting' aetiological mechanisms for fatigue being missed. Our data support the concept of a common process (dysautonomia-associated fatigue, DAF) that may be responsible for some fatigue development in several disease settings, and which may be amenable to common approaches to treatment (Figure 5). This model needs to be tested and confirmed in CFS and PBC, and extended to other fatigue-associated disease settings.

Initial enthusiasm for therapeutic approaches should be tempered by the recognition that dysautonomia-directed approaches to therapy have, to date, proved disappointing in clinical practice. However, the limited apparent response to therapy may reflect that only some CFS patients have autonomic dysfunction-associated fatigue (and thus would be expected to respond to such



**Figure 5.** Model for the role played by dysautonomia-associated fatigue (DAF) in the clinical expression of CFS and PBC. DAF represents a ‘cross-cutting’ phenomenon that can contribute to the expression of fatigue in seemingly disparate conditions. In CFS (in which all patients are by definition fatigued), DAF is present in the majority of patients. The non-DAF minority of CFS presumably have fatigue generated by other pathological processes. In PBC (in which only a proportion of patients are fatigued), DAF is present in a sizeable minority of patients. In contrast to CFS, the pathological processes responsible for the non-DAF fatigue component in PBC have begun to be identified, and include excessive daytime somnolence. The implication of this model is that dysautonomia-directed approaches to therapy should be restricted in CFS (and, indeed, PBC patients) to the DAF subgroup of patients. Failure to restrict the application of these approaches in this way may help explain the apparent lack of efficacy of these approaches in clinical trials to date.

therapies). Our observation that autonomic dysfunction is a feature in only a proportion (albeit a significant one) of CFS patients, and our identification of a diagnostic criterion to identify such patients, should allow better-targeted therapeutic trials.

This study aimed to examine the strength and nature of the association between the symptoms of autonomic dysfunction and fatigue in CFS, and to identify diagnostic criteria for significant autonomic dysfunction. It did not aim to reveal the nature of the association. One key question is whether the development of autonomic dysfunction in CFS patients is causally related to the development of fatigue. It may be, for example, that autonomic dysfunction occurs as a consequence of physical or behavioural changes in fatigued patients, and such deconditioning has previously been postulated as an explanation for the presence of autonomic dysfunction in CFS patients. However, the existence of a clear group of significantly fatigued CFS patients

who do not exhibit autonomic dysfunction, suggests, at the very least, that deconditioning is not a universal phenomenon. Further, there was no association between the degree of autonomic dysfunction as assessed by COMPASS and the length of time that patients had experienced fatigue as part of their CFS. If autonomic dysfunction resulted from deconditioning caused by impaired activity, more prolonged experience of fatigue should be associated with increased autonomic dysfunction.

Studies in other conditions in which fatigue is associated with autonomic dysfunction, such as PBC, have demonstrated associations between physical parameters of blood pressure regulation (including on dynamic testing in the context of tilt testing) and severity of fatigue.<sup>19,21,23</sup> Ongoing studies in PBC are addressing the extent to which these blood pressure dysregulation phenomena affect peripheral muscle function through oxygen delivery abnormalities. Such studies are badly needed in CFS, and identification of a diagnostic criterion for fatigue-associated dysautonomia in CFS will assist in the design of such studies by enabling the identification of suitable subjects. These studies will be of real importance, not only for our understanding of the pathogenesis of fatigue in a significant proportion of CFS patients, but also, potentially, in the design of treatments for these patients.

## Acknowledgements

Funding provided by ME Research UK and MRC. None of the authors have any conflict of interest, all participated in the study and all have read the final version of the manuscript. The funders had no input into the performance or interpretation of the research presented in this manuscript. JN is the guarantor of the data. The study was reviewed and approved by the Newcastle and North Tyneside LREC. All researchers are independent of the funders.

## References

1. Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (encephalopathy); diagnosis and management. [<http://www.nice.gov.org>]
2. Rowe PC, Calkins H. Neurally mediated hypotension and chronic fatigue syndrome. *Am J Med* 1998; **105**:15–21S.
3. Schondorf R, Freeman R. The importance of orthostatic intolerance in the chronic fatigue syndrome. *Am J Med Sci* 1999; **317**:117–23.

4. Schondorf R, Benoit J, Wein T, Phaneuf D. Orthostatic intolerance in the chronic fatigue syndrome. *J Auton Nerv Sys* 1999; **75**:192–201.
5. Winkler AS, Blair D, Marsden JT, Peters TJ, Wessely S, Cleare AJ. Autonomic function and serum erythropoietin levels in chronic fatigue syndrome. *J Psychosom Res* 2004; **56**:179–83.
6. Freeman R, Komaroff AL. Does the chronic fatigue syndrome involve the autonomic nervous system? *Am J Med* 1997; **102**:357–64.
7. Karas B, Grubb BP, Boehm K, et al. The Postural Orthostatic Tachycardia Syndrome: A Potentially Treatable Cause of Chronic Fatigue, Exercise Intolerance, and Cognitive Impairment in Adolescents. *PACE* 2000; **23**:344–51.
8. LaManca JJ, Peckerman A, Walker J, Kesil W, Cook S, Taylor A, Natelson BH. Cardiovascular response during head-up tilt in chronic fatigue syndrome. *Clinical Physiology* 1999; **19**:111–20.
9. De Becker P, Dendale P, De Meirleir K, Campine I, Vandeborne K, Hagers Y. Autonomic testing in patients with chronic fatigue syndrome. *Am J Med* 1998; **105**:22–26S.
10. Yoshiuchi K, Quigley KS, Ohashi K, Yamamoto Y, Natelson BH. Use of time-frequency analysis to investigate temporal patterns of cardiac autonomic response during head-up tilt in chronic fatigue syndrome. *Autonom Neurosci* 2004; **113**:55–62.
11. Yamamoto Y, LaManca JJ, Natelson BH. A measure of heart rate variability is sensitive to orthostatic challenge in women with chronic fatigue syndrome. *Exp Biol Med* 2003; **228**:167–74.
12. Pagani M, Lucini D. Chronic fatigue syndrome: a hypothesis focusing on the autonomic nervous system. *Clin Sci* 1999; **96**:117–25.
13. Stewart J, Weldon A, Arlievsky N, et al. Neurally mediated hypotension and autonomic dysfunction measured by heart rate variability during head-up tilt testing in children with chronic fatigue syndrome. *Clin Auton Res* 1998; **8**:221–30.
14. Timmers HJ, Wieling W, Soetekouw PM, Bleijenberg G, Van Der Meer JW, Lenders JW. Hemodynamic and neurohumoral responses to head-up tilt in patients with chronic fatigue syndrome. *Clin Auton Res* 2002; **12**:273–80.
15. Peckerman A, La Manca JJ, Krishna KA, et al. Abnormal impedance cardiography predicts symptom severity in chronic fatigue syndrome. *Am J Med Sci* 2003; **326**:55–60.
16. Stewart JM. Autonomic nervous system dysfunction in adolescents with postural orthostatic tachycardia syndrome and chronic fatigue syndrome is characterized by attenuated vagal baroreflex and potentiated sympathetic vasomotion. *Pediatr Res* 2000; **48**:218–26.
17. Soetekouw PM, Lenders JW, Bleijenberg G, Thien T, van der Meer JW. Autonomic function in patients with chronic fatigue syndrome. *Clin Auton Res* 1999; **9**:334–40.
18. Timmers HJLM, Wieling W, Soetekouw PMMB, Bleijenberg G, Van Der Meer JWM, Lenders JWM. Hemodynamic and neurohumoral responses to head-up tilt in patients with chronic fatigue syndrome. *Clin Auton Res* 2002; **12**:273–80.
19. Newton JL, Allen JA, Kerr S, Jones DEJ. Reduced heart rate variability and baroreflex sensitivity in primary biliary cirrhosis. *Liv Int* 2006; **26**:197–202.
20. Newton JL, Davidson A, Kerr SR, Bhala N, Pairman J, Burt JA, Jones DEJ. Autonomic dysfunction in Primary Biliary Cirrhosis correlates with fatigue severity. *Eur J Gastroenterol Hepatol* 2007; in press.
21. Flackenecker P, Rufer A, Bihler I, Hippel C, Reiners K, Toyka K, et al. Fatigue in MS is related to sympathetic vasomotor dysfunction. *Neurology* 2003; **61**:851–3.
22. Chaudhuri A, Behan P. Fatigue in neurological disorders. *Lancet* 2004; **363**:978–89.
23. Newton JL, Jones DEJ. The population prevalence of autonomic dysfunction and daytime somnolence in Primary Biliary Cirrhosis. *Hepatology* 2007; in press.
24. Suarez GA, Opfer-Gehrking TL, Offord KP, Atkinson EJ, O'Brien PC, et al. The Autonomic Symptom Profile: a new instrument to assess autonomic symptoms. *Neurology* 1999; **52**:523.
25. Kollensperger M, Stampfew-Kountchev M, Seppi K, Geser F, Frick C, et al. Progression of dysautonomia in multiple system atrophy: a prospective study of self-perceived impairment. *Eur J Neurol* 2007; **14**:66–72.
26. Kihara M, Nakashima H, Takahashi M, Kawamura Y. A dysautonomia case of Guillain-Barré syndrome with recovery: Monitored by Composite Autonomic Scoring Scale. *J Auton Nerv Syst* 1998; **73**:186–9.
27. Cariga P, Ahmed S, Mathias CJ, Gardner BP. The prevalence and association of neck (coat-hanger) pain and orthostatic (postural) hypotension in human spinal cord injury. *Spinal cord* 2002; **40**:77–82.
28. Allcock LM, Kenny RA, Burn DJ. Clinical phenotype of subjects with Parkinson's disease and orthostatic hypotension: Autonomic symptom and demographic comparison. *Mov Disord* 2005; **21**:1851–5.
29. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. International Chronic Fatigue Syndrome Study Group. The Chronic Fatigue Syndrome: A Comprehensive Approach to Its Definition and Study. *Ann Int Med* 1994; **121**:953–9.
30. Prince M, James OF, Holland NP, Jones DE. Validation of a fatigue impact score in primary biliary cirrhosis: towards a standard for clinical and trial use. *J Hepatol* 2000; **32**:368–73.
31. Anonymous. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* 1996; **93**:1043–65.