Orthostatic symptoms predict functional capacity in chronic fatigue syndrome: implications for management

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Summary

Objectives: To establish the relationship between the functional impairment experienced by Chronic fatigue syndrome (CFS) patients and the symptoms frequently experienced by those with CFS; specifically cognitive impairment, fatigue and orthostatic symptoms.

Design: Cross sectional questionnaire survey.

Setting: Specialist CFS Clinical Service.

Subjects: Ninety-nine Fukuda diagnosed CFS and 64-matched controls.

Main outcome measures: Symptom and functional assessment tools completed and returned by post included; PROMIS HAQ (Patient-Reported Outcomes Measurement Information System, Health Assessment Questionnaire), CFQ (Cognitive Failures Questionnaire), FIS (Fatigue Impact Scale) and OGS (Orthostatic Grading Scale) assessment tools.

Results: CFS patients experience greater functional impairment than controls [mean (95% CI) PROMIS HAQ scores CFS 36 (31–42) vs. controls 6 (2–10); P < 0.0001], especially in the functional domains of activities and reach. Poorer functional ability impairment is significantly associated with greater cognitive impairment (P = 0.0002, r = 0.4), fatigue (P < 0.0001, r = 0.5) and orthostatic symptoms (P < 0.0001, r = 0.6). However, only orthostatic symptoms (OGS) independently associated with functional impairment (β = 0.4, P = 0.01).

Conclusions: Treatment of orthostatic symptoms in CFS has the potential to improve functional capacity and so improve quality of life.

Introduction

Chronic fatigue syndrome (CFS) is a common debilitating condition thought to affect 0.2–2% of the UK population.1–5 CFS is associated with a constellation of symptoms that lead to considerable disability. The level of impaired functional ability in CFS is not homogenous with studies showing it to be comparable with a number of other chronic diseases, most notably multiple sclerosis, hypertension, congestive heart failure, acute myocardial infarction, depression, end-stage renal disease, heart disease and untreated hyperthyroidism.6–10

A number of studies have suggested that functional impairment in CFS is related to cognitive deficits.11–15 Recent studies have confirmed that in addition to the classically recognized symptoms of fatigue and cognitive impairment almost 90% of those with CFS experience symptoms related to orthostasis.16,17 The relationship between functional capacity and the other symptoms described by those with CFS is currently unclear. Understanding this will allow treatment to be directed to those symptoms whose improvement has the potential to lead to the greatest functional gain. Here, we measured using a patient reported outcome tool, the degree of functional impairment experienced by those with CFS and the impact of the symptoms of CFS (cognitive impairment, fatigue and autonomic dysfunction) upon this functional impairment. The purpose of this...
study was to discover how these symptoms relate to functional capacity in CFS with the aim of improving understanding and appreciation of how, and in what particular functional domains, CFS affects patients’ lives.

Methods

Subjects

Subjects were 135 consecutive patients referred to the Newcastle upon Tyne Royal Victoria Hospital over the 6 months from January to June 2009 who fulfilled the Fukuda diagnostic criteria for CFS.4

The control group was recruited by asking each CFS patient to invite one non-CFS friend (of comparable age and sex) to complete the symptom assessment tools. No selection (positive or negative) was made with regard to co-morbidity, fatigue status or functional ability.

Measures

Four functional and symptom assessment tools were sent by post to a total of 135 CFS patients. Subjects were asked to complete these measures and return them in a prepaid envelope. The assessment tools included were:

1. PROMIS HAQ—Patient-Reported Outcomes Measurement Information System, Health Assessment Questionnaire.18,19

This tool assesses the functional impact of CFS on subjects, by measuring the functional and physical ability of the subjects. The PROMIS HAQ was derived from the HAQ and consists of 20 questions that ask patients to rate their ability to carry out daily activities on a 5-point scale of ‘0 = without any difficulty’ to ‘4 = unable to do’. The 20 questions are divided into eight domains of physical function: dressing, arising, eating, walking, hygiene, reach, grip and activity. The highest scoring question in each domain is used as the domain score. All eight-domain scores are added together, divided by eight and multiplied by 25 to calculate the total PROMIS HAQ score. Higher scores indicate worse functional ability and therefore greater functional impairment.

2. CFQ—Cognitive Failures Questionnaire.20–22

In order to determine whether CFS patients experienced cognitive symptoms more frequently than matched controls, indicating worse cognitive impairment, the CFS patients and controls completed the CFQ, which assessed their level of cognitive ability. The presence and severity of cognitive symptoms were compared between the two groups.

This tool assesses the prevalence of cognitive symptoms, by measuring the frequency of cognitive slips or failures occurring in everyday life. The cognitive abilities assessed in the CFQ include memory, attention, concentration, forgetfulness, word-finding abilities and confusion. The questionnaire consists of 25 items covering failures in perception, memory and motor function and asks patients to rate how often these failures occur, on a 5-point Likert scale of 0–4 (0 = never, 4 = very often). The responses for the 25 questions are added together to obtain the total CFQ score. The higher the score, the greater the cognitive impairment.

3. FIS—Fatigue Impact Scale.23

The FIS measures fatigue experienced by CFS patients, and how the fatigue functionally limits them in their lives and activities. The FIS assesses patients’ perception of how fatigue affects their cognitive, physical and psychosocial functions. This includes the impact of fatigue on their work, family and financial responsibilities, their mood, their reliance on others, their social activities, and on their quality of life. It is made up of 40 items and subjects must rate how badly affected these items are due to fatigue on a 5-point scale ranging from 0 (no problem) to 4 (extreme problem). The total FIS score is calculated by adding all answers from the 40 questions together. Higher scores indicate greater impact of fatigue.

4. OGS—Orthostatic Grading Scale.24

The OGS is a self-report assessment tool consisting of five items, which assess the frequency of orthostatic symptoms, severity of orthostatic symptoms, conditions under which orthostatic symptoms occur, activities of daily living and standing time. Patients are asked to grade each item on a scale of 0–4, 0 being the lowest and 4 the highest. The total OGS score is calculated from adding up the scores from each item. Higher scores indicate greater severity of autonomic dysfunction.

Data analysis

Analysis was performed using the statistical analysis software Prism 3.0 and SPSS. It was determined whether data was normally or non-normally distributed. Where data was normally distributed it is presented as mean ± standard deviation, and comparisons were made between groups using un-paired t-tests. Where data was non-normally distributed the data is presented as median and range and comparisons were made by Mann–Whitney
U-test. To determine whether the degree of functional impairment experienced by CFS sufferers was influenced by the symptoms they experienced, we explored the univariate relationship between functional capacity and the symptom assessment tools of cognitive symptoms, fatigue and autonomic dysfunction. Univariate analysis was performed by correlations using Spearman and Pearson tests where appropriate for parametric and non-parametric data. To determine whether the relationships between functional ability and the symptoms of CFS (cognitive impairment, fatigue and autonomic dysfunction) are independent of each other, a multivariate analysis was performed using the log-rank test. Differences in proportions were determined using Chi-squared tests. A statistically significant result was considered when $P < 0.05$.

**Ethical permission**

The programme of research is approved by the Newcastle and North Tyneside LREC. The project was funded by ME Research UK. Consent for data use was implied by return of the assessment tools.

**Results**

Ninety-nine CFS patients who were sent the assessment tools participated in this study (response rate of 99/135; 73%). Mean ± standard deviation age of the patients was 57.3 ± 15, and 87% were female (86 female, 13 male). The CFS patients were matched group wise (by mean age and proportion of females) to 64 control subjects whose mean age was 59.3 ± 17, and 83% were female (53 female, 11 male).

**Overall functional impairment**

Functional capacity was significantly reduced in the CFS group compared to controls when assessed using the total PROMIS HAQ score (Figure 1; $P < 0.0001$) with the mean ± standard deviation for the CFS patients (36.4 ± 27) almost seven times greater than that of the controls (5.9 ± 15) [median (25 percentile) CFS 34.4 (12.5–56.3) vs. controls 0 (0–2.5)]. On examining the proportion of the total groups who experienced no functional impairment, only nine out of the total 99 CFS subjects (9%) scored 0 on the PROMIS HAQ, marking themselves as being able to do a task ‘without any difficulty’, whereas 37 out of the 64 control subjects scored 0 (57.8%) ($P < 0.0001$).

**Examining the domains of functional ability**

The PROMIS HAQ assessment tool comprises eight separate domains of physical function: dressing, arising, eating, walking, hygiene, reach, grip and activities. Table 1 shows the individual PROMIS HAQ domain scores (scored out of four) for CFS patients compared to matched controls.

In all domains of functional ability those with CFS recorded significantly higher scores compared to controls, signifying CFS patients have worse physical ability/functioning than controls across the whole spectrum of functional activities.

**Relationship between functional capacity and symptoms in CFS**

As expected the CFS group experienced higher levels of fatigue and orthostatic symptoms compared to controls. The total score on the cognitive failures questionnaire was higher for the CFS group than the control group, demonstrating that as with other

![Figure 1. Mean total PROMIS HAQ score for CFS patients and for controls.](https://academic.oup.com/qjmed/article-abstract/103/8/589/1524268)

| Domain     | CFS Median (Interquartile range) | Control Median (Interquartile range) | $P$-value |
|------------|----------------------------------|-------------------------------------|-----------|
| Dressing   | 1 (2)                            | 0 (0.5)                             | 0.005     |
| Arising    | 1 (2)                            | 0 (0)                               | <0.0001   |
| Eating     | 1 (2)                            | 0 (0)                               | <0.0001   |
| Walking    | 1 (3)                            | 0 (0)                               | <0.0001   |
| Hygiene    | 1 (3)                            | 0 (0)                               | <0.0001   |
| Reach      | 2 (2)                            | 0 (1)                               | <0.0001   |
| Grip       | 1 (2)                            | 0 (0)                               | <0.0001   |
| Activities | 3 (3)                            | 0 (0)                               | <0.0001   |
cognitive assessment tools CFS patients have greater cognitive impairment than the controls (Figure 2).

On univariate analysis, there were strong significant correlations between cognitive symptoms, fatigue and autonomic symptoms (Table 2) with increased symptoms being associated with worse functional capacity.

### Independent associations between functional capacity and symptoms in CFS

The results of the multivariate analysis are shown in Table 3. The results confirm that worsening autonomic symptoms are independently associated with increased functional impairment, whereas worsening cognitive impairment or fatigue is not.

A similar multivariate analysis was performed for each of the individual PROMIS HAQ domains with the CFQ, FIS and OGS scores. This analysis found that higher autonomic symptom burden was independently associated with functional impairment in the walking \( (P=0.017; \beta=0.37) \), arising \( (P=0.034; \beta=0.34) \), activities \( (P=0.041; \beta=0.285) \) and eating \( (P=0.029; \beta=0.355) \) domains, and that increased fatigue independently associated with higher scores also in the walking \( (P=0.032; \beta=0.402) \) and activities \( (P=0.001; \beta=0.620) \) domains, and in the hygiene domain \( (P=0.016; \beta=0.229) \). There were no independent predictors of impairment in the dressing, reach and grip domains; and no domains were found to be independently associated with CFQ scores.

### Discussion

This study confirms that functional capacity is reduced in patients with CFS compared to that of normal subjects. The ability of the patients to carry out everyday activities was found to be lower than that of control subjects in all of the eight domains of functional ability measured by the PROMIS HAQ assessment tool. Significant associations between the functional impairment of CFS patients and symptoms of cognitive deficits, fatigue and autonomic symptoms were identified; confirming that greater functional impairment associates with greater cognitive impairment, fatigue and worse orthostatic symptoms. However, only higher burden of orthostatic

### Table 2 Multivariate analysis for independent associations between symptoms and functional ability in CFS

| Model | Unstandardized coefficients | Standardized coefficients | t  | P-value |
|-------|-----------------------------|---------------------------|----|---------|
|       | \( \beta \)                  | \( \text{Standard error} \) | \( \beta \) |         |
| Constant | -2.121              | 19.166                  | -0.178 | 0.860   |
| CFQ    | 0.055              | 0.205                   | 0.045 | 0.266   |
| FIS    | 0.253             | 0.132                   | 0.334 | 1.917   |
| OGS    | 2.062             | 0.800                   | 0.370 | 2.576   |

### Table 2 Correlation between PROMIS HAQ domains and symptom assessment tools

|                  | COGFAIL       | FIS           | OGS           |
|------------------|---------------|---------------|---------------|
|                  | \( P\text{-value} \) | \( r\text{-value} \) | \( P\text{-value} \) | \( r\text{-value} \) | \( P\text{-value} \) | \( r\text{-value} \) |
| Total score      | 0.0002        | 0.37          | <0.0001       | 0.55          | <0.0001       | 0.49          |
| Dressing         | 0.0062        | 0.27          | <0.0001       | 0.44          | 0.0023        | 0.38          |
| Arising          | 0.0001        | 0.37          | <0.0001       | 0.43          | 0.0005        | 0.43          |
| Eating           | <0.0001       | 0.39          | <0.0001       | 0.49          | 0.0003        | 0.44          |
| Walking          | 0.0041        | 0.29          | <0.0001       | 0.46          | <0.0001       | 0.48          |
| Hygiene          | 0.0011        | 0.32          | <0.0001       | 0.50          | 0.0014        | 0.39          |
| Reach            | <0.0001       | 0.38          | <0.0001       | 0.54          | 0.0008        | 0.41          |
| Grip             | 0.0001        | 0.38          | <0.0001       | 0.42          | 0.0053        | 0.35          |
| Activities       | 0.0080        | 0.27          | <0.0001       | 0.51          | 0.0005        | 0.43          |
symptoms independently associated with functional impairment when multivariate analysis of the data was performed.

This study confirms that orthostatic symptoms and the underlying autonomic dysfunction that is found frequently in those with CFS is the key symptom to impact on functional ability. Therefore, the focus of treatment of CFS should be the orthostatic symptoms rather than the symptom of fatigue. If orthostatic symptoms were treated and the autonomic dysfunction was improved, it would potentially decrease functional impairment in this patient group and hence improve/increase their functional capacity.

Since functional impairment also has a positive correlation with both cognitive impairment and fatigue, it implies that if the functional impairment was reduced by treating the autonomic dysfunction, the severity of cognitive difficulties and fatigue might also decrease. Studies in fatigue and non-fatigue associated diseases suggest a link between autonomic dysfunction and cognitive impairment, with poorer scores on cognitive function tests in those patients with postural dysregulation of blood pressure, the physiological abnormality increasingly recognized in CFS.

Functional impairment in all domains was significantly associated with orthostatic symptoms, with the most significant and strongest relationship being in the domain of walking. Furthermore, the multivariate analysis showed functional impairment in the domains of walking, arising, eating and activities to be independently associated with orthostatic symptoms. Walking, arising and activities all involve standing up or being stood upright. The autonomic nervous system plays an important role when standing upright in overcoming the gravitational effect of blood pooling in the lower limbs, causing an imbalance in arterial and venous blood pressures. If not addressed, this would lead to insufficient perfusion and malfunction of organs and tissues. The autonomic nervous system overcomes this by increasing sympathetic activity to induce vasoconstriction of large veins in the legs in order to re-equilibrate arterial and venous blood pressures by promoting increased venous return. With autonomic dysfunction these compensatory mechanisms may be impaired and as a result standing up and related activities would be adversely affected leading to functional impairment. Our recent study confirming impaired muscle bio-energetic function in CFS the degree of which associates with autonomic dysfunction could also explain why if muscles are functioning sub-optimally this leads to inability to perform activities of daily living. It could, therefore, be predicted that if autonomic dysfunction was treated in CFS patients, the domains involving standing or an upright posture may show the greatest improvement in functional ability. Despite this, the UK CFS/ME NICE guidelines which recommend the investigation and management strategy for those with CFS does not include objective or subjective evaluation of autonomic function in this important patient group.

One treatment of autonomic dysfunction in CFS that has recently been investigated in a clinical trial of 38 CFS patients is home orthostatic training (HOT). This intervention in a small feasibility study was found to improve autonomic function (decrease in blood pressure whilst standing, increase in total peripheral resistance) and improve patients’ reports of fatigue over a 6-month period measured by the FIS, showing an encouraging trend towards eliminating fatigue by improving orthostatic symptoms. HOT is considered to be an effective and established treatment in other diseases associated with autonomic dysfunction.

This study has some limitations. Since the nature of the assessment involved self-report questionnaires, the responses are all subjective. One patient’s opinion of the assessment scale may be different to another patient, and hence the responses may not be completely consistent in their description of severity of symptoms. However, the magnitude of the differences between the patients and the controls would suggest that even if the patients over reported by 50% the differences would still be dramatically different. Furthermore, it is possible that the results were influenced by the design of the study; non-responders may be too symptomatic to respond to the questionnaires or conversely be too active to respond.

In summary, this study has confirmed that functional capacity is reduced in CFS patients compared to that of control subjects, and that functional impairment in CFS is significantly related to the symptom of autonomic dysfunction, therefore treating autonomic dysfunction would be expected to improve patients’ functional capacity particularly in the upright position, and hence improve quality of life. Future research should focus on treatments of autonomic dysfunction in CFS, both pharmacological and physiological in nature in order to determine whether improvements in autonomic function are paralleled by increased functional capacity.

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