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Fatigue severity remains stable over time and independently associated with orthostatic symptoms in chronic fatigue syndrome: a longitudinal study

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Abstract. Jones DEJ, Gray J, Frith J, Newton JL (UK NIHR Biomedical Centre in Ageing, Institute of Cellular Medicine, Institute for Ageing and Health, Newcastle University, Newcastle, UK) Fatigue severity remains stable over time and independently associated with orthostatic symptoms in chronic fatigue syndrome: a longitudinal study. *J Intern Med* 2011; **269**: 182–188.

Objectives: To examine fatigue variability over time in chronic fatigue syndrome (CFS) and the effect of other symptoms on its predictability.

Design: Longitudinal cohort study of patients with CFS (Fukuda criteria).

Setting: Specialist CFS clinical service.

Subjects: Phase 1: 100 patients who participated in a study of CFS symptoms in 2005 were revisited in 2009. Phase 2: 25 patients completed fatigue diaries to address intra- and inter-day variability in perceived fatigue.

Main outcome measures: Phase 1: subjects completed fatigue impact scale (FIS), Epworth sleepiness scale (ESS), orthostatic grading scale (OGS) and hospital anxiety and depression scale (HADS). Changes in variables represented the differences between 2005 and 2009. Phase 2: subjects rated fatigue on a scale of 0 (no fatigue) to 10 (severe fatigue) four times a day for 5 weeks.

Results: Symptom assessment tools were available in both 2005 and 2009 for 74% of patients. FIS and HADS depression (HAD-D) and anxiety (HAD-A) scores significantly improved during follow-up whereas ESS and OGS remained stable. FIS improved in 29/74 (39%) subjects, and by ≥10 points in 19 (26%). FIS worsened by ≥10 points in 33/74 (45%) subjects. On multivariate analysis, independent predictors of current fatigue (FIS in 2009) were FIS in 2005, HAD-D in 2009, OGS in 2009 and change in HAD-A. Reported fatigue was stable from week to week and from day to day. Patients reported higher fatigue in the morning (mean ± SD; 6.4 ± 2), becoming significantly lower at lunchtime (6.2 ± 2; $P < 0.05$) and increasing again to 7 ± 2 at bedtime.

Conclusions: Current fatigue is independently associated with current autonomic symptom burden, current depression and change in anxiety during follow-up. These findings have implications for targeted symptom management in CFS.

Keywords: chronic fatigue syndrome, fatigue, follow-up, orthostatic symptoms.

Introduction

Chronic fatigue syndrome (CFS) is a common condition that is thought to affect between 0.2% and 2% of the UK population; it affects all age groups and is associated with significant impairment of quality of life [1–4]. In addition to the debilitating symptom of fatigue, those with CFS frequently describe significant problems related to orthostatic intolerance [5, 6], the severity of which has recently been shown to be associated with impaired functional ability [7]. The natural history of fatigue and the other symptoms that affect those with CFS is unclear, and whether symptoms are likely to improve with time is a question frequently asked by patients with this debilitating disease. The paucity of such data from large longitudinal cohort studies is surprising considering the prevalence of CFS, the recognition that it is associated with poor outcomes, and the dependency on state benefits of many of those affected, the

application for which requires awareness of the likely outcome.

In this study, we have examined fatigue in terms of its variability and whether it could be predicted by the other symptoms associated with fatigue severity. Understanding the symptom of fatigue, its variability and predictability, in those with CFS may point towards the specific biological abnormality in this patient group and thus have important implications for the clinical management of patients.

Methods

Study design

This study was performed in two cohorts of patients with CFS. The longitudinal study phase: 100 patients who fulfilled the Fukuda diagnostic criteria for CFS and had been recruited via the local patient support group ME Northeast to participate in a study of symptoms and their severity in 2005 [8] were sent by post a follow-up series of symptom assessment tools in 2009. These included the fatigue impact scale (FIS), Epworth sleepiness scale (ESS), orthostatic grading scale (OGS) and hospital anxiety and depression scale (HADS). We also recorded the length of history. In addition, we measured the change in variables to summarise how they changed between 2005 and 2009 (calculated as score in 2009 minus score in 2005; a positive score indicates an increase in score, and thus a worsening of symptom impact whereas a negative score indicates a decrease in score, and thus improvement in symptom severity between 2005 and 2009).

The short-term variability phase: to assess intra- and inter-day variability in perception of fatigue, 25 CFS patients (classified using Fukuda criteria [8]) completed fatigue diaries. Subjects were asked to rate their fatigue on a scale of 0 (no fatigue) to 10 (severe fatigue) four times a day, every day for 5 weeks.

Symptom assessment tools

Orthostatic grading scale. Studies suggest a role for autonomic dysfunction and fatigue in CFS. Subjects therefore completed the OGS [9], a fully validated self-report assessment tool for the symptoms of orthostatic intolerance because of orthostatic hypotension (e.g. severity, frequency and interference with daily activities). 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. Studies have shown that scores from the OGS correlate with conventional tests of the integrity of the autonomic nervous system.

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

Hospital anxiety and depression scale. The HADS [11] is a 14-item measure of current anxiety (HAD-A) and depression (HAD-D). The HADS was specifically developed for use in physical illness by excluding items related to somatic symptoms.

Fatigue impact scale. The FIS [12], a 40-item generic scale of fatigue impact, was used to assess fatigue severity. The FIS has previously been validated for and extensively used in CFS.

Analysis

Longitudinal study. Mean scores for each parameter were determined from both 2005 and 2009 data and compared using paired *t*-tests. Regression analysis was performed to explore those variables that predicted current fatigue (assessed using the FIS in 2009) and current depression (assessed using HAD-D in 2009). To determine whether the change in symptoms over time was associated with the variables in 2009, change in variables measured at the two time-points of 2005 and 2009 was also included in the regression analysis. In the initial analysis of independent predictors of current symptoms, for all models, the baseline value (FIS or HAD-D in 2005 as appropriate) was always included; other variables were added individually, in turn, to the baseline value and assessed for significance. Variables with a *P*-value of 0.1 or lower were considered in the subsequent multivariate model. If both score in 2009 and change in score (2005–2009) were individually significant, they were considered as a pair (along with outcome in 2005) to determine whether both status in 2009 and change in status were jointly predictive of the outcome.

The final multivariate model was constructed by adding those variables identified in the first stage (or pairs of variables if both status in 2009 and change in status were jointly predictive) to the model. Variables with a *P*-value of 0.05 or lower were included in the

final model. The residuals of the final models were checked for normality (using probability plots) and for any trend with predicted values to ensure that the final model was a reasonable fit.

Short-term variability phase. Average daily, time of day and weekly values of perceived fatigue severity were calculated from fatigue diaries and compared using analysis of variance (anova).

Results

Short-term variability of fatigue in CFS

In the patients with CFS who completed 5 weeks of fatigue diaries, perceived fatigue was stable over time with no significant differences in reported fatigue from week to week or from day to day. There were also no differences between weekdays and weekends. However, there was variability in fatigue severity through the day, with CFS patients reporting high levels of fatigue in the morning (mean ± SD; 6.4 ± 2), which became significantly lower at lunchtime ($P < 0.05$), and then increased again (7 ± 2) at bedtime (Fig. 1).

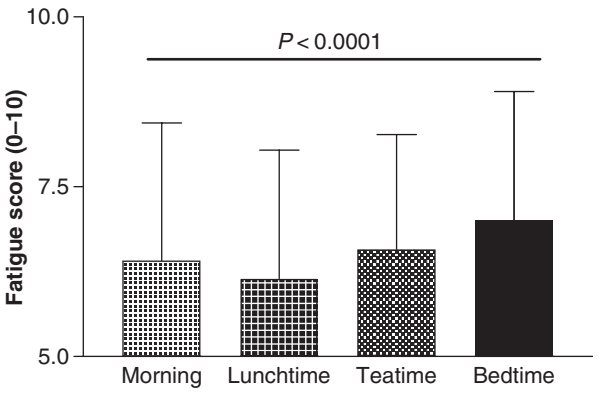

Fig. 1 *Mean self-rated fatigue severity (0 = no fatigue; 10 = severe fatigue) throughout the day every day for 5 weeks.*

Longitudinal variability of fatigue in CFS

Of the 100 patients with CFS who completed symptom assessment tools in 2005, 74 completed a second set in 2009 (74%). There were no significant differences in FIS at baseline between those who returned the tools in 2009 (98 ± 28) and those who did not (96 ± 22). HADS anxiety and depression scores in 2005 were higher in those who completed follow-up tools compared to those who did not, although the difference was not significant (HAD-A: no follow-up, 6.6 ± 4; follow-up, 9.3 ± 5; HAD–D: no follow-up, 7.8 ± 3; follow-up, 8.7 ± 4). The mean ± SD age of the population in 2009 was 54 ± 12 years with a median duration of CFS of 10 years (range 1–35 years). The availability of symptom assessment tools at two timepoints of follow-up allowed us to examine the variability of symptoms over longer-term follow-up in CFS. In those patients who responded in 2009, FIS, HAD-A and HAD-D scores appeared to significantly improve over 4 years of follow-up whereas ESS and OGS remained relatively stable (Table 1). Although this suggests that the natural history of fatigue in CFS over time is for it to improve, we found for individual subjects that only 29/74 (39%) had improved FIS scores over 4 years of follow-up with 19 having FIS scores that improved by ≥10 points (26%). A total of 33/74 (45%) subjects had FIS scores that worsened by ≥10 points over the follow-up period.

Relationship between fatigue severity and other symptoms in CFS

In agreement with previous studies, in 2005 and 2009, there were significant correlations between

Table 1 *Change in symptoms between 2005 and 2009*

	2005	2009	Change in score (2005–2009)			
	Mean (SD)	Mean (SD)	*n*	Mean (SD)	Min	95% CI for change
FIS	97.4 (26.8)	92.9 (28.0)	74	−5.0 (22.8)	−74 to 55	−10.3 to 0.3
HAD-D	8.5 (3.7)	7.5 (3.6)	73	−1.1 (3.4)	−10 to 6	−1.9 to −0.3
HAD-A	8.7 (4.7)	8.5 (4.9)	73	−0.6 (3.5)	−11 to 8	−1.4 to 0.2
ESS	8.6 (5.2)	8.5 (5.1)	74	−0.2 (3.5)	−9 to 6	−1.0 to 0.6
OGS	7.2 (8.9)	6.8 (4.3)	71	0.2 (3.2)	−7 to 8	−0.6 to 0.9

HAD, hospital anxiety and depression; FIS, fatigue impact scale; OGS, orthostatic grading scale; ESS, Epworth sleepiness scale; CI, confidence interval.

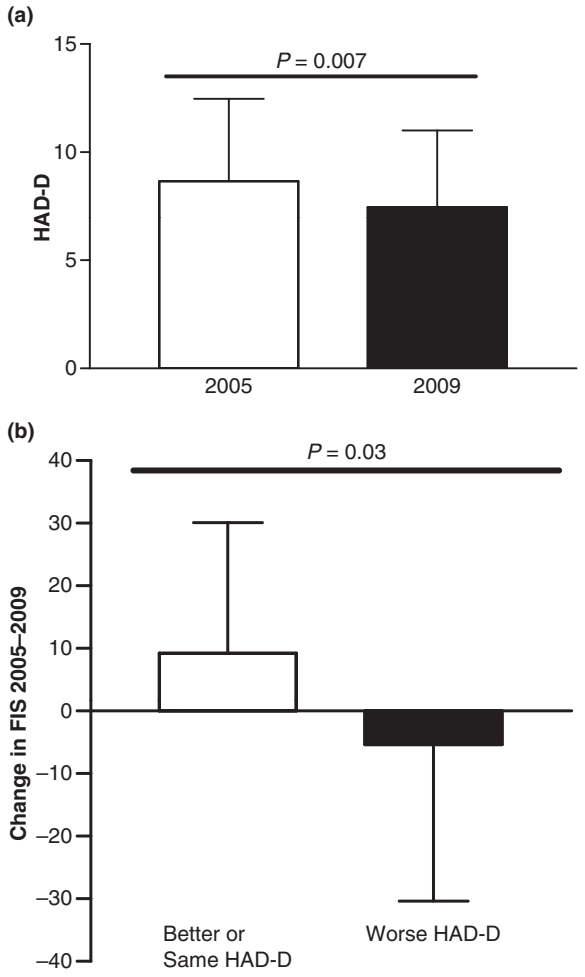

Fig. 2 *(a) Depression determined using HAD-D significantly improved during follow-up. (b) Change in fatigue scores during follow-up in those with an improvement in or a worsening of depression.*

fatigue severity and daytime sleepiness, orthostatic symptoms, anxiety and depression scores. It is interesting that there were no significant associations between age and duration of CFS and fatigue severity. When we considered the change in fatigue severity over the follow-up period, it was clear that those who became more depressed had significantly smaller changes in their fatigue scores (Fig. 2).

Predictors of fatigue in 2009

As anticipated, FIS in 2009 was highly correlated with FIS in 2005. In a bivariate model in which we considered other potential predictors of current fatigue severity (FIS in 2009) taking into consideration fatigue at baseline (FIS in 2005), there were significant relationships between fatigue and all the parameters, most notably HAD-A, HAD-D, ESS, OGS and change in all variables (Table 2); age did not show any significant association with FIS in 2009. We then went on to perform a multivariate analysis to consider independent predictors of current fatigue (FIS in 2009) and found that most variables became insignificant.

The final model included FIS in 2005, HAD-D in 2009, OGS in 2009 and change in HAD-A (Table 2); these variables accounted for 64% of the variability in FIS in 2009 which confirms that current fatigue is independently related to current autonomic symptom burden, current depression and the change in anxiety during follow-up. The relationship between these parameters is summarised in Fig. 3.

Predictors of depression in 2009

As anticipated, HAD-D in 2005 was a good predictor of HAD-D in 2009. Considering each of the predictors individually (along with HAD-D in 2005), HAD-D in 2009 was significantly related to FIS in 2009, change in FIS, HAD-A in 2009 and change in HAD-A, but no relationship was seen between HAD-D in 2009 and OGS or ESS, or changes in these variables (Table 3). In the final multivariate model, independent predictors of current depression (HAD-D in 2009) were HAD-D in 2005, and FIS and HAD-A in 2009; these variables accounted for 56% of the variability in HAD-D (adjusted R^2 value). These findings confirm that current depression is independently related to previous depression, current fatigue and current anxiety, as summarised in Fig. 3.

Discussion

The results of this study confirm that although the symptom of fatigue described by those with CFS does not vary from day to day, over longer periods of follow-up it does appear to improve slightly when considered in the whole cohort and quantified with the FIS. However, what this means in terms of physical functioning for patients with CFS is unclear, particularly when only a third of patients have scores that improve at all, and one-quarter that improve by more than 10 points on the FIS. In addition, recent studies suggest that improvements in fatigue do not lead to improvements in functional capacity whereas improvements in orthostatic symptoms were independently associated with function in CFS [7].

Table 2 *Predictors of FIS in 2009 using regression analyses*

	Bivariate models[a]		Final multivariate model	
	Regression coefficient	95% CI	Regression coefficient	95% CI
FIS in 2005	0.67	0.49 to 0.85	0.53	0.37–0.69
Age	−0.12	−0.55 to 0.30		
HAD-D in 2009	2.85	1.47 to 4.23	2.38	1.12–3.64
Change in HAD-D	2.53	1.19 to 3.87		
HAD-A in 2009	0.97	−0.06 to 1.99		
Change in HAD-A	2.75	1.48 to 4.03	1.55	0.30–2.79
OGS in 2009	1.99	0.92 to 3.06	1.48	0.50–2.46
Change in OGS	2.15	0.54 to 3.76		
ESS in 2009	1.32	0.34 to 2.30		
Change in ESS	1.63	0.27 to 2.99		

[a]All models included FIS in 2005 plus the variable in question.
HAD, hospital anxiety and depression; FIS, fatigue impact scale; OGS, orthostatic grading scale; ESS, Epworth sleepiness scale; CI, confidence interval.

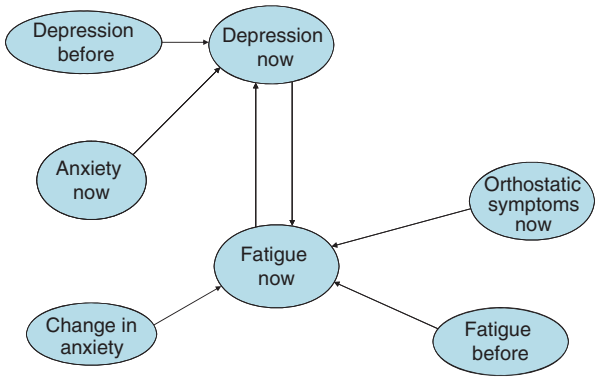

Fig. 3 *Schematic representation of the two multivariate models showing the inter-relationship between the current symptoms of fatigue and depression as determined using the follow-up data.*

We have previously reported that there were no differences in the severity of perceived fatigue over 4 years [13], or between days and between weeks [14], in patients with the fatigue-associated, chronic, autoimmune liver disease primary biliary cirrhosis. There was however a progressive and significant increase in perceived fatigue through the day. As a result, we recommended that maximum participation could be obtained in the morning, the time of least symptoms, for interventions to combat fatigue such as exercise or rehabilitation. We have found a different pattern of variability through the day in CFS, with lower fatigue levels reported at lunchtime. This suggests that mornings are not the most appropriate time for patients with CFS to participate in rehabilitation or other functional activities.

Despite fatigue appearing to improve slightly in the CFS group, the other symptoms characteristically seen in those with CFS, particularly daytime sleepiness and autonomic symptoms, did not appear to improve during follow-up. This suggests that the management focus in CFS should be multifaceted to address all of the symptoms experienced by those with this disease. Also it might point towards an uncoupling in the relationship between symptoms in CFS; that is, if fatigue itself or a common underlying mechanism is the driver for other CFS symptoms, then we would expect that improvements in fatigue would be associated with parallel improvements in other symptoms.

Of importance for patients living with CFS, improvements were also seen in anxiety and depression levels during follow-up. This is interesting and may represent adaptive coping or a local positive approach to the management of symptoms of depression, or may represent a positive experience of participating in a research study.

Our multivariate analysis confirms that fatigue and depression are inter-linked in CFS; however, the direction of the relationship is unclear. By examining the independent predictors of both fatigue and depression in 2009, we have developed a model that

Table 3 *Predictors of depression in 2009 using regression analyses*

	Bivariate models[a]		Final multivariate model	
	Regression coefficient	95% CI	Regression coefficient	95% CI
HAD-D in 2005	0.53	0.34 to 0.71	0.31	0.15–0.48
Age	−0.01	−0.07 to 0.05		
FIS in 2009	0.05	0.03 to 0.08	0.04	0.01–0.06
Change in FIS	0.05	0.02 to 0.08		
HAD-A in 2009	0.29	0.16 to 0.41	0.18	0.06–0.31
Change in HAD-A	0.38	0.19 to 0.57		
OGS in 2009	0.09	−0.07 to 0.25		
Change in OGS	0.01	−0.22 to 0.25		
ESS in 2009	0.06	−0.09 to 0.21		
Change in ESS	0.01	−0.19 to 0.21		

[a]All models included HAD-D in 2005 plus the variable in question.
HAD, hospital anxiety and depression; FIS, fatigue impact scale; OGS, orthostatic grading scale; ESS, Epworth sleepiness scale; CI, confidence interval.

could act as a basis for the development of innovative management strategies in CFS (Fig. 3). We believe that the relationship between fatigue and depression is bidirectional (i.e. fatigue can be a manifestation of depression and *vice versa*). Although in the current series very few patients moved from being not depressed to meeting the criteria for caseness on the HAD-D score, we believe that the existence of this cohort will allow us to track the relationship between fatigue and depression very closely in future studies. Further confirmation of the exact relationship between fatigue and depression comes from other biologically based symptoms, such as orthostasis, which are independently associated with fatigue in CFS but not with depression. The results of this study provide further support of the bi-directional relationship and confirm that fatigue is not entirely dependent on depression in this patient group. However, we acknowledge that further longitudinal studies are needed to determine the exact relationship between fatigue and depression.

Our study raises important clinical management issues for patients with fatigue and an orthostatic phenotype; orthostatic symptoms are a potentially modifiable risk factor for fatigue [5, 6], with recent studies suggesting that noninvasive treatments such as tilt training may have the potential to improve fatigue in CFS [15]. It is unfortunate that we were not able to determine the impact of treatment upon long-term symptoms in the current cohort, and it would be important to establish further longitudinal cohorts of patients with fatigue to explore the effect on outcome of different management strategies.

Our finding of a change in anxiety during follow-up is interesting. This suggests that strategies to reduce anxiety such as cognitive behavioural therapy might have a role in helping people to cope with their fatigue symptoms. However, the modelling (Fig. 3) confirms that this is not the whole answer and that if clinicians focus entirely on treatment of anxiety, opportunities to treat other factors such as orthostasis will be missed. The input of a clinical psychologist to the multi-disciplinary team is extremely important. There is considerable reluctance in many areas for all professional groups to work together. However, to maximise long-term improvements in symptoms, it is vital that we eliminate any stigma attached to the psychologist's role and adopt a multidisciplinary approach to fatigue management.

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Conflict of interest

None of the authors has any conflict of interest.

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