Perceived fatigue is comparable between different disease groups

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Summary

Background: Studies have established that levels of fatigue vary between different patient groups. It is less clear whether the nature, as opposed to severity of fatigue differs between groups.

Objective: To examine descriptions of fatigue by patients with a range of chronic diseases and determine the relationship between symptom domains.

Design: Retrospective review of Fatigue Impact Scale (FIS) data.

Setting: Fatigue Research Group.

Participants: Six hundred subjects in five chronic disease groups and one (n=45) normal control group.

Main outcome measures: Statistical analysis was performed to assess the effect of increasing fatigue and the overlap of FIS domain scores between disease groups by calculation of geometric means as proportions summed to 1 in each FIS domains, whilst controlling for total score.

Results: Those with lower scores exhibit relatively higher physical scores than patients with higher total scores. In contrast, as total score increases, so does the proportion accounted for by the cognitive and psychosocial scores. This was not related to a threshold effect as the maximum total score of 40 in the physical domain was only achieved in three patients (<1%). Average domain proportions between patient groups did not vary to any degree among physical (0.30–0.39), cognitive (0.15–0.23) and psychosocial (0.42–0.47) domain proportions of the patient groups.

Conclusion: Perceived fatigue is similar between patient groups. Increasing scores were not related to simply reaching the maximum threshold in the physical domain. Studies have confirmed a positive-structured approach to symptom management in one fatigue-associated chronic disease, primary biliary cirrhosis, leads to significant improvements in quality of life. We suggest that, with a similar approach, the same might be true in other chronic diseases where moderate fatigue is a significant problem.

Introduction

In surveys, 25% of the population describe themselves as ‘tired all of the time’ and fatigue is the principle symptom in up to 10% of primary care consultations. Fatigue can present for the first time in all age groups, can affect an individual’s ability to work and attend school, and can impact dramatically upon quality of life.

It is now recognized that the symptom of fatigue can occur in association with a wide range of chronic diseases, can be unexplained (chronic fatigue or idiopathic fatigue) or can occur in conjunction with a constellation of symptoms that form the chronic fatigue syndrome or myalgic encephalopathy (CFS/ME) syndrome. Despite the apparent importance of fatigue in terms of population impact, it is only recently that the pathophysiological mechanisms that result in fatigue have begun to be elucidated and targeted treatments developed.

Although fatigue is described as an important problem by patients with a number of chronic diseases, can be unexplained (chronic fatigue or idiopathic fatigue) or can occur in conjunction with a constellation of symptoms that form the chronic fatigue syndrome or myalgic encephalopathy (CFS/ME) syndrome. Despite the apparent importance of fatigue in terms of population impact, it is only recently that the pathophysiological mechanisms that result in fatigue have begun to be elucidated and targeted treatments developed.
diseases, it is not clear whether the apparently similar descriptions of fatigue, and its impact, made in these different settings, reflect a shared symptom experience resulting, potentially, from common pathophysiological processes, or distinct processes and their resulting experiences giving rise to only superficial similarities. This question is of more than academic interest. If the apparent similarities between fatigue in different disease settings does indeed reflect the effects of a ‘final common pathway’, then fatigue may, potentially, be amenable to the same intervention in different disease settings suggesting that generic management strategies have the potential to be of benefit to the large number of people affected by fatigue.

There are already numerous studies which have established that level of fatigue vary between different patient groups. The question which has not been addressed to date, is whether the nature, as opposed to the severity of fatigue differs between different patient groups. The hypothesis which we set out to address, in this study, is that perceived fatigue is a symptom which is comparable between disparate patient groups with the potential implication that it may be amenable to the same or similar treatments. In order to address this hypothesis, we have examined descriptions of fatigue by patients with a range of chronic diseases in order to determine the relationship between the three symptom domains captured in the Fatigue Impact Score (cognitive, physical and psychosocial).

Methods

Subjects

Six subject groups were included in this study. All groups were recruited as part of an on-going programme of work to investigate the biological basis of fatigue in a range of chronic disease settings.

Primary biliary cirrhosis

Primary biliary cirrhosis (PBC) is a chronic, cholestatic, autoimmune liver disease, in which over 50% of patients describe debilitating fatigue. Importantly, the severity of fatigue is unrelated to any biochemical or histological parameters of liver disease severity in PBC. A total of 183 consecutive patients with definite or probable PBC all of whom were attending our local PBC clinic at Freeman Hospital were included.

Chronic fatigue syndrome

Consecutive subjects attending our local CFS/ME clinical network were studied (n=82). All subjects fulfilled the Fukuda diagnostic criteria for CFS.

Non-alcoholic fatty liver disease

It has recently been recognized that fatigue is a significant problem in patients with the liver disease, non-alcoholic fatty liver disease (NAFLD). As in PBC, fatigue severity is unrelated to parameters of liver disease severity, nor is it related to degree of insulin resistance. We recruited 166 consecutive patients with histologically diagnosed NAFLD attending the tertiary referral Hepatology service.

Vasovagal syncope

Vasovagal syncope (VVS) is an exaggerated tendency towards the common faint. VVS patients have recently been shown to describe fatigue more frequently than controls. We included 96 consecutive patients with head-up tilt diagnosed VVS attending a specialist Falls and Syncope Service.

Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a further cholestatic liver disease where fatigue is described by patients. We identified 73 consecutive patients with PSC attending the Freeman Liver Unit who were included in the study.

Healthy controls

Forty five healthy controls were included who were recruited via notices around the hospital.

Fatigue impact assessment

All subjects completed the generic fatigue measure, the Fatigue Impact Scale (FIS). This assessment tool has been validated for use and then applied in a range of chronic disease settings, in normal volunteers and in CFS. The FIS comprises a total of 40 questions, each scored from 0 to 4 (potential total score range 0–160) and is split into three subscales; the psychosocial subscale (comprising 20 questions, potential score 0–80), the physical subscale (comprising 10 questions, potential score 0–40) and the cognitive subscale (comprising 10 questions, potential score 0–40), which delineate independent manifestations of the potential impact of fatigue. In this study, we were interested in determining whether the relative contribution of the individual subscales of the total score varied between patient groups, indicating the presence of different factors contributing to the fatigue experience in different patient groups. In order to do examine this, each subscale
score was converted to a proportion of the total score.

**Statistical analysis**

Subscale scores are each divided by the total FIS score in order that they are each represented as a proportion of the total score—thus, relative contribution of each subscale to the total can be assessed—that is, the composition of the total score can be studied. However, the sum total of all of the proportions must equal 1 (as a consequence of how the proportions were calculated) and so standard statistical techniques cannot be used on compositional data of the type derived here. Since the sum of the proportions making up the composition must equal 1 (constant sum constraint), knowledge of the first two proportions (of a three proportion composition) is sufficient to calculate the third and so specify the full composition. This restriction must be allowed for in the analysis of the data. Of particular importance, compositions provide information about relative, not absolute, values of components; the ratios of components can thus be analysed. Log-ratios are much easier, mathematically, than the ratios to work with and remove the constraint of the constant sum; thus standard statistical methods can be employed on the log-ratios with inferences translatable back into compositional statements.\(^{20}\)

Techniques have been developed, called compositional regression, to allow for this structure of the data and to relate compositions to independent variables.\(^{21,22}\) In brief, the technique models the joint distribution of log-ratios of proportions on independent variables, in our example, patient group. First, it should be pointed out that any techniques can only look at the subset of patients who score positively on the FIS; clearly those who have a total score of 0 will provide no information about the composition of the total score. A drawback of compositional regression using log-ratios is that it does not allow for zero proportions (since 0 values cannot be logged). Thus, patients who score 0 on one or more subscales of the FIS cannot be easily included in the analysis. A pragmatic decision was, therefore, taken to exclude from further analysis any patient scoring <10 on the FIS on the grounds that these patients would provide least information about the composition of the total score and were most likely to score 0 on one or more subscales.

Ratios of physical and cognitive to psychosocial proportions were created and logged for analysis. The psychosocial score was chosen as the denominator for the two ratios as, of the three subscales, it has a score range of 80 as compared with physical and cognitive scores which both have a range of 40.

In this way, the two sets of ratios (physical/psychosocial and cognitive/psychosocial) should be comparable. Within the restricted sample, a number of zero proportions remained; 17 within the cognitive proportion (distributed evenly between all diagnoses) and 1 physical proportion when patients with FIS of \(\geq 10\) were included. These proportions were set to 0.01 and the corresponding remaining proportions were each reduced by 0.005 in order to preserve the constant sum.

Initial model fitting indicated severe imbalance in variability (heteroscedasticity) across the range of total score with log-ratios being much more variable for small total scores, with decreasing variability as total score increased. Thus, non-parametric bootstrapping (a computer-intensive method of resampling from the observed data in order to estimate properties of an estimator, such as standard deviation) was used to estimate standard errors in the multivariate regression models, using stratified sampling within diagnostic groups and 50 replications per group. Model fit was assessed by plotting residuals and assessing them for normality and by plotting residuals against predicted values to assess homoskedasticity. The modelling was repeated on patients with FIS total scores of \(\geq 40\), where imbalance in variability was less of a problem to assess the sensitivity of the model estimates to the imbalance in variability. Results are presented as \(P\)-values for predictor variables and estimated proportions for each of FIS subscales. STATA v10 mvreg command was used to fit all models.

**Results**

**Fatigue impact scale domain scores in individual subject groups**

As previously documented in the literature, the severity of fatigue as delineated by the total FIS score varied greatly in the six subject groups, and this variability was reflected in the individual domain scores. Median FIS total and individual domain scores for each group are shown in Table 1, as are the number of subjects in each group with FIS scores >10. CFS patients exhibited much higher levels of total fatigue, and higher individual domain scores than either the controls or any of the other patient groups. Furthermore, all CFS patients had a total FIS score >10 and were therefore included in further analysis compared with 79% of the PBC patients, 79% of NAFLD patients, 62% of PSC patients and 58% of VVS patients. Only 15 (33%) of the controls had a total FIS score >10,
thus control patients were not included in any formal modelling.

**Table 1** Median (range) domain scores and number (percentage) with total FIS >10, by patient group

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>FIS median</th>
<th>Physical domain</th>
<th>Cognitive domain</th>
<th>Psychosocial domain</th>
<th>FIS &gt; 10 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBC</td>
<td>183</td>
<td>41 (0–160)</td>
<td>15 (0–40)</td>
<td>11 (0–40)</td>
<td>17 (0–80)</td>
<td>144 (79)</td>
</tr>
<tr>
<td>CFS</td>
<td>82</td>
<td>102 (1–160)</td>
<td>29 (8–40)</td>
<td>23 (1–40)</td>
<td>47 (8–80)</td>
<td>82 (100)</td>
</tr>
<tr>
<td>NAFLD</td>
<td>166</td>
<td>33 (0–136)</td>
<td>12 (0–34)</td>
<td>6 (0–33)</td>
<td>13 (0–69)</td>
<td>131 (79)</td>
</tr>
<tr>
<td>PSC</td>
<td>73</td>
<td>18 (0–132)</td>
<td>9 (0–36)</td>
<td>3 (0–38)</td>
<td>7 (0–58)</td>
<td>45 (62)</td>
</tr>
<tr>
<td>VVS</td>
<td>96</td>
<td>16 (0–127)</td>
<td>6 (0–31)</td>
<td>3 (0–35)</td>
<td>6 (0–61)</td>
<td>56 (58)</td>
</tr>
<tr>
<td>Controls</td>
<td>45</td>
<td>11 (0–88)</td>
<td>1 (0–17)</td>
<td>1 (0–29)</td>
<td>1 (0–45)</td>
<td>15 (33)</td>
</tr>
<tr>
<td>Total</td>
<td>645</td>
<td>55 (0–160)</td>
<td>12 (0–40)</td>
<td>8 (0–40)</td>
<td>14 (0–80)</td>
<td>473 (73)</td>
</tr>
</tbody>
</table>

**Table 2** Geometric mean (rescaled to sum to 1) subscale proportion by patient group for patients with a FIS total score ≥10

<table>
<thead>
<tr>
<th>Geometric mean domain proportion</th>
<th>Physical domain</th>
<th>Cognitive domain</th>
<th>Psychosocial domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBC</td>
<td>0.36</td>
<td>0.21</td>
<td>0.42</td>
</tr>
<tr>
<td>CFS</td>
<td>0.30</td>
<td>0.23</td>
<td>0.47</td>
</tr>
<tr>
<td>NAFLD</td>
<td>0.35</td>
<td>0.20</td>
<td>0.45</td>
</tr>
<tr>
<td>PSC</td>
<td>0.39</td>
<td>0.15</td>
<td>0.46</td>
</tr>
<tr>
<td>VVS</td>
<td>0.33</td>
<td>0.21</td>
<td>0.45</td>
</tr>
</tbody>
</table>

**Figure 1.** Average subscale proportion estimated from the regression model, by increasing score category. Analysis is restricted to experimental subjects with total FIS score ≥10.

**Does the composition of total FIS change with increasing total score?**

Next, we set out to determine whether the relative proportions contributed by the individual domains of the FIS to the total FIS score changed as fatigue increased in the combined dataset. Unsurprisingly, the variability of the log-ratios increased with total score; we further investigated whether there was any relationship between the average values of the log-ratios and the total score. Total FIS score was quite skewed thus it was logged for inclusion in the model and found to be significantly related to the mean log-ratios ($P<0.001$). In order to demonstrate the effect of increasing fatigue, we grouped the patients into bands of fatigue severity (FIS 10–39, FIS 40–79, FIS 80–119 and FIS 120–160) and these were included as categorical variables in the model. The results are shown in Table 2 and Figure 1.

Figure 1 shows that patients with lower scores exhibit relatively higher physical scores than patients with higher scores; in contrast, as total score increases, so does the proportion accounted for by the cognitive and psychosocial scores. This may be related to a threshold effect, i.e. it is only possible to score a maximum of 40 in the physical domain and it is only once this maximum is met that scores accumulate in the other domains. In order to consider this, all individual scores for the physical domain were reviewed and it was found that, in fact, the maximum total score of 40 in the physical domain was only achieved in two of the PBC patient group (1%), one CFS patient (1%) and in no other subjects. We therefore concluded that it is unlikely that the increasing scores were related to simply reaching the maximum threshold in the physical domain.

With these results in mind, the following models comparing patient groups will adjust for the total score; given that the groups have very different levels of overall fatigue and we have established that the composition of the total FIS score in terms of the subscales differs according to total level of fatigue, it is of interest to ascertain whether patient groups differ in composition by more than that might be expected due to differing absolute levels of fatigue—thus a model adjusting for total FIS score compares fatigue composition between groups assuming they all have the same overall level of fatigue.
Relationship between domain scores in different patient groups

A triangular plot of the three domain proportions, split by disease group, is shown in Figure 2 for patients with FIS $\geq 10$. Geometric means were calculated for proportions in each of the FIS domains and rescaled to ensure that they summed to 1. Results are presented in Table 2. It appears that average domain proportions between the patient groups do not vary to any degree between patient groups. These findings suggest that overall perceived fatigue is similar between the patient groups.

Multivariate regression modelling of the log-ratios on disease category, adjusted for the total score suggested that the log-ratios varied significantly by patient group (Wald test, $P < 0.001$). Further inspection of the confidence intervals of the regression coefficients suggested that patients with NAFLD and VVS have a statistically significantly lower proportion of their total score accounted for by physical symptoms than other groups and PSC has a statistically significantly lower cognitive score proportion than other groups. Average subscale proportions were estimated from the regression coefficients and shown in Table 3. Whilst there are statistically significant differences between the patient groups, the clinical significance of these results is questionable. In order to test the stability of the models, they were refitted on the subset of patients scoring $\geq 40$ on FIS where heteroscedasticity was much less of a problem; the pattern of results was very similar, the main difference being in the proportion of total score accounted for by the physical symptoms which was slightly lower (varying between 0.28 and 0.32) than in the dataset including only those scoring $\geq 10$. Given the relationship between the composition and total score this was not unexpected; the results from these supplementary analyses are not presented.
Discussion

Fatigue is a common symptom that can impact significantly upon the quality of life and which can be difficult to manage. Community surveys have shown that fatigue is common in developed countries with a British survey of those attending general practice finding that \(\sim 10\%\) of men and women had substantial fatigue for over a month\(^2\) and that this leads to functioning problems.\(^3\) Our understanding of the pathogenesis of fatigue in chronic diseases is beginning to increase and the finding in this current study that the phenotype of fatigue appears to be comparable across disease groups has potentially important implications for our understanding and management of this difficult symptom. We believe that the findings of our study which suggest that patient descriptions of fatigue are similar across disease groups could point to common pathophysiology, and therefore offer a real potential opportunity for the adoption of a systematic approach to the treatment of fatigue with the development of generic treatment approaches.

A number of recent studies in one of the chronic disease groups included in this study (PBC) have now suggested that fatigue associates with the presence and severity of autonomic dysfunction and also with the presence of excessive daytime somnolence. In studies from our group, these two fatigue-associated phenotypes are present in the majority of those with PBC. A recent study has drawn parallels from qualitative interviews between the fatigue experienced by those with PBC and that seen in patients with CFS\(^4\) and this study further emphasizes the potential benefits that might arise from applying the same management approach more widely to other fatigue-associated diseases as that shown to be of benefit in PBC. In other studies where we have included two of the patient groups included in this current study (PBC and CFS), we have shown a strong relationship between the presence severity of symptoms attributable to the autonomic nervous system and fatigue, which led us to develop the new diagnostic criteria of dysautonomia-associated fatigue syndrome (DAFS). We believe that this study further underlines the possibility that symptoms such as fatigue arise due to generic chronic disease processes.\(^5\) Importantly, for fatigue management in the more general sense, we have also shown that a positive multidisciplinary approach to fatigue management focusing upon managing DAFS can lead to significant improvements in quality of life in those with PBC.\(^6\)

The study of the biological basis of CFS/ME has been limited historically by the lack of a diagnostic tool. This has led to the advancement of knowledge of the pathophysiological mechanisms that result in fatigue in a range of fatigue-associated chronic diseases such as PBC. We believe that the results of this study suggest that application of these biological techniques and management approaches is fully justified.

Our study has some limitations. Modelling of compositional data is not straightforward and the methods used within this study might be considered to have several drawbacks. First, a proportion of the dataset was excluded from the compositional analysis due to zero proportions in the domains and differing proportions of the different patient groups had to be excluded—ranging from \(\sim 40\%\) of the PSC and VVS groups to none of the CFS group. This is an obvious source of bias but unavoidable within this analysis framework. However, it is postulated that those patients with very low levels of fatigue will provide little information about the overall composition of their fatigue, and therefore detract little from the analysis. We would suggest, however, that results can only be generalized to those patients with moderate fatigue and not those with very mild fatigue, so care should be taken when applying these results to patient groups as a whole. A second drawback of the analysis is that the proportions estimated on small total scores are much more variable than those estimated on larger total scores which results in severe heteroscedasticity. This has been partially overcome by estimation of standard errors using bootstrapping. Further, the sensitivity of the models to the heteroscedasticity was assessed by refitting on the subset of patients scoring \(\geq 40\) on total FIS where heteroscedasticity was less of a problem. The overall pattern of results was similar, thus supporting the results we present. Finally, the use of whole clinic cohorts meant that different numbers of patients in each chronic disease group were included which may have lead to some bias in our findings.

Our modelling indicates that the composition of fatigue is highly dependent upon the total score, but substantially less dependent on the nature of the underlying pathology. The proportion of the total FIS accounted for by physical symptoms decreases with increasing total score and is replaced by increasing cognitive and psychosocial scores. This is intuitively plausible. Those with higher absolute levels of physical fatigue are more likely to have a relatively larger effect on other areas of their day-to-day lives, particularly cognitive and psychosocial; hence there is an increase in scores in these domains with increase in physical symptoms. Thus, the larger the direct impact of physical limitation, the more there are subsequent knock-on effects on other aspects of higher function as quantified by
cognitive and psychosocial domains of the FIS. If this interpretation is correct (and intervention studies able to reduce the impact of physical fatigue will be required to determine this), then an effective intervention for cognitive and psychosocial fatigue might be to target physical fatigue in order to have lower impact to levels at which cognitive and psychosocial impacts are less marked.

Once FIS total score was allowed for in the models, some differences remain between patient groups with a suggestion that NAFLD and VVS groups suffered proportionately less physical fatigue compared with other groups. It is important, however, to appreciate that the proportions did not vary greatly between patient groups and the clinical significance of the results is debatable.

Considering the number of people affected by the symptom of fatigue and its impact upon quality of life, education and work, we believe that this study has potential implications for our understanding of the physiological basis of fatigue. Developing novel approaches to understanding the symptom of fatigue will lead to improvements in management and as a result, have benefits for individuals and health care systems. Recent studies have confirmed that with a positive structured approach to symptom management in the fatigue-associated chronic disease PBC, significant improvements in quality of life can be achieved. This study suggests that with a similar approach the same might be true in other chronic diseases. Further studies involving such an intervention are urgently needed.

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**References**


