Cognitive impairment in patients with chronic fatigue: a preliminary study

Elizabeth McDonald, Helen Cope, Anthony David

Abstract
Subjective impairment of memory and concentration is a frequent complaint in sufferers from chronic fatigue. To study this, 65 general practice attenders identified as having chronic fatigue were administered a structured psychiatric interview and a brief screening battery of cognitive tests. Subjective cognitive impairment was strongly related to psychiatric disorder, especially depressed mood, but not fatigue, anxiety, or objective performance. Simple tests of attention and concentration showed some impairment but this was influenced by both fatigue and depression. Subjects with high levels of fatigue performed less well on a memory task requiring cognitive effort, even in the absence of depression. There was no evidence for mental fatiguability. The relationship between depression, fatigue, and cognitive function requires further research.

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The current definition of the chronic fatigue syndrome (CFS) states that the fatigue is “severe, disabling and affects physical and mental functioning” (italics added). United States criteria include neuropsychological complaints, such as difficulty in thinking and inability to concentrate, as “minor criteria”. These definitions reflect accurately the emphasis given to cognitive difficulties by patients with a presenting complaint of severe and persistent fatigue. Some sufferers are so impressed by the severity of such symptoms as to regard them as evidence for an encephalitic process, although this is unsupported by research.

The most familiar complaints range from forgetfulness and anoma, to difficulty in carrying out a complex task. Concentration difficulties seem to be the most common problem in patients with chronic fatigue. A hospital-based study reported just over 50% of cases had impairment in concentration and attention and over a quarter complained of problems with memory. The overall prevalence of self-reported cognitive impairments in chronic fatigue has been estimated at approximately 50–70%.

These neuropsychological symptoms are a cause of considerable morbidity and are frequently implicated in occupational failure. Study of these phenomena is therefore of obvious clinical relevance. Moreover, the presence of cognitive difficulties also provides avenues which may lead to further understanding of the nature of chronic fatigue. It has been pointed out that the prominence given to mental fatigue in most subjective accounts of the syndrome is, in itself, strong evidence against the view that CFS is a purely neuromuscular as opposed to a “central” disorder. This view is supported by Wessely and Powell who showed that questions on mental fatigue including items on concentration, memory, and word finding, clearly discriminated between hospitalised CFS patients, and controls with neuromuscular disease. CFS cases who were, in addition, depressed had the highest mental fatigue scores although interestingly, a number of non-depressed cases also scored highly.

The effect of depressed mood on cognitive function has been well studied. This is relevant to CFS since epidemiological, primary care, and hospital based studies all show a strong association with affective disorder as well as other psychiatric conditions. Hence some degree of cognitive impairment in chronically fatigued patients is to be expected.

Four studies have been published to date which carried out psychometric testing on CFS patients. Millon et al studied 24 fatigued patients with serological evidence of Epstein Barr virus exposure. They showed no impairment on the Mini-Mental State Examination, or overall memory deficit on the Weschler Memory Scale (WMS). More striking was the high level of psychological symptomatology. Atlay et al published a preliminary report on 21 subjects and found no impairment in a timed test of attention, coupled with scores in the superior range on two subtests of the Weschler Adult Intelligence Scale (WAIS-R) and other measures of language and abstraction. This curious result is best explained by the selection of cases being biased towards those of high occupational status. The authors made an interesting observation that there was a discrepancy between the patients’ subjective complaints and assessment of their abilities, and the test results. Smith, carried out a questionnaire survey on patients from a self-help group of CFS patients. Cognitive failures were reported more often in comparison with controls but this was explained by the presence of anxiety and depression. Detailed assessment was carried out on 18 polysymptomatic patients who were found to
have slowed reaction time and impaired performance on tests of visual attention and memory, in relation to nine normal controls. Recognition and digit span were unaffected. The influence of psychological symptoms in the second phase of the study was not addressed. Finally, Riccio et al\textsuperscript{18} report neuropsychological test scores on nine hospital outpatients with postviral fatigue and found impairment on the WMS in comparison with healthy controls. The patients also reported significantly more symptoms of depression yet no measurement of the effect of this on cognition was attempted.

One concern about the work reviewed above is that it was based on biased samples, either through self-referral, unusual disability, or because of suspected viral infection. A recent study\textsuperscript{19} attempted to avoid this problem by surveying a random sample of general practice attenders with a variety of physical and psychosocial complaints, and selecting those suffering from severe, recurring fatigue, defined according to a specially designed fatigue questionnaire. The authors confirmed the high prevalence of psychiatric illness. In addition, preliminary information was gathered on neurological signs and both objective and subjective cognitive impairment.

The aims of the study were:

1. to determine the prevalence of subjective impairment of cognitive functioning in an unselected sample of patients with chronic fatigue
2. to screen for the presence of objective impairment of cognitive functioning
3. to examine the relationship between psychiatric morbidity—especially depressed mood and anxiety—and cognitive dysfunction, both subjective and objective.

Methods

SAMPLE

The sample was drawn from general practice attenders aged between 18 and 45 years, with 'chronic fatigue', defined as those scoring nine or more on a questionnaire (range 0–27) designed to assess fatigue, who had suffered symptoms for six months or more, although a minority were persistently disabled. The cut off separated the most fatigued 10% from an original cohort of 686 attenders and has been found to be specific and sensitive to a chronic fatigue syndrome.\textsuperscript{18} There were 77 eligible patients of whom 65 were contactable and agreed to be interviewed. Of these, 50 were women, reflecting the sex ratio of practice attenders, Mean age (SD) was 32.5 (6.4). Some 26% had received education beyond high school; 18% left with no qualifications. The remainder had O or A levels.

ASSESSMENTS

Psychiatric assessment

A variety of medical, psychiatric, and social assessments were carried out. These included a standardised psychiatric interview, the revised Clinical Interview Schedule (CIS-R),\textsuperscript{19} which was used to elicit and quantify current (during the past week) symptoms of minor psychiatric disorder. There are 14 items including depression, concentration, worry, anxiety, somatic symptoms, fatigue, etc. Each section is scored on a 0–4 scale (except depressive ideas; 0–5) depending on the symptom’s severity and frequency. Individual symptom ratings can be summed to yield an overall score. A cut off of $\geq 12$ indicates a level of significant psychiatric morbidity. The CIS-R overall score can be adjusted to remove the symptom of fatigue (CIS-f) lowering the cut off to $\geq 11$.\textsuperscript{19}

Neuropsychological evaluation

The Quantitative Neurological Examination (QNE)\textsuperscript{20} is a structured clinical examination with emphasis on the motor system. Subjective cognitive impairment. The CIS-R includes an item on concentration and forgetfulness. A problem in this domain noticed by the patient in the past week scores 1. Further questions probe ability to concentrate on a newspaper article, etc, whether anything important has been forgotten, and whether the subject has given up anything through lack of concentration. A positive response to each probe scores an additional point. Cognitive assessment. A brief screening battery was used. Concentration was tested with serial 7s (subtracting 7 from 100), and digit span (DS) forwards and backwards.\textsuperscript{21} Visual attention was examined with the star cancellation test.\textsuperscript{21} The paired associate learning test from the WMS was used to test memory. Ten pairs of words are presented, some of which are commonly associated (for example, fruit—apple) and others which are not (for example, crush—dark). Easy and difficult pairs are mixed together. There are three presentations of all pairs; after each, one word is said to the subject who then attempts to recall its companion. The forwards DS, easy paired associates, and star cancellation allow for relatively automatic processes to be examined while the remainder require more cognitive effort.

Results

No neurological abnormalities were detected on the QNE, except in one patient who had old poliomyelitis. Power, praxis and coordination were normal and there was no impairment.

The mean CIS-R score was 17.1 (SD 7.1); the mean after adjustment to remove fatigue (CIS-f) was 13.9 (SD 6.8). Forty nine (75%) met the criterion for caseness on the CIS-R and 42 on the CIS-f. Forty seven subjects (72%) were given an ICD-9 diagnosis, 24 of whom had neurotic depression and 8 an anxiety state, the rest receiving miscellaneous diagnoses.

The items for anxiety and worry were combined (mean 2.9; SD 2.3; range: 0–8) and depression and depressive ideas (mean 2.25; SD 2.1; range 0–9). Forty five (69%) and 53 (81.5%) scored $\geq 1$ on the depression and anxiety totals, respectively. The mean score on the fatigue questionnaire was 12.14 (SD 6.5); 70% scored 9 or above. Fatigue correlated with CIS-R and CIS-f; $r = 0.43$ and 0.39, respectively ($p < 0.001$).

Subjective cognitive impairment

Forty seven (72.3%) scored on this item;
**Table 1** Relationship between positive scores on depression and concentration items of the CIS-R

<table>
<thead>
<tr>
<th>Concentration item score</th>
<th>No</th>
<th>Yes</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>13</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>Yes</td>
<td>12</td>
<td>35</td>
<td>47</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>

χ² = 10.1; p = 0.002 (with Yates’ correction)

mean (SD) 1.59 (1.2). There was a significant relationship between subjective cognitive impairment and the presence of depression (see table 1). There was also a relationship with somatic complaints (p = 0.005) but not anxiety (p = 0.5), or any other symptom including fatigue. Those scoring on the concentration item had higher total CIS-R (and CIS-f) scores (Mann-Whitney U test; p < 0.001) but not fatigue questionnaire scores (p = 0.13). There was no relationship between subjective concentration and performance on serial 7s, star cancellation, DS, or tests of memory.

**Serial 7s.** Forty eight (74%) performed six subtractions without error; 14% produced one error and the remainder gave between two and nine errors. Many subjects required encouragement to persist with the task.

**Star cancellation.** Forty four (68%) performed without error; 23% omitted 1 star and the remainder missed between 2 and 9. Those failing on these tests were not significantly more fatigued nor did they have greater psychiatric morbidity.

Healthy controls would be expected to perform without error.

**Digit span (forwards).** Mean (SD) 7.1 (1.1); range 4-9. **Digit span (backwards).** Mean (SD) 4.9 (1.5); range 0-9.

**Paired associates.** Easy: mean No recalled (SD) 15.6 (2.3). Hard: mean No recalled (SD) 7.2 (3.2).

The DS and paired associate scores were well within the normal range. The relationship between fatigue, psychiatric morbidity and cognitive performance was examined using Pearson’s correlation (see table 2).

<table>
<thead>
<tr>
<th></th>
<th>Digit forward</th>
<th>Span backward</th>
<th>Easy</th>
<th>Hard</th>
<th>Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIS-R</td>
<td>-0.09</td>
<td>-0.31**</td>
<td>-0.02</td>
<td>-0.04</td>
<td>-0.05</td>
</tr>
<tr>
<td>CIS-f</td>
<td>-0.08</td>
<td>-0.29**</td>
<td>0.01</td>
<td>-0.01</td>
<td>0.00</td>
</tr>
<tr>
<td>Fatigue Q</td>
<td>-0.29**</td>
<td>-0.33***</td>
<td>0.00</td>
<td>-0.14</td>
<td>-0.19</td>
</tr>
<tr>
<td>Depression</td>
<td>-0.10</td>
<td>-0.35**</td>
<td>-0.24*</td>
<td>-0.07</td>
<td>-0.10</td>
</tr>
<tr>
<td>Anxiety (total)</td>
<td>-0.08</td>
<td>-0.13</td>
<td>0.11</td>
<td>0.00</td>
<td>-0.07</td>
</tr>
</tbody>
</table>

*p < 0.05; **p < 0.01; ***p < 0.005; (one tailed significance).

The current study reports on patients with CFS identified within a primary care setting so is less liable to selection bias which may influence the results. The main findings are:

1. Subjective complaints of poor concentration and forgetfulness are common in these patients, affecting nearly three quarters, a rate comparable to previous studies.

2. Objective evidence for impaired cognitive function comes from two simple *bed-
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