Increased illness experience preceding chronic fatigue syndrome: a case control study

ABSTRACT - **Background:** Almost all published work on chronic fatigue syndrome (CFS) has involved retrospective surveys of cases, which may introduce recall bias. Only medical records collected before diagnosis of CFS can eliminate this.

**Methods:** Using data collected several years prior to the development of the illness, we performed a case control study, comparing the reported illness records of all people who subsequently made an insurance claim as a result of CFS, with those of future multiple sclerosis (MS) claimants, and those of non-claimant controls (NC).

**Results:** The study encompassed 133 CFS, 75 MS and 162 NC cases. CFS cases had recorded significantly more illnesses at time of proposal for insurance than the two control groups, and had significantly more claims between proposal and diagnosis of their disorder. Almost all disease categories were reported higher in future CFS sufferers, lethargy having the highest odds ratio after adjustment in a multivariate model.

**Interpretation:** The results of this paper on CFS patients who claim permanent health insurance do not support a specific viral or immunological explanation for CFS. We conclude that abnormal illness behaviour is of greater importance than previously recognised.

Chronic fatigue syndrome (CFS) is defined by fatigue lasting six months or more, which cannot be explained by the presence of other illnesses. Several alternative names exist, including myalgic encephalomyelitis and postviral fatigue syndrome; CFS is the preferred term, since it does not imply that the causation is understood. Widely different opinions exist about the aetiology of CFS, with proponents arguing in favour of viral, immunological or psychological theories. The prevalence in primary care is about 0.5%.

In general, clues to pathogenesis may be found in the past history, leading to the identification of risk markers. However, faulty recollection by patients or preconceived ideas on the part of the investigator may distort, or even invalidate, these results. Elimination of such recall bias is therefore crucial in determining whether any detected predisposition is real. This can only be done by using medical information collected before the condition has developed and which was not originally intended to support or rule out a particular hypothesis. Prior routine health checks carried out for other reasons (eg insurance policies), meet these requirements.

**Methods**

We studied the records of Medical Sickness Group, an insurance company based in the UK with approximately 100,000 holders of permanent health insurance policies. These policies provide benefit should the policyholder be prevented from working by sickness or accident. At the time of proposal for insurance, clients itemise their current and past illnesses on a form, and a report is completed by their general practitioner from their medical records. A medical examination is requested either when large insurance premiums are involved, or if the proposal form or general practitioner’s report suggests that the client is at particular risk. Full disclosure of all relevant conditions is encouraged, as the insurance policy may be invalidated by the failure to disclose important information.

All claims on permanent health insurance policies are categorised by the diagnosis given on the claim form by the claimant’s general practitioner, forming a diagnostic database. All claimants with a diagnosis of CFS were entered into the study. Two control groups were chosen: current non-claimants (NC) selected randomly from the company register and all claimants with a diagnosis of multiple sclerosis (MS). This disease was selected because many aspects of MS mirror those of CFS: both are severe debilitating illnesses that can affect either sex, and involve similar age groups. All CFS and MS claimants had their diagnosis confirmed by at least one consultant physician. Reports were also available from their general practitioner, and, when deemed necessary for claims control, an independent specialist report was commissioned from the appropriate specialty, usually a consultant physician or psychiatrist.

Medical and demographic details of cases and controls, obtained at entry to the scheme, were rendered anonymous and then collated. Equivalent self-reported conditions were grouped under one illness category by a researcher blinded to case-control status. For example, lumbago, sciatica, slipped disc or similar descriptions were recorded as ‘back pain syndrome’. Only conditions reported in more than five cases were analysed.

Descriptive variables such as age and sex were compared by standard statistical methods, using EPI Info and Logistic Module. Medians, or geometric means, were calculated for variables where the distribution was skewed, and non-parametric analysis used where appropriate. The degree of association between each illness category and case or control status was assessed by analysis of 2x2 tables and calculation of odds ratios. The two control groups were combined for multivariate analysis, using logistic
regression, and correlations between variables were calculated.

Results

Proposal data were available from a median of 10 years before the onset of the claim (interquartile range 7–20). Some physical and lifestyle characteristics for the three groups at the time of proposal for insurance are shown in Table 1. There were no significant differences between the groups in height, weight, blood-pressure or other baseline characteristics, but there were fewer men in the CFS group. The time interval between proposal and claim for CFS is shorter than between proposal and claim for MS or entry into the study as NC (Table 1). During this interval, future CFS cases had a geometric mean of 0.7 claims (95% CI, 0.5–0.9), compared with future MS controls of 0.2 (0.08–0.4), and non-claimant controls of 0.2 (0.08–0.3) claims. These means were significantly different from the mean for the CFS cases (p=0.002, p<0.001 respectively, Mann-Whitney U test, 2-tailed).

Twenty-six illness categories were analysed; the number of people reporting each category in the cases and controls are shown in Table 2. It is striking that all odds ratios, with the exceptions of tonsillectomy/adenoidectomy and appendicectomy, between CFS claimants and either control group are greater than 1. However, there were no significant differences in odds ratios between non-claimant controls and MS controls (data not shown). The mean number of illnesses reported at the time of proposal for future CFS cases was 6.5 (5.9–7.0), 3.6 (3.0–4.0) for MS controls, and 3.9 (3.4–4.4) for NC controls. This was highly significant (p<0.001) for comparison between CFS and either set of controls, but not significantly different between non-claimants and MS controls (p=0.27). The correlation coefficient between variables was less than 0.25 in all cases.

The difference in the proportion of women, and of year of proposal for insurance, between case and control groups raised the possibility of confounding by these variables. A multiple logistic regression analysis was therefore performed using both groups combined, as they were similar at entry, with ‘CFS or not’ as the dependent variable. Seven variables were retained in the final equation as exerting a significant effect, and are shown in Table 3. Lethargy at the time of proposal had an odds ratio of 70 for the development of CFS compared to controls, even after adjustment for other variables. Female sex also remained significant (odds ratio = 2.8 [CI 1.5–4.9]). In addition, the NC controls were analysed separately for the number of illnesses reported at time of proposal, stratified by sex, or by year of proposal (in five-year bands). There was no significant difference between the sexes - male mean was 4.0 and female mean 3.4 (Mann Whitney U test 2-tailed p=0.68 ). The number of illnesses reported gradually fell over time, stratified in five-year bands; the mean number of illnesses reported in proposals for the period 1960–4 inclusive was 11.3, whilst for 1990–4, the figure was 19 ( ANOVA across all bands F=4.6, p<0.001). CFS cases had a similar reduction in reported illnesses over time.

Discussion

Several years before CFS is diagnosed, future sufferers are reporting much more illness than controls. Any hypothesis about the causation of CFS must be able to explain this. Studies using different methodologies have shown a high lifetime number of unexplained medical symptoms in CFS patients, with a worse prognosis for CFS patients with the highest numbers of symptoms. A retrospective study has also noted that psychiatric disorders occur frequently prior to development of CFS.

Our findings suggest the possibility that CFS may be a
disorder of illness behaviour which has been present for several years at least. In such a disorder, common symptoms such as fatigue, are regarded as illnesses. Fatigue is highly prevalent in Western society, with studies in primary care in the UK and the USA identifying fatigue as a major problem in 16–24% of those attending general practice\textsuperscript{12}. Most individuals have symptoms, but visit their doctor for about one symptom in ten\textsuperscript{13,14}, with a wide variety of social and cultural factors influencing the decision to seek medical help\textsuperscript{14,15}. Having a diagnosis to explain one’s symptoms is regarded as helpful by patients for several reasons, including the removal of worry about possible life-threatening illness like cancer. It also serves to legitimise the patient’s inability to fulfil his or her social and employment roles\textsuperscript{15,16} – indeed, in one study, 90% of patients stated that being given the diagnosis of CFS was the single most helpful event in the course of their illness\textsuperscript{16}. The diagnosis generally leads to an improvement in symptoms\textsuperscript{16}, but can allow underlying social or personal factors to be ignored\textsuperscript{15,17}. If symptoms are described by patients or their doctors as ‘illness’, then they will be recorded on their insurance proposal, giving the impression of a greater liability to disease.

Three studies of the illness behaviour of CFS patients have been reported\textsuperscript{8,18,19}. All showed high scores on the hypochondriasis and disease conviction scales. These scores were significantly higher than controls from general practice\textsuperscript{8}, but not higher when MS patients are controls\textsuperscript{18}. The authors of the last study\textsuperscript{19} postulated that their findings may be a corollary of chronic illness, and cast doubt on the value of the Pilowsky rating scale in CFS. The view that CFS can be placed somewhere on an axis between psychological and physical disease – which can delegitimise sufferers who find their illness dismissed as psychosomatic and therefore ‘not real’\textsuperscript{20} – is unhelpful, because it ignores these important aspects of illness behaviour\textsuperscript{21}. The lack of benefit from drug therapies such as antidepressants\textsuperscript{22}, antihistamines\textsuperscript{23}, and antiviral agents\textsuperscript{4}, coupled with the promising results seen in cognitive behavioural therapy\textsuperscript{24}, strengthen this argument.

Although free from recall bias, other possible methodological faults in our study must be considered. Our CFS group is one of the largest series reported, and the first from an insurance database. The insured population is self-selected, and contains older individuals than other series, so the findings may not be of general applicability. However, all retrospective studies on CFS have the potential for selection bias; studies set in specialist CFS clinics are more
Table 3. Logistic regression analysis: CFS/No CFS as dependent variable.

| Predictor variable                                  | Coefficient | Odds ratio (CI) | Significance |
|------------------------------------------------------|-------------|-----------------|--------------|
| Total number of illnesses reported                   | 0.122       | 1.1 (1.07–1.2)  | <0.0001      |
| Years between proposal and time of study             | -0.083      | 0.9 (0.89–0.95) | <0.0001      |
| URI recorded on proposal form                        | 1.068       | 2.9 (1.6–5.3)   | 0.0005       |
| Female sex                                           | 1.011       | 2.8 (1.5–4.9)   | 0.0007       |
| Glundular fever recorded on proposal form            | 1.089       | 3.0 (1.3–6.7)   | 0.008        |
| Lethargy recorded on proposal form                   | 1.949       | 7.0 (1.4–36.3)  | 0.008        |
| Virus infection (excluding glundular fever and URI) recorded on proposal form | 0.593 | 1.8 (1.0–3.2) | 0.04 |

Constant: 1.5491

Increased illness experience preceding chronic fatigue syndrome

likely to include people in higher socio-economic groups and physical illness attribution, than are studies of CFS patients in primary care25. The preponderance of women in MS and CFS has been demonstrated before15,26. The increased illness reporting in the CFS group cannot be explained by this sex difference – the NC control group showing more illnesses reported by men than by women. The CFS cases entered the insurance scheme a median of four years later than NC controls, raising the possibility of a cohort effect as a partial explanation for the difference. However, fewer illnesses were reported by later entrants, eliminating this possibility.

One advantage of using cases derived from an insurance background is the quality of medical reports. Although case definition was based on the diagnosis by the claimant’s own consultant physician – to ensure comparability between CFS and MS groups – all CFS cases had been examined by a second, independent, consultant physician. The primary function of this examination was to verify unfitness for work, so did not always include application of the Centre for Disease Control criteria (1994)27, but no alternative diagnoses were established.

Insurance claimants with CFS must be unfit for their work, and so probably define a worse prognosis group. There may have been different wastage rates, by death or withdrawal from the insurance scheme, between proposal and study, but we have no evidence to suggest this. We have not been able to check the validity of diagnoses of past illnesses, which are self-reported. However, all the odds ratios are in the same direction, and those for the more objectively verifiable conditions (hernia, fracture and haemorrhoids) are closest to 1. The high values of some of the odds ratios make attribution solely to chance or unrecognised confounding factors very unlikely.

It is difficult to equate our findings with a viral cause for CFS, because any such infection would have to have been present several years before development of the syndrome, and comprise a disparate group of illnesses. One large prospective study28 has found no correlation between clinically diagnosed infections and chronic fatigue six months later, but did detect a predisposition to chronic fatigue in those with fatigue or psychological distress prior to infection. A small number in our series may have the fatigue syndrome that has been shown to follow glandular fever29,30, but the long mean time interval between reporting glandular fever and developing CFS, coupled with the lack of evidence for viral persistence in CFS4, supports the argument against a viral cause for the large majority. Indeed, belief in a viral cause for CFS is linked with a poorer prognosis31,32, so doctors should be wary of persisting in attempts to find a viral cause for every CFS patient, lest they reinforce such a belief; it is more probable that viral infections are a trigger in someone predisposed to develop the CFS.

Our results, which indicate increased reporting of illness experiences long before establishment of chronic illness, support the view that abnormal illness behaviour is a major factor in CFS. We therefore conclude that CFS may be a manifestation of a tendency to succumb to illness, and that behavioural factors are of greater importance than previously recognised.

References

1. Holmes G, Kaplan K, Gantz N, Komaroff AL, et al. Chronic fatigue syndrome: a working case definition. Ann Intern Med 1988;108:387–9.
2. Scadding JG. Essentialism and nominalism in medicine: logic of diagnosis in disease terminology. Lancet 1996;348:594–6.
3. Leitch AG. Neuroarthropathy, myalgic encephalitis or cryptogenic chronic fatigue syndrome? QJM 1995;88:447–50.
4. Report of the Joint Working Group of the Royal Colleges of Physicians, Psychiatrists and General Practitioners. Chronic fatigue syndrome. London: RCP, 1996.
5. Yousel G, Bell E, Mann G, et al. Chronic enterovirus infection in patients with postviral fatigue syndrome. Lancet 1988;1:146–50.
6. Bates DW, Buchwald D, Lee J, Kith P, et al. Clinical laboratory test findings in patients with chronic fatigue syndrome. Arch Intern Med 1995;155:97–103.
7. DeLuca J, Johnson SK, Biedowicz D, Natelson BH. Neuropsychological impairments in chronic fatigue syndrome, multiple sclerosis and depression. J Neural Neurosurg Psychiatry 1995;58:38–43.
8. Taerk G, Gnam W. A psychodynamic view of the chronic fatigue syndrome. The role of object relations in etiology and treatment. Gen Hosp Psychiatry 1994;16:319–25.
9. Dallal GE. LOGISTIC: A logistic regression program for the IBM PC. American Statistician 1998;42:272.
10. Katon W, Russo J. Chronic fatigue syndrome criteria: a critique of the requirements for multiple physical complaints. Arch Int Med 1992;152:1569–70.
11. Clark MR, Katon W, Russo J, Kith P, et al. Chronic fatigue: risk factors for symptom persistence in a 2 year follow-up study. Am J Med 1995;99:187–95.
12. Lewis G, Wessely S. The epidemiology of fatigue: more questions than answers. J Epidemiol Community Health 1992;46:92–7.
13. Tuckett D (ed). An introduction to medical sociology. London: Tavistock, 1976.
14. Verbrugge L, Asione S. Exploring the iceberg: common symptoms and how people care for them. Med Care 1987;25:539–63.
15. Pendleton P, Schefield T, Tate P, Havelock P. The consultation: an approach to learning and teaching. Oxford: Oxford University Press, 1984.
GUIDELINES FOR CLINICIANS ENTERING RESEARCH

Clinical practice benefits from research carried out by doctors with a training in the methods and ethics of medical research, because they are in a position to ask clinically relevant questions and direct the results of such studies towards better care of patients.

These guidelines have been prepared by the Academic Medicine Group of the Medical Royal Colleges for doctors in training who wish to undertake research as an integral part of a career in academic medicine. They complement the recommendations for some research experience for trainees who aim for a clinical career or NHS consultants.

The guidelines offer advice on why, when and where to undertake this training in research. Before setting out, the future clinician-researcher is advised to be clear about the area of research, the arrangements for continuing clinical training and the absolute need for full-time support by the funding bodies. Because all these considerations have implications for university and NHS authorities, and research institutes, the guidelines helpfully provide a list of contact addresses, medical organisations and regional postgraduate deans, from whom further advice may be obtained.

Price: £5.00 (including p&p) £7.00 overseas A4, soft cover, 16 pages ISBN 1 86016 061 1

AVAILABLE FROM THE ROYAL COLLEGE OF PHYSICIANS