Myalgic encephalomyelitis – a warning: discussion paper

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At a recent symposium[1] on new developments in the field of myalgic encephalomyelitis (ME), or the postviral fatigue syndrome (PVFS), Clare Francis spoke movingly of the torment she had undergone since developing the syndrome. Her description of the destruction of body and mind, and subsequent descent into suicidal despair, made one question whether ME should ever again be called benign. At the same meeting Professor James Mowbray reviewed his work on the VPI antigen implicating enterovirus infection in postviral fatigue[2], whilst Dr Len Archard presented new evidence using molecular hybridization techniques to demonstrate the presence of enteroviral RNA in the muscle biopsies of 21 out of 96 cases of PVFS[3]. Several other groups are also engaged in research projects throughout the country. In addition to the upsurge of academic and media interest there is also an apparent epidemic of new cases with Professor Mowbray announcing that his group had already received ten thousand samples to be screened for the VPI antigen. A similar situation exists in the USA[4].

Why then sound a warning? A recent discussion paper[5] pointed out the flaws in much of the existing research, and asked for greater attention to methodological detail, in particular the choice of population samples and the adoption of operational criteria. As yet there is little evidence that this advice has been heeded, although two recent publications have emphasized the need for explicit operational criteria[4-6], in addition to presenting persuasive arguments for the use of the term 'chronic fatigue syndrome' (CFS) to replace previous inadequate labels.

The central problem remains: what constitutes a case of postviral fatigue? There is agreement that CFS is a condition characterized by fatigue on physical and mental exercise, emotional symptoms, of which anxiety and depression are the commonest, and an absence of abnormalities on conventional neurological investigations[7]. There consensus ends, or, to put it more bluntly, there information ends. Specifically, little is known of the genetics, prognosis, risk factors, epidemiology or treatment response of the new syndrome. There is still very little information concerning aetiology. Cases can therefore only be selected by the clinical picture.

Yet, at present, this clinical picture is not specific. Fatigue is a ubiquitous symptom of disease both physical and psychological[8]. It is also common in the general population. In a recent UK community survey[9] 20% of men and 25% of women felt they 'always feel tired', whilst in a US National Probability Survey[10] 14% of men and 20% of women rated themselves as significantly fatigued. In both this and other samples of non-patient populations[11] the strongest factors associated with fatigue were depression, anxiety and lack of exercise. Depression as a symptom is not synonymous with depression as a syndrome, but this highlights the need to consider the relationship between affective disorder and CFS.

Fatigue and affective disorder

No general practitioner, nor hospital doctor can fail to be aware that many patients presenting with fatigue and emotional symptoms will be regarded as suffering from affective disorder. The writings of Kraepelin[12] and Lewis[13] contain the richest clinical descriptions of patients with profound fatigue on physical and mental exertion who could easily be classified as CFS or major depression. Specifically, large cross-sectional studies of patients with affective disorders have consistently shown that significant fatigue is present in 60-97% of cases[14-20]. Furthermore, in all these reports other symptoms, such as headache, vertigo, paraesthesiae, palpitations, breathlessness, gastrointestinal disturbance, tinnitus etc., are reported in similar proportions to those described in CFS[7,21,22]. Studies of milder depressive disorders show a lower prevalence of fatigue[23,24], but it is consistently one of the three most commonly reported features. A longitudinal study of primary care patients[25] found that somatic symptoms, of which fatigue was prominent, preceded the development of typical affective symptoms, whilst a longitudinal population survey found that depressed affect was a significant factor in the development and continuation of somatic symptoms[26], emphasizing the need for more information on the prognosis of CFS. All these studies used patients in whom a diagnosis of depression was made on standard criteria and none stray into the grey and unsatisfactory area of 'masked depression' or 'depressive equivalents'.

Affective disorder and the chronic fatigue syndrome

Conversely, a Canadian study of CFS[27] found a high prevalence of major depression, but, given the problems already discussed, this result is difficult to interpret. Instead, a more interesting finding was that 50% of cases had experienced a previous episode of depression. The most comprehensive study to date, a joint medical and psychiatric assessment of 100 patients with fatigue seen in a university health centre reported that 66% had a psychiatric disorder (with 47% having abnormalities of mood), 5% had medical diagnoses, leaving 31% with unexplained fatigue[28].

It can be concluded that affective disorder is a common condition which shows symptomatic overlap

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with CFS, and in which, despite a major investment in biological research, the aetiology is also far from clear.

Sadly, few of the current workers in the field of CFS seem aware of this problem. Recent research has been restricted to highly selected populations, with many cases being drawn from the ranks of a self-help group, or from specialized hospitals. Thus most cases are long-standing, drawn from upper social class and contain an overrepresentation of the medical professions, perhaps reflecting the fact that many sufferers make their own diagnosis. In addition, a powerful selection bias may result from patterns of symptom attribution and psychological awareness, which may affect both patients and doctors. Depressed patients with particularly severe somatic symptoms, especially insomnia and lack of energy, are more likely to visit (or be referred to) non-psychiatric specialists before their depression is recognized[24,29]. Misdiagnosis of such patients may have severe consequences[30]. Patterns of referral may add yet further bias. For example, do general practitioners only refer to units with an interest in viral fatigue those in whom they have already established high titres to common viruses?

Future directions

At the symposium both Professor Mowbray and Dr Archard declared themselves at the mercy of clinicians who have to diagnose suitable cases as a starting point for sophisticated research. Unfortunately, clinicians have not always served researchers well. It is now time to take account of the many selection factors that influence the diagnosis of CFS. Furthermore, it is now time to include, either as cases or controls, those patients who, often for equally arbitrary reasons, have other diagnoses such as affective disorders. With such patients also comes a wealth of painstaking research into natural history[31] that has been created over the years, as well as pertinent work concerning the boundaries of depression and somatization[32]. There is also an increasing body of knowledge on immunological abnormalities and affective disorder[33].

Case definitions will clearly help to solve some of the current confusion, but alone will not be sufficient. For example, both the recent operational case definitions[4,6] permit the inclusion, albeit as minor criteria, of patients with cognitive difficulties, depression, somatic symptoms and insomnia as well as fatigue. Thus patients may fulfil both the criteria for CFS and the Research Diagnostic Criteria for definite minor depression simultaneously, and only require to have either appetite disturbance or a loss of interest to satisfy probable major depression[34]. Such criteria, although a major step forward, still do not acknowledge the importance of mood disorder as a 'characteristic feature'[35] of CFS, and hence ignore the unresolved difficulties in determining the interaction of psychological symptoms and fatigue[36].

More must therefore be discovered about the similarities and differences between CFS and the various disorders of mood. In what way do cases of CFS without evidence of mood disorder differ from those with such features? Is the fatigue experienced in CFS phenomenologically different from that experienced in either depression or in neuromuscular diseases? Does the presence of mood disorder, whether premorbid or the result of infection, influence the subsequent development of a postviral syndrome? A prospective study suggested that prolonged convalescence from an acute infection is influenced by psychological factors, including prior history of emotional disturbances and current attribution of the symptoms of depression to the infectious condition[37].

Perhaps the major research activity should be directed towards longitudinal studies of cohorts of patients fulfilling criteria for the syndrome. In particular, are different symptom patterns present at different stages, and do different aetiological factors operate over time? Firstly, diagnostic categories may themselves change. Some may later develop clearcut affective features, such as psychosis or bipolarity, whilst others may develop overt neurological syndromes. Secondly, the nature of the syndrome itself may also change. It is this author's belief that patients seen in primary care with persistent fatigue shortly after an acute infection represent a very different population from those with longer periods of illness who are seen in hospital practice. One may tentatively suggest that symptom clusters suggestive of a fatigue syndrome without emotional disorder will be commoner in the former.

No one will claim that most cases of CFS are simply cases of affective disorder, or any single syndrome, psychiatric or otherwise[27]. Instead, it is likely that both affective disorders and CFS are heterogenous conditions. However, we must remember Occam's razor, and not make premature divisions until the evidence permits. If not, poor research design may significantly lessen the validity and usefulness of potentially exciting discoveries. There is now an excellent opportunity to increase our understanding of both these disabling disorders, and it must not be squandered.

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