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Editorial

Chronic fatigue syndrome

Three years ago David *et al*[1] reviewed the available information concerning what was then known as postviral fatigue syndrome, and concluded that little was certain except that the issue was controversial. Since then there have been many welcome changes,[2] including the name, which has shifted to the more appropriate label of chronic fatigue syndrome (CFS), but controversy remains. This editorial attempts a brief summary of the current position, emphasising issues relevant to the neurologist.

CFS and neuromuscular disorder

The role of neuromuscular disorder in the pathogenesis of CFS is becoming clearer, although areas of disagreement remain. Such ultrastructural abnormalities that have been located are non-specific, and deficits in intermediate metabolism have not been demonstrated.[3] The significance of an often cited case report of abnormalities on nuclear magnetic spectroscopy[4] remains disputed,[5,6] and even if relevant, was unusual. Nerve conduction studies are invariably normal, but there is conflict concerning the results of single fibre electromyography, which measures the organisation and synergy of nerve fibres, rather than their absolute conduction velocities. Two experienced investigators reported abnormal jitter values in 75% of a selected sample.[7] However, impulse blocking, a feature of deficits in neuromuscular transmission, did not occur, nor did the results correlate with the presence of enteroviral RNA in muscle biopsies.[8] Others have argued that abnormal jitter alone cannot be related to fatiguability.[9,10] In response, the original authors report similar isolated abnormalities in cases of myasthenia (G Jamal, personal communication), which only later progress to show typical impulse blocking. Nevertheless, such progression has not been demonstrated in CFS, despite the often long duration of illness, and an attempt at replication only demonstrated abnormal values of jitter in four out of 30 cases.[11]

Even when identified, two lines of observation suggest that such neuromuscular abnormalities may not often be clinically relevant. Studies of dynamic muscle function have demonstrated essentially normal muscle strength, endurance and fatiguability, other than as a consequence of physical inactivity.[9,10,12,13] Two of these studies deserve further comment. One sample[10,13] consisted of subjects defined on the basis of immunological abnormalities, whilst another[14] consisted of subjects with post infectious fatigue following serologically defined Epstein Barr virus infection. Despite claims to the contrary, it has also been impossible to find evidence of delayed fatiguability.[10,15] Lloyd *et al*[13] concluded that "neither poor motivation, nor muscle contractile failure is important in the pathogenesis of 'fatigue' in patients with the chronic fatigue syndrome".

Evidence also comes from studies comparing psychiatric morbidity in CFS and neuromuscular diseases. Wessely and Powell[16] found that 72% of a consecutive series of chronically fatigued patients seen at the National Hospital in London fulfilled Research Diagnostic Criteria for psychiatric disorder even if fatigue was excluded as a symptom, whilst Wood *et al*[17] in a series from a specialist unit in Liverpool used a different set of criteria and found that 41% were psychiatric cases. The differences reflect the more liberal criteria for psychiatric disorder used in the London study. However, more important than the overall prevalences are the relative risks of psychiatric disorder in cases compared with controls with neuromuscular disease. This was two in the London series, and 3·3 in the Liverpool series. A similarly designed study using controls with rheumatoid arthritis found over a six fold increase in psychiatric disorder in the CFS cases.[18] Neuromuscular abnormalities, or the consequence of physical disease, cannot alone account for the clinical features of CFS.

CFS and psychiatry

Patients with severe chronic fatigue are at high risk of psychosocial morbidity. It is a matter of regret that each generation of physicians appears to need to discover this afresh,[19] and that such observations continue to inspire the same futile "organic versus psychological" polemics. Once again there are an increasing number of studies confirming that perhaps the majority of those seen in specialist centres with a chief complaint of chronic fatigue fulfil operational criteria for psychiatric disorder.[20,21] The diagnoses vary, but depression is the commonest, followed by anxiety disorders (with and without hyperventilation) and somatisation disorders.

Rather than considering what this means, it is preferable to start with what it does not mean. It does not mean that symptoms are factitious in origin, which is still an issue in the media, even though never considered by serious investigators of CFS,[2] nor that psychiatric disorders are the cause of CFS. In the context of CFS, Kendell[22] pointed out that "the statement that someone has a depressive illness is merely a statement about their symptoms. It has no causal implications...". There is no single explanation for these findings. In some, psychological disorder is a consequence of physical disorder. In others, both are due to an underlying condition, and, for yet others, psychological disorder has been misdiagnosed as CFS.[23] What it does mean is that screening for psychological disorders should now be mandatory. Most psychological disorders are easier to treat than CFS, and if ignored are likely to have an adverse effect on prognosis.

CFS and infection

As well as neuromuscular and psychiatric studies, there is an increasingly complex literature on possible serological abnormalities in CFS, although such speculations are certainly nothing new.[24] Initial enthusiasm for the role of

Epstein-Barr virus in the USA has now subsided. In the United Kingdom similar enthusiasm greeted reports of an association with the Coxsackie virus, but it is now clear that these also require re-evaluation (see below). Attention has also shifted to a possible role of HHV-6 infection, but as with EBV many believe that any such associations in chronic illness are usually either artefactual or the consequence of reactivation.[25]

Recently sophisticated molecular techniques have been used to investigate evidence of exposure to virus. Enteroviral RNA was detected by in situ hybridisation of muscle biopsies in 24% of selected cases of CFS,[8] whilst another study detected enteroviral sequences with the sensitive polymerase chain reaction (PCR) in the muscle biopsies of 32 of 60 cases, compared with six out of 41 non fatigued older controls having various surgical procedures.[26] No correlation was seen, however, between serological evidence of enteroviral exposure and muscle findings, and there was no difference in serological exposure between cases and controls. Should we believe the serology, or the molecular virology? A recent case control study demonstrated the unreliability of serology, and concluded that enteroviral serology has little place in the diagnosis of CFS.[27] The implication is that a number of previous reports linking exposure to Coxsackie virus to CFS are unreliable. It was the same studies, however, that inspired the current investigations — serendipity continues to play a role in medical research.

These virological studies[8 26] are both sophisticated and innovative, but may not be easily generalised. Cases for both studies were recruited from the same tertiary referral centre. In a less selected sample of post viral fatigue cases in situ hybridisation apparently detected enteroviral persistence in the muscles of only 8% of cases.[28] Few details are given of psychiatric status in any of these studies, except that over half had symptoms of depression with diurnal variation, despite excluding all those with a previous history of psychiatric disorder[26] (which could itself be a risk factor for post infectious fatigue). Furthermore, in the light of the evidence of normal muscle function in CFS, as described earlier, the clinical relevance of such findings can also be questioned. The authors note the absence of conventional evidence of structural damage in CFS, and draw analogies with animal studies suggesting that viral persistence is possible without conventional evidence of morphological damage. However, it is still necessary to demonstrate clinically significant impairment in the function of the cell. Alternatively, although Gow *et al*[26] suggest that viral persistence in muscles may have aetiological significance, they also speculate that persistence may occur in the central nervous system. This is both plausible and consistent with the clinical picture, and would imply that enteroviral fragments in muscle are a marker for viral persistence elsewhere. Other evidence is appearing of subtle central nervous system abnormalities,[29] but in pursuing these leads researchers will face formidable methodological problems familiar to biological and neuropsychiatrists.

Why have there been such efforts to find a microbiological cause of CFS, and so many mutually exclusive claims of success over the years? Many patients give a history of an initial "viral" illness. Other mysterious illnesses have been established as of infective origin, whilst the concept of an external agent is a familiar one for both doctor and patient, and can serve to preserve the patient's self esteem and protect them from stigma.[30] However, premature claims have also resulted from a neglect of basic epidemiological principles. In recognition of the complexities of retrospectively linking laboratory abnormalities and the clinical syndrome, it has been suggested that the term "post-viral fatigue syndrome" should be replaced by "post-infectious fatigue syndrome", and reserved for those in whom the illness has developed after a proven infective episode.[31] Generally, this will require greater reliance on longitudinal studies, and less on the cross-sectional approaches which are more commonly performed, but more open to bias.

CFS and the immune system

Potential immunological abnormalities in CFS are now attracting increasing attention, especially in the USA. Once again, the results are bewildering, whilst the tendency for results to appear in the popular press before (and occasionally instead of) the professional journals has led to the occasional false dawn. Two authoritative reviews concluded that although there is evidence of some abnormalities, such as raised circulating immune complexes and decreased natural killer cell function, acceptance of their importance has been hampered by their inconsistency, non specificity and lack of relationship to clinical findings.[32 33] Other problems included poor attention to methodological detail, especially the control of confounding factors such as inactivity and psychiatric morbidity.

It would, however, be a mistake to ignore such findings. Newer studies are in progress in several centres in both the United States and Australia, whose sophisticated methodology promises more interpretable results. Greater attention is being paid to reliability, and nearly all either routinely incorporate psychiatric assessments, or recruit appropriate controls. This is particularly welcome, since by choosing to incorporate, rather than ignore, the links between CFS and psychiatric disorder, research gains in credibility, and promises a better understanding of the pathogenesis not only of CFS, but perhaps also of some psychiatric disorders. Most of these studies have yet to report their findings formally, but preliminary results give support to concepts of a non-specific dysregulation of immune function in a minority of cases that occurs irrespective of psychiatric morbidity.

CFS and the neurologist

What can be made of this maze? An analogy with the epidemiology of hypertension may prove helpful.[34] Like blood pressure, chronic fatigue may be a dimensional, rather than a categorical variable. As with blood pressure, no discrete boundary exists to separate the normal from the abnormal, yet in both the end of the spectrum can be associated with severe morbidity mandating treatment. The role of such apparently mundane factors in the epidemiology of hypertension as diet, smoking, stress and obesity may be replaced in CFS by variables such as depression, inactivity, anxiety and common infections. Nevertheless, just as the cardiologist must be alert to the possibility of renal artery stenosis and phaeochromocytoma, the occasional patient with CFS will have profound immune disturbance,[35] unusual myopathies,[36 37] and no doubt other aetiologies yet to be discovered.

In the meantime, what should the neurologist do? No specific treatment yet exists. There is still no role for therapy directed at virological or immunological abnormalities.[38 39] Treatment remains symptomatic. Promising lines of inquiry include the role of antidepressants, not only because of their mood elevating properties, but perhaps also because of direct effects on sleep disorder and muscle pain, supported by controlled studies in fibromyalgia,[40] a similar syndrome also characterised by fatigue and myalgia. Advice[41] that antidepressants may be counterproductive because they reinforce the patient's belief that the condition is "psychogenic" is misguided, and reveals

more about the continuing stigma of psychological illness than the management of CFS. More surprisingly, controlled studies have recently reported success using essential fatty acids[42] and magnesium.[41] Patients should certainly not be automatically dissuaded from trying these and other non-specific treatments, so long as they are cheap and free from side effects.[38] However, excessive emphasis on these or other pharmacotherapies may distract attention from the crucial area of rehabilitation.[43] There is increasing consensus that a broadly based physical and psychological approach is desirable.[44] Previous over zealous counselling of rest as the mainstay of treatment has little to commend it, supported by controlled evidence in fibromyalgia, and uncontrolled evidence in CFS,[45] and instead patients may be encouraged to cautiously interrupt the "cycle of inactivity, fatigue, pain and inactivity"[46].

Many neurologists will, however, not see the treatment of CFS as part of their role, and may feel, with justification, that the general practitioner has more to offer in both the diagnosis and management of this disorder than any physical or psychiatric specialist.[47] Nevertheless, patients will continue to be referred to the neurologist for the foreseeable future. In these circumstances two caveats must be borne in mind. Misdiagnosis of a number of conditions, both physical and psychiatric, is not unusual in those who have acquired the label of CFS/ME. However, the simple combination of history, examination and basic tests will establish those who require further investigation.[48 49] In the majority this simple screen will be normal, and over investigation should be avoided. Not only is it a waste of resources, it may not be in the patients' interest, and may reinforce maladaptive behaviour in a variety of ways. "As patients undergo more tests, they will focus on a laboratory abnormality and subsequently find researchers interested in studying these abnormalities".[50] This may help the researchers, but not the patient.

Whilst over investigation is usually well intentioned, though not advisable, such behaviour must be criticised if it is motivated by a need to find such an abnormality before accepting the patient's predicament as genuine. There remains a tendency to denigrate those subjects unlucky enough to still have normal results once the round is complete, whose illnesses are thus labelled as "psychogenic", and of little concern. It is still possible to encounter such comments as "this suggests an organic cause for their complaints, and means the syndrome should not be dismissed out of hand as a psychiatric entity".[51] Armon and Kurland[50] provide wiser counsel — "psychosocial disability is real, significant and worthy of treatment even when there are no biochemical or immunologic abnormalities present".

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Chronic fatigue syndrome.

S Wessely

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