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Letters to the Editor

Immune responsiveness in chronic fatigue syndrome

Sir,

The paper by Milton and colleagues[1] challenges the hypothesis that patients with postviral fatigue syndrome (myalgic encephalomyelitis) have a persisting viral infection along with consequent immune dysregulation. The protocol employed in the study suggests that their conclusions may not be valid.

Firstly, the 31 patients were selected from a group attending a 'muscle clinic' who complained of 'unexplained chronic fatigue'. Of these only 15 had a clear history of a precipitating viral illness – a key diagnostic feature of postviral fatigue syndrome. Secondly, although other research groups have also demonstrated that raised levels of Coxsackie B virus IgG and IgM antibodies are not diagnostic of the syndrome,[2] these findings cannot be used to exclude the possibility of persisting viral infection within either muscle or the central nervous system.

As far as muscle is concerned, Gow and colleagues[3] have recently detected enteroviral RNA sequences in muscle biopsies of 53% of patients with a well-defined postviral fatigue syndrome compared to 15% in a control group, and Archard *et al.*[4] have shown that this persisting enterovirus is poorly replicating.

Demonstrating the presence of persisting virus within the central nervous system is obviously far more difficult without autopsy material. However, Daugherty *et al.*[5] in America have published the results of MRI scans and cognitive function tests on 20 patients (with age and sex matched healthy controls) showing abnormalities consistent with an organic brain syndrome similar to that seen in patients who are positive for human immunodeficiency virus.

Thirdly, a large number of papers have been published in the UK, America and Australia documenting laboratory evidence of various changes in immune regulation. The differences in results may well be related to variable factors such as duration and severity of the illness as well as age of the patients. If there is any consensus it appears to be in the area of abnormalities within natural killer lymphocyte subsets where researchers on both sides of the Atlantic have come to similar conclusions.[6]

I would accept that chronic fatigue syndrome is a perfectly acceptable umbrella term to cover a wide heterogeneous group of patients suffering from persisting fatigue – an extremely common symptom in primary care. However, if conclusions are to be drawn about the virology, immunology and neuromuscular pathology of a particular subgroup, that is, those with postviral fatigue or myalgic encephalomyelitis, then researchers must adhere to the guidelines laid down at Oxford[7] which the authors refer to but have not followed. These state very clearly that post-infectious patients do form a distinct subgroup, and that to fulfil research criteria there must be 'definite evidence of infection at onset or presentation'.

Charles Shepherd
Medical Advisor, ME Association,
Friars Cottage,
Queens Square,
Chalford Hill,
Glos, GL6 8EH, UK.

References

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We have shown this letter to Drs Milton, Edwards and Clements, who reply as follows:

Thank you for giving us an opportunity to comment on the points raised in Dr Shepherd's letter.

First, we have investigated patients in the broad category of chronic fatigue syndrome, not those classified under the sub-heading postviral fatigue syndrome.[1] We think this is reasonable since there is no obvious clinical difference between those patients with and without evidence of an episode of viral infection as an initiating feature of their chronic fatigue. Of course those patients with such a viral onset should also be investigated as a separate group, but with patients of long duration of fatigue it is often difficult to ascertain accurately whether there was any preceding viral infection.

Second, the evidence provided by the finding of enteroviral RNA in the muscle of more patients than controls is indeed suggestive of a persistent viral infection, but as it is not known whether the presence of viral RNA in the cells alters their metabolism,[2] the significance of this finding is as yet unknown. Our point in this regard is that we find no altered cellular immune responsiveness to enteroviruses in our patients. We do make the point in discussion that the small number of patients who had increased circulating immune complexes came mostly from those patients who had an indication of a viral origin of their fatigue.

Third, regarding immune regulation, of which there are various contradictory reports, the possible involvement of natural killer cells awaits an elucidation of the function, if any, of the various sub-sets thereof in viral containment.[3]

In summary, we would restate that we find no indication, in the limited number of parameters we have investigated, of persistent viral infection or altered immune regulation in patients with chronic fatigue syndrome, though we provide no hard evidence against it.