EDITORIAL COMMENTARIES

Chronic fatigue syndrome: is it physical?

It is increasingly recognised that chronic fatigue syndrome (CFS) is heterogeneous. A significant proportion of patients fulfilling operative criteria for a diagnosis of CFS will also fulfill criteria for a psychiatric disorder, such as depression or somatisation. Failure to recognise this heterogeneity prejudices attempts to understand CFS in cross sectional studies. In this issue (pp 302–307) Fulcher *et al* report a study of muscle strength, aerobic exercise capacity, and functional incapacity in a group of patients with CFS without concurrent psychiatric disorder, compared with patients with major depression and a group of normal but sedentary subjects.¹ In an incremental treadmill exercise test, patients with CFS and depressed patients had lower peak oxygen consumption rates, maximal heart rates, and plasma lactate concentrations than the sedentary controls; but this reflected the shorter duration of exercise tolerated by these patients. At submaximal work rates, patients with CFS and depressed patients experienced greater perception of effort than sedentary controls at the same level of work. This is in keeping with the finding that such patients show greater sensitivity to bodily sensations than normal subjects. Overall, there was little difference between the patients with CFS and the depressed patients in exercise characteristics, yet the patients with CFS reported significantly greater degrees of physical fatigue and physical incapacity.

The authors did find one important difference, however. The patients with CFS were significantly weaker than either the depressed patients or the sedentary controls as judged by measurement of quadriceps strength. This is the first study to demonstrate such physical weakness in patients with CFS and the authors suggest that this is because they studied a more coherent group of patients than others have previously.

Fatigue is a complex symptom. In its strictest sense the word means “inability to sustain force”, indicating dysfunction in the neuraxis or neuromuscular apparatus, whether physiological (after strenuous exercise) or due to disease processes. In its colloquial context (*fatigare*-to tire), it is the sensation experienced when the effort to perform work, whether physical, mental or both, seems disproportionate for the task involved. Physiological fatigue recovers with rest. Chronic fatigue typically does not. Although

chronic fatigue is a very common complication of a wide range of medical and neurological diseases, such as multiple sclerosis and Parkinson's disease, it can also occur in the absence of readily definable pathology, notably in CFS.

What is the cause of this physical weakness in CFS? The authors think that it is related to physical deconditioning due to inactivity and this view is supported by improvement in wellbeing, strength, and exercise capacity after a graded aerobic exercise programme.² However, graded exercise therapy improves tolerance and exercise capacity in many disorders, including muscle diseases such as mitochondrial myopathies.³

Some patients with CFS show abnormal increases in plasma lactate after exercise at low work rates.⁴ Heart rate responses to exercise in that study did not suggest that these patients with CFS were more “deconditioned” than those with normal lactate responses. They also proved less likely to have psychiatric disorder. Furthermore, recent spectroscopic studies of the forearm muscles, which are not usually subject to the effects of deconditioning, showed abnormal muscle energy metabolism in such cases.⁵ Deconditioning may well be an important factor in the pathogenesis of CFS, but these findings raise the possibility that some patients with CFS have a form of metabolic myopathy.

Whatever the mechanisms underlying “fatigue”, exercise therapy is likely to become an increasingly important therapeutic modality in various fields and particularly in the management of chronic fatigue syndromes.

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What contributes to quality of life in patients with Parkinson's disease?

The question posed by Schrag *et al*¹ (this issue, pp 308–312) is fundamental, but can it be answered? Quality of life belongs to a family of terms which has an improbably wide range of applications, from “quality” as an object of philosophical contemplation² to “QoL” as an economic variable.³ It must be borne in mind that measures such as the PDQ-39 and the SF-36 differ considerably in content. More detail on the parallelism between the PDQ-39 and two other measures would be

helpful but the data seem to support the assumption, which is gaining ground in the literature, that such measures reflect a single underlying dimension. Scales specific to Parkinson's disease and to inflammatory bowel disease have been found to be congruent, again suggesting that disease specific quality of life is a unitary construct.⁴ However, we must not lose sight of the fact that at the deepest level, quality of life is inherently unquantifiable.

Philosophical considerations aside, there is practical merit in the more precise question: "What are the associations between *this particular measure* and other variables?" We need to understand which aspects of Parkinson's disease weigh most heavily on patients. Although the authors recognise that associations do not indicate causality their bias is revealed when they write of the "influence" of factors such as mood on quality of life. The converse is equally likely. The two dimensions, mood and quality of life, are logically related, and the extent to which the Beck depression inventory correlates with the PDQ-39 tells us as much about the nature of the two measures as about the patient population under study. Much of the variance was not shared, suggesting that a fraction of the putative quality of life construct did not influence mood (why not?); or that aspects of the measure of mood did not influence quality of life: which sounds paradoxical.

The authors found that severity of disease (or rather severity of physical impairment, as this is what the Hoehn and Yahr scale measures) was more predictive than disability of the PDQ-39 score. The relation between physical impairment and quality of life therefore seems to have been indirect, and not mediated through the obvious effects of impairment on activities of daily life. This is consistent with several other studies showing that the association between disability and quality of life is weak.⁵ Severity of impairment might have been a marker for diverse experiences which were not individually predictive of

PDQ-39 score. It is not clear whether the association between postural instability and PDQ-39 was direct or indirect.

Similar considerations apply to the association between the mini mental state examination (MMSE) score and PDQ-39. We should not accept uncritically the implication that dementia is experienced negatively. It could be an indirect marker of some other negative influence, such as carer stress. One problem which the authors do not consider is that quality of life and also depression are notoriously difficult to measure validly in people with dementia. In this sort of study it is virtually impossible to avoid the influence of carers' opinions on questionnaire responses, especially at the lower end of the MMSE scale, and the authors apparently made no attempt to do so. Carers add a further layer of complexity to the interpretation of these results.

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Can a neuropsychological follow up contribute to the diagnosis of parkinsonian syndromes?

Although an akinetic rigid syndrome is the hallmark of idiopathic Parkinson's disease (PD), striatonigral degeneration (SND), and progressive nuclear palsy (PSP), cognitive and behavioural dysfunctions are often found in these parkinsonian syndromes. If the neuropsychological deficits directly reflect underlying brain neuronal lesions, we may expect that the cognitive and behavioural changes associated with these syndromes depend on the specific pattern of subcortical or cortical lesions that characterise each disease. The earliest and major cognitive deficit in all three diseases is impairment of executive functions as shown by performance on tests sensitive to frontal lobe function. Is it possible to distinguish, among the deficits contributing to this subcorticofrontal syndrome, patterns that are more specific to one or another of the three diseases? This might be useful for clinical diagnosis, especially in early stages of the diseases when the signs often overlap, accurate diagnosis being important for devising investigational and therapeutic strategies. In the paper by Soliveri *et al*¹ in this issue (pp 313-318) patients with PSP performed worse than patients with PD and those with SND on most tests during their initial evaluation, whereas patients with PD and those with SND performed similarly. These results are in agreement with other recently published studies.^{2,3} Patients with SND had, however, reduced phonemic fluency compared with patients with PD. This difference has to be confirmed by other studies, but might be clinically relevant. Dementia was found only in PSP, and corresponds to a severe subcorticofrontal syndrome

caused by lesions in the the striatohalamocortical pathways resulting in deafferentation of premotor and prefrontal areas.

Because the natural history of these disorders also varies widely, Soliveri *et al* attempted to enlarge the differential diagnosis by a longitudinal assessment. Unfortunately, after 2 years, significant proportions of patients with SND or PSP were too disabled or had died, confirming that these two diseases progress more rapidly than PD. Among the patients who could still be tested, those with PSP declined significantly more than the two other groups on the Wisconsin card sorting test, which evaluates conceptualisation and set shifting. Patients with PSP or SND, however, had worsened significantly more than patients with PD on the visual search test assessing attention and visual scanning. There was no correlation between motor and cognitive decline. The proportion of demented patients increased only in PSP. This is not surprising given the more diffuse neuronal lesions in this disease.

In conclusion, clinical studies indicate that a parkinsonian syndrome is the presenting feature of several different diseases. Although most patients with parkinsonism have an idiopathic Parkinson's disease, others have multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration or Lewy body dementia. Neuropsychological assessment in the early stages of the disease can contribute to the clinical diagnosis.⁴ The time course and pattern of progression of cognitive and behavioural decline can also