LETTERS TO THE EDITOR

Creutzfeldt-Jakob disease and stress

As part of a study on risk factors for Creutzfeldt-Jakob disease, we compared frequencies of stressful life events in cases of Creutzfeldt-Jakob disease and controls. Cases were patients classified as definite or probable sporadic Creutzfeldt-Jakob disease according to the criteria of Masters *et al*[1]; they were matched on sex and age (± five years) with non-demented hospital controls. Data on history of patients with Creutzfeldt-Jakob disease were obtained from close relatives.

The study sample consisted of 55 case-control pairs (61·8% women); mean ages were 64·0 for cases and 63·8 years for controls. In the present analysis, we focused on events which had occurred between one year and five years before the onset of disease. Overall, we found that 27 patients with Creutzfeldt-Jakob disease (49%) and four controls (7·2%) had experienced emotional disturbances due to life events (table). The proportion of major life events was significantly higher in patients with Creutzfeldt-Jakob disease than in controls (χ^2 (matched pairs) = 19·6, df = 1, $P < 0·001$).

Studies on life events are subjected to much criticism. Recall bias is the most important issue. Relatives of patients with Creutzfeldt-Jakob disease may pay more attention to the occurrence of life events than controls. However, as shown in the table, we have restricted analysis to major events. It is unlikely that relatives of patients have reported events which have not occurred and that controls have forgotten such important personal events. Differential referral of cases of Creutzfeldt-Jakob disease and hospital controls according to past life events may be another issue.

Other studies have shown that stressful life events could be risk factors for different diseases, especially cardiovascular diseases and cancer. Mechanisms of the associations have not been totally elucidated, but some plausible hypotheses have been proposed. Regarding the association between Creutzfeldt-Jakob disease and life events, different interpretations can be proposed. Stress related biological conditions might enhance the formation of abnormal prion protein. Stress might also increase the severity of subclinical symptoms. This hypothesis has been proposed to explain the early age of onset of bovine spongiform encephalitis in animals which had been moved between herds.[2]

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Wasting, weakness, and the MRC scale in the first dorsal interosseous muscle

The Medical Research Council (MRC) scale[1] retains its popularity as a robust clinical tool for assessing hand muscle strength. It is, however, non-linear and a change of one unit in the scale, say from 5 to 4, represents a much greater loss of muscle force than from 1 to 0. An opportunity to explore the nature of this non-linearity arose during a serial study of the first dorsal interosseous muscle in a series of 40 patients with amyotrophic lateral sclerosis. In both hands of each patient, a single observer documented the MRC scale for strength and estimated the degree of wasting of the first dorsal interosseous muscle on a four point scale (no wasting 4; mild 3; moderate 2; or severe wasting 1). Subsequently, the peak to peak amplitude of the compound muscle action potential (CMAP) evoked by supramaximal ulnar nerve stimulation at the wrist was measured. As this is a purely objective measurement, there was no biasing of the force or wasting estimates by prior knowledge of the CMAP amplitude. Patients were assessed at three month intervals with the assessor blind to the results from previous visits. The study yielded 183 observations on which to base an analysis.

The force generating capacity of a muscle is directly related to the volume of active tissue.[2] The surface recorded CMAP represents the summation of all muscle fibre action potentials evoked in the muscle. Each fibre action potential at source will have an amplitude roughly related to the diameter of the fibre. The CMAP amplitude, therefore, will depend on the number of fibres generating action potentials and on the average single fibre action potential amplitude. The volume of excitable tissue in the muscle and the amplitude of the CMAP evoked by supramaximal nerve stimuli are therefore interrelated estimators of the force generating capacity of the muscle.

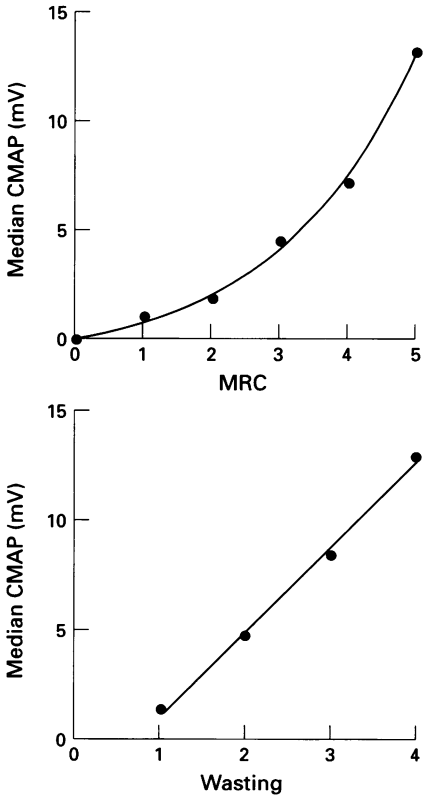
The CMAP amplitude is known to have a skewed distribution in healthy subjects; this was also true in the current series of measurements. The median (rather than the mean) CMAP amplitude was therefore used as a measure of central tendency to relate to the MRC and wasting estimates. The figure shows a curvilinear relation between MRC score and CMAP amplitude. Given the arbitrary nature of definition of the MRC scale points, it is remarkable that the relation of MRC score to CMAP amplitude can be fitted so well by an exponential function ($y = -1·28(1-e^{-0·48x})$, $r = 0·99$). In effect, a reduction of one point on the scale is associated, on average, with an approximate halving of CMAP amplitude. By contrast, the wasting score, equally arbitrary, is linearly related to CMAP amplitude ($y = 3·82x - 2·68$, $r = 0·99$)

Weakness of hand muscles in amyotrophic lateral sclerosis can be due to either a lower motor neuron lesion (LMN), an upper motor neuron lesion (UMN), or to a combination of the two. Weakness due to UMN lesion is not associated with wasting or a reduction in CMAP amplitude. It is pertinent to ask whether the curvilinear relation seen in the figure could be due to additional UMN weakness in some patients. At a given MRC scale point, if the weakness had a UMN component, CMAP amplitude would tend to be higher and the relation between MRC and CMAP would tend to be less curved, the reverse of what is actually found. The curvilinear relation between CMAP amplitude and MRC score is, therefore, not due to the effect of weakness resulting from UMN lesion.

Wasting could be due to a reduction in the number of active fibres or a reduction in diameter of fibres, or both. Clearly, wasting

Life events in patients with Creutzfeldt-Jakob disease (CJD) and hospital controls

Type of life events	*Patients with CJD (n = 55)*	*Controls (n = 55)*
Death of close relatives: (husband or wife, siblings, parents, children, or grand children)	8	3
Major professional events: (unemployment, moving to another town)	7	0
Serious familial problem: (illness of a relative, serious familial conflict)	12	1



The relation in the first dorsal interosseous muscle between MRC score and median CMAP amplitude (above) and wasting score and median CMAP amplitude (below) based on 183 observations from 40 patients with sporadic ALS. The curve relating MRC and CMAP has been fitted with an exponential function; the relation between wasting and CMAP is linear.

due to either of these mechanisms will lead to a fall in the CMAP. It seems that on the scale of wasting used here, the relation to CMAP amplitude is linear. Thus wasting progressing from mild to moderate is associated with the same relative change in CMAP amplitude as wasting progressing from moderate to severe.

Two clinically relevant conclusions can be drawn from these findings. Firstly, an LMN lesion, causing the CMAP to fall by roughly half, may be present and yet the MRC score may not register weakness. This holds true whether the reduction in CMAP amplitude is due to axonal degeneration and hence reduction of either the number or diameter of excitable muscle fibres, or due to conduction block, in which the number of muscle fibres may remain normal but they are inaccessible from nerve stimulation—that is, conduction block may be present even though there is no overt weakness. Secondly, wasting on a simple four point classification better reflects the amount of excitable tissue than does the MRC score, at least in the first dorsal interosseous muscle.

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Management of parkinsonism and psychotic depression in a case of acute intermittent porphyria

Although parkinsonian syndromes are common,[1] and the acute porphyrias affect one in 10 000 of the population in the United Kingdom,[2] little is known of the effects of dopamine agonist drugs on porphyrin metabolism. Most people with inherited porphyria remain asymptomatic[2] but all are at risk of developing an acute attack if exposed to precipitating factors, of which drugs are the most common. Although levodopa, benserazide, and anticholinergic drugs have been used safely in patients with acute porphyria,[3] both lysuride and bromocriptine may precipitate an acute porphyric attack.[4] Similarly, tricyclic antidepressants and monoamine oxidase inhibitors are contraindicated in porphyria,[5] and there is conflicting evidence concerning the safety of selective serotonin reuptake inhibitors (SSRIs) in patients with acute intermittent porphyria (AIP).[4]

A 56 year old right handed woman was found to have biochemical AIP on screening prompted by the acute presentation of her brother with bilateral radial nerve palsies. She had never experienced symptoms which could have been due to an acute attack of porphyria, her blood level of porphobilinogen deaminase activity was 12·7 units (normal female range 30–54 units), but her urinary porphyrins had never been significantly raised.

Eight years previously she was diagnosed as having a parkinsonian syndrome but treatment was difficult from the onset. Although she displayed levodopa responsiveness, there was pronounced end of dose bradykinesia, and prominent peak dose dyskinesiae which became remarkably sensitive to the size and frequency of the levodopa unit dose. She had no history of exposure to dopamine receptor blocking agents and no autonomic symptoms.

As her parkinsonism advanced she became increasingly depressed with hypochondriacal and paranoid delusions. She fulfilled the criteria for a severe depressive episode with psychotic symptoms (International Classification of Diseases (ICD) 10), but she also described visual hallucinations and was noted to have a fluctuating level of consciousness.

Neurological examination disclosed increased axial tone, impaired postural reflexes, and a short stepped, festinant gait. She had hypometric saccadic eye movements, orofacial bradykinesia, and slow rapid alternating movements of her tongue. There was a resting tremor in all four limbs, associated with a symmetric akinetic rigid syndrome. On three hourly co-beneldopa (62·5 mg) she alternated between profound bradykinesia prelevodopa (motor subsection of the unified Parkinson's disease rating scale[6] (UPDRS) = 44; Hoehn and Yahr stage 47), and a florid dyskinesia 30 minutes after her medication. The lowest periods of her mood coincided with the periods of choreodystonia. There was no evidence of pyramidal, cerebellar, or autonomic dysfunction.

The patient is one of 13 siblings. Two brothers and five other sisters have biochemical AIP. One brother with biochemical AIP also fulfills UK Brain Bank criteria for Parkinson's disease (three hours after levodopa of 24 motor subsection UPDRS = 24). A maternal aunt was also diagnosed as having Parkinson's disease.

Acanthocytes were absent on a blood film. Urinary organic acid, amino acid, and copper studies were normal. No basal ganglia abnormalities were found on CT and MRI and autonomic function studies were within normal limits.

Benzhexol led to a modest improvement in her tremor. After this, pergolide was slowly introduced in weekly 50 μg increments to 250 μg thrice daily. Her urinary porphyrin concentrations were monitored every 48 hours and remained undetectable. Her mobility and independence improved. Three weeks of lofepramine led to a modest improvement in her affect but the psychotic symptoms persisted. She responded well to six applications of electroconvulsive treatment (ECT) using propofol as the anaesthetic agent. Over the subsequent eight months she did not develop any symptoms suggestive of acute porphyria and her urinary porphyrins remained within the normal range. Her psychotic depression relapsed within three months despite lofepramine maintenance but she again responded to further ECT.

This patient had idiopathic Parkinson's disease in addition to biochemical AIP. The erratic and "brittle" response to levodopa treatment experienced by this patient may have been a result of porphyria modulating the expression of her parkinsonism or the therapeutic "window" for levodopa. Similarly, although porphyria may have been responsible for or have influenced the expression of her affective disorder, the visual hallucinosis and clouding of consciousness raises the possibility of diffuse Lewy body disease, or an adverse effect of her antiparkinsonian medication.

In some case reports, ECT has improved both bradykinesia and depression in patients with idiopathic Parkinson's disease,[8] and it was effective in treating our patient's depression. Her parkinsonian syndrome improved while the pergolide dose was being increased without adverse consequences, providing some evidence to support the safety of pergolide in the treatment of porphyria

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A case of Machado-Joseph disease presenting with spastic paraparesis

Machado-Joseph disease is the most common autosomal dominant spinocerebellar degeneration.[1] The pathogenic gene responsible for the disease, which was recently identified, contains an abnormal CAG expansion in the coding sequence of a novel protein, MJD1.[2] The CAG expansion is inversely correlated with the age at onset, as in other triplet diseases.[2–4] Four clinical subtypes of Machado-Joseph disease are well known.[1] Type I patients show pronounced pyramidal signs and extrapyramidal signs such as dystonia, with a relatively early onset. Type II patients have cerebellar and pyramidal signs. Type III patients present with cerebellar signs and peripheral neuropathy, with a later onset. Type IV patients develop predominantly parkinsonism with distal amyotrophy. In this report, we describe a patient with Machado-Joseph disease who presented with spastic paraparesis without dystonia or ataxia.

A 38 year old woman was admitted to our hospital complaining of gait disturbance. She began to walk at the age of 1 year and 6 months. At the age of 7 years, she attended a school for mentally handicapped children. She walked on her toes, and sometimes she felt stiffness in her legs. At the age of 27 years, she became unable to go downstairs and walk without assistance.