Mutation analysis of the glucocerebrosidase (GC) gene. Father (lane 1); mother (lane 2); patient (lane 3). Genomic DNA was isolated from leucocytes and the GC mutations were performed by restriction enzyme digestions on polymerase chain reaction amplification of genomic DNA exactly as described by Boot *et al.*¹. The upper panel shows the analysis of the L444P mutation. The control fragment is 706 bp and the mutant fragments are 536 and 170 bp (the latter is not shown). The father and the patient were heterozygous for the L444P mutation. The lower panel shows the analysis of the D409H mutation. The control fragments are 396, 156, 64, 56 and 37 bp and the mutant fragments are 396, 153, 93, and 64 bp. The mother and the patient were heterozygous for the D409H mutation.

enzyme for the mutation D409H. The figure legend describes the way each mutation altered the restriction digest pattern.

The treatment was started at the age of 27 by the cerebroside β glucosidase of placental origin alglucerase (Ceredase, Genzyme, Cambridge, MA, USA), with 60 Units/kg body weight, by intravenous perfusion every 2 weeks until the age of 31. After this period, alglucerase was replaced by the recombinant enzyme imiglucerase (Cerezyme, Genzyme, Cambridge, MA, USA) and the patient has been treated up to the present (age 34) with the same posology and an identical time interval. Thus the patient has been treated for 8 years so far.

The propositus was heterozygous for the L444P and the D409H mutations. Sequencing showed that the patient did not have other point mutations. His father carried the L444P mutation and his mother the D409H mutation (figure). Informed consent was obtained for genetic studies.

The treatment was well tolerated. No antibodies against either form of the enzyme were found. The asthenia rapidly disappeared. His spleen, still hypertrophied at the age of 28, was found to be normal (7.5 cm for the great axis) at the age of 31. The aggravation of the gait stopped. The ophtalmoplegia remained unchanged. The paroxysmic dystonic manifestations disappeared. The tremor of the head and of the arms had also decreased in intensity. During this period, the only new medications were the substitutive enzymatic therapy and carbamazepine (600 mg/day). We are aware of the fact that the prescription of carbamazepine may in itself ameliorate paroxysmic dystonic manifestations. No clastic attacks occurred after 2 years of the treatment. At the age of 34, neuropsychological evaluation was as follows: mini mental state examination score 25/30; Mattis scale for memory 23/25; Wisconsin test for verbal fluency: 2/6. Conceptualisation was correct for precise tasks. Brain MRI was still normal except for a slight cortical atrophy. There was a normal concentration of thrombocytes: 110 000/mm³ after 6 months and between 130–150 000/mm³ thereafter. Acid phosphatases tested at the age of 28 were normal (2.7 Units). The patient and his family noted a great improvement in his behaviour and dependency.

In infancy, this patient presented with the apparent type 2 acute neuronopathic form. Although death usually occurs by 2 years of age in the infantile form,⁴ this patient is still alive, and able to lead a nearly normal life with a professional activity. In type 3 Gaucher's disease, neurological signs develop between 6 and 15 years of age although there are some cases with earlier manifestations.

The number of mutations involved in Gaucher's disease is great.^{4,5} The L444P mutation is often associated with a more severe neurological manifestation. Patients carrying the L444P mutation and the D409H mutation have been reported to develop a form of type 3 Gaucher's disease in which the oculomotor signs are predominant and the visceral symptoms are discrete. This case differed significantly from these other cases.

In conclusion, the patient had a neurological form of Gaucher's disease and could be evaluated over 3 decades. Before enzyme substitutive therapy, the patient and his family reported a progressive deterioration of his neurological state. When he was treated, visceral and haematological symptomatology became normal; and there was a stabilisation or even a slight improvement of his neurological symptoms as well as modification of mood and behaviour, allowing a better integration

in social life. Thus some patients with Gaucher's disease with early neuronopathic manifestation may have a benign course and profit considerably from enzyme supplementation.

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Creutzfeldt-Jakob disease in a young person with valine homozygosity at codon 129: sporadic or variant?

To date there have been 52 reported cases of variant Creutzfeldt-Jakob disease (vCJD) in the United Kingdom. All cases that have undergone genetic investigation have been methionine homozygotes at codon 129 in the prion protein (PrP) gene. There has been speculation as to whether valine homozygosity or heterozygosity at codon 129 confers resistance to vCJD, delays clinical onset of disease,¹ or may lead to a clinical syndrome distinct from cases of CJD described so far.² Here we report on a young patient with CJD who was a valine homozygote at codon 129.

A previously well 27 year old electrical engineer complained that he had difficulty concentrating at work. His wife noticed that he had become more forgetful and increasingly agitated which she attributed to stress at work. He was seen in December 1997 and at this stage appeared anxious and with communication difficulties in that he could understand what his wife was saying to him but could not understand anyone else. Neurological examination was otherwise unremarkable. Haematology and biochemistry, a cranial CT, and an EEG were normal. He was diagnosed as having an anxiety state and referred to a psychiatrist who thought that an

organic brain syndrome was more likely. By February 1998 it was clear that he had a receptive and expressive dysphasia and right extensor plantar response. Thyroid function, B12 and folate, an autoimmune screen, protein electrophoresis, serum copper, serum caeruloplasmin, heavy metal screen, porphyrin screen, IgA antibodies to gliadin, serological tests for *Treponema* and human immunodeficiency virus tests were all normal. Protein in CSF was mildly raised at 0.62 g/l and contained 2 white cells/mm³. Oligoclonal bands and CSF 14-3-3 protein were negative. Repeat EEG demonstrated a left hemispheric slow wave focus, cranial MRI showed atrophy of the whole of the left hemisphere, and a SPECT perfusion scan demonstrated marked underperfusion of the posterior temporoparietal cortex on the left. A tonsillar biopsy for protease resistant PrP was negative. The open reading frame of the prion protein gene demonstrated no mutations. The codon 129 genotype was valine homozygous.

By October 1998 he was dependent on his wife for dressing, toileting, and feeding. He was mute with eyelid apraxia, generalised myoclonus, marked primitive reflexes with Gegenhalten tone in the limbs, and bilateral extensor plantar responses. In March 1999 he was in a state of akinetic mutism and died in August 1999. Necropsy disclosed cerebral atrophy, and neuropathological studies showed a spongiform encephalopathy which was most marked in the basal ganglia, with widespread neuronal loss and gliosis. No amyloid plaques were identified. Immunocytochemistry showed a positive reaction in a reticular and perineuronal distribution in the cerebral cortex and the cerebellum, but no PrP plaques were present. Immunocytochemistry for PrP on lymphoid tissue in the spleen and appendix was negative. Western blot analysis of frozen cerebral tissue showed a PrP^{RES} type 1 pattern.³

Early age of onset, protracted psychiatric prodrome, and duration of illness distinguish variant CJD clinically from sporadic CJD. Two possible explanations arise for the case described. Firstly, the case represents sporadic CJD, of which there have only been two cases younger than 30 in the United Kingdom since 1970.⁴ Neuropathological review of these two earlier cases has found changes in the brain consistent with sporadic CJD; full clinical and genetic data are not available on these cases, but neither showed evidence of PrP^{RES} accumulation in lymphoid tissues. The lack of characteristic neuropathology of vCJD in the brain, the absence of detectable PrP in the tonsil appendix and spleen, together with a PrP^{RES} type 1 pattern in the cerebral cortex all provide supportive evidence for this being a case of sporadic CJD, similar to the other rare cases occurring in valine homozygotes with a type 1 PrP^{RES}.³ A less likely explanation is that this case may represent bovine spongiform encephalopathy (BSE) infection in a valine homozygous person without the characteristic pattern of PrP glycosylation occurring in BSE and related disorders in animals and humans.⁵ This case emphasises the importance of detailed clinical, neuropathological, genetic, and biochemical studies in all cases of suspected CJD, particularly in young people with a valine homozygous or heterozygous codon 129 PrP genotype. Further investigation of such cases by strain typing studies may be required to establish their relation to the BSE agent.

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Multiple sclerosis treatment trial precipitates divorce

We have noted an unusually high rate of divorce among participants in a recent small treatment trial of multiple sclerosis.¹ Of the 29 patients in the study, 19 were married at entry. During the 18 months of follow up, six patients (31%) became involved in divorce proceedings. In four of these, the unaffected spouse left the marriage for another partner. There was a transient breakdown in one other marriage, which did not lead to divorce, after an extramarital affair by the unaffected partner. Since the study ended, there has been one further divorce after an affair by the unaffected spouse. Those patients who became divorced were not distinguishable by their disability, the efficacy of their treatment, or the duration of their disease or marriage.

The divorce rate in this study, equivalent to an annual rate of 21% of married couples, is considerably greater than the annual divorce rate in the United Kingdom for age and sex matched married couples of 2.4%-3.1%.² Physical disability due to any cause is a risk factor for divorce³ and multiple sclerosis is no exception.⁴ However, this effect is not sufficient explanation to account for the exceptionally high divorce rate seen during this study. In one Australian study, the most severely disabled patients with multiple sclerosis were four times more likely to have been divorced than the less disabled; but even among the most disabled the prevalence of divorce was only 13%-18% of all prevalent patients.⁵ We suggest that participation in a treatment trial indirectly precipitates divorce, by exposing marital dissatisfaction in the unaffected spouse. One possible explanation may be that trial participation focuses attention on the affected spouse's disability. Alternatively, perhaps the frequent attentions of an interested medical team during a trial relieve the unaffected partner of a sense of responsibility towards his or her spouse. Another

interpretation might be that recruitment to therapeutic trials is biased towards those patients who perceive a greater degree of dissatisfaction with their personal situation. To the best of our knowledge, in no previous treatment trial in multiple sclerosis, nor indeed of any other disease, has such a high rate of divorce been noted.

In the light of these findings it may be prudent to make patients and their spouses (or partners) aware, during the recruitment interviews for clinical trials, of the strains which participation may expose in their relationship.

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Allodynia: a sensory analogue of motor mirror neurons in a hyperaesthetic patient reporting instantaneous discomfort to another's perceived sudden minor injury?

Parietal injury may affect spatial cognition in at least three ways: right sided damage may cause left inattention (unilateral neglect), whereby the patient ignores or fails to attend to objects or events on the contralateral (left) side of extrapersonal space¹; in a rare extension of this disorder, the patient may also experience the presence (often fluctuating) of an additional, supernumerary or phantom limb²—for example, a further arm at the midline in addition to a normal one on the right, and a paralysed, neglected, or "missing" one on the left. Finally, in the Gerstmann syndrome there may be, after left parietal damage, simultaneously, left-right disorientation, acalculia, agraphia, and problems with finger (or other body part) localisation or identification. Conversely, with amputation or loss (even congenital) of a limb in an otherwise healthy individual, a phantom limb may be experienced,³ with the vivid hallucinatory experience of the continued presence of that limb; parietal mechanisms have again been invoked.

The parietal cortex interconnects with the ventral premotor cortex which, as area F5 in monkeys, contains neurons that discharge both when an animal grasps or manipulates objects, and when it sees another individual making similar actions.⁴ These "mirror neurons" seem to represent a system that matches observed events to similar, internally generated actions, and thus forms a link, as the authors note, between observer and actor.