Cerebrospinal fluid changes during treatment

	Week 0	Week 2	Week 4
CSF Protein (g/l)	0.98	0.87	0.74
CSF Leucocytes ($\times 10^9/l$)	170	94	50
CSF Lymphocytes (%)	20	50	100
CSF Neutrophils (%)	80	50	0
CSF Glucose (mmol/l)	4.6	5.1	8.0
Blood glucose (mmol/l)*	11.8	9.8	10.7

*Blood glucose measured simultaneously with CSF glucose.

teen minutes later he developed a diffuse erythematous skin rash, pyrexia of 39°C, a tender, swollen throat, and became hypotensive. The streptokinase infusion was discontinued and intravenous hydrocortisone and chlorpheniramine were administered. His symptoms settled within 24 hours. He made an uncomplicated recovery and was discharged after 5 days. Two days later he returned with a painful, swollen throat and a similar rash, which again responded to hydrocortisone and chlorpheniramine treatment. Four days later, 11 days in total after the streptokinase, he developed general malaise, an occipital headache of gradual onset, double vision, vomiting, and word finding difficulty. There was no photophobia, neck stiffness, or skin rash, but he had a pyrexia of 40°C, an abbreviated mental test score of 7 out of 10 (he failed to recall the date, current year, and prime minister), bilateral sixth nerve palsies, an indistinct left optic disc, mild dysarthria, and an expressive dysphasia. Muscle power, reflexes, and sensation were normal. Investigations included a normal brain CT, plasma glucose of 15.3 mmol/l, leucocyte count of $20.6 \times 10^9/l$ (79% neutrophils), otherwise normal routine biochemistry and haematology, electroencephalographic evidence of a diffuse encephalopathic process, and CSF values in keeping with an infective process (table, week 0). Treatment with broad spectrum intravenous antibiotics, intravenous acyclovir, and insulin was begun. Despite this he developed inappropriate behaviour, progressing to coma requiring ventilatory support. Further investigations showed negative cultures of both blood and CSF, no serological evidence of a viral infection, raised C reactive protein to 17.9 mg/l, normal autoantibody screen, normal serum angiotensin converting enzyme concentrations, no serological evidence of syphilis, no CSF oligoclonal bands, and CSF values progressing through a pleomorphic to a monomorphic state (table, week 2 and 4). A gradual recovery over 8 weeks was made and he was well enough for discharge, but he was left with disabling symptoms of urinary incontinence, depression, and cognitive dysfunction. Further outpatient investigations included brain MRI, which disclosed only a minor degree of cortical atrophy, a raised titre of GM1 antibody to 1:800 (normal 1:200), and a negative titre of GQ1b antibody.

We think that this is the first reported case of a meningoencephalitis after streptokinase treatment. Our patient experienced an immediate IgE mediated allergic reaction within minutes of streptokinase administration; 7 days later he developed a serum sickness-like allergic reaction consistent with immune complex formation and deposition between streptokinase and pre-existing antibodies to streptokinase. Although these events have been described previously in 3.5%–4.4% of patients after streptokinase, neurological dysfunction as part of an allergic reaction has not previously been reported.² Guillain-Barré syndrome occurs some 10–14 days after

streptokinase treatment; it is characterised by GM1 antibodies and is thought to be autoimmune mediated. Although our patient had strongly positive GM1 antibodies, there was no clinical evidence to support this diagnosis. GM1 antibodies have also been documented in other autoimmune conditions, such as systemic lupus erythematosus.^{3,4} Therefore, their presence in our patient suggests an autoimmune response to the streptokinase. Because our patient had no further skin rash or arthritic symptoms, and the CSF findings and clinical features were in keeping with isolated central neurological involvement the cause of the meningoencephalitis was most likely autoimmune in origin and not vasculitic. Our patient is unique in that he had all three of the reported "allergic" reactions after streptokinase therapy; immediate, serum sickness-like, and autoimmune. In future, meningoencephalitis occurring as a complication of streptokinase therapy should be borne in mind.

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Atypical course of neuropathic

Gaucher's disease: follow up from early infancy until adulthood

Gaucher's disease¹ is caused by a deficiency in glucocerebrosidase which gives rise to the accumulation of glucosylceramide (glucocerebroside) in the lysosomes of cells mainly found in the reticuloendothelial system. Type 1, the chronic adult form, is the most frequent, and characterised by splenomegaly, hepatomegaly, pancytopenia, and skeletal degeneration, but does not involve neurological manifestations. Type 2, also called acute neuronopathic, is an early infantile form, usually terminating life in 1 or 2 years. Type 3 is a chronic form which affects the nervous system, usually in late childhood or adolescence. We report here the case of a patient with Gaucher's disease who was diagnosed in early infancy (6 months) in a paediatric insti-

tution. He was followed up again between the ages of 26 and 34, a period during which he benefited from enzyme substitutive therapy.

This male patient had no familial history of Gaucher's disease. Pregnancy and birth were normal. At 6 months, he presented with dysfunction of ocular motility in the vertical gaze, oculocephalic asynergy, hepatosplenomegaly, and was found to carry Gaucher's cells in his bone marrow. Abnormal gait and pyramidal signs followed around 4 years of age. There was a macular cherry red spot. Acid phosphatases were increased at that age. Nevertheless, there were no abnormalities of stature and milestones and no cognitive dysfunction. He went to school until the age of 16.

The patient was seen at the age of 26. He had difficulties in walking which progressively worsened and falls became frequent. He could, however, walk without aid and work as a clerk. He also complained of paroxysmic dyspnoea. Neurological examination displayed a static and kinetic cerebellar syndrome associated with a tetrapyramidal syndrome. Falls were mainly due to paroxysmic dystonic movements of the legs. Attacks of dyspnoea were also concomitant with paroxysmic and abnormal contractions of the abdominal musculature which were considered of dystonic origin. The paroxysmic manifestations were not as brisk as myoclonus and were actually reinforcements of abnormal dystonic postures which could be seen in both the arms and legs. Both dystonia and cerebellar syndrome were responsible for a dysarthria. A tremor of the head and of the arms was seen. There was an oculomotor paralysis. Voluntary movements were abolished in both vertical and horizontal gaze. The oculocephalic movements were, however, preserved, although at a very low speed and low amplitude, in the horizontal movements. The abdominal echography showed the absence of hepatomegaly, but the size of the spleen was increased (18.5 cm along its major axis). There were no radiographic bone abnormalities. Bone scintigraphy was also normal. Neuropsychological testing showed the following: Binois-Pichot test for cognitive capacities 91/100; Wechsler test for memory 80/100. There was a slowness of thought, but no significant defect. Behavioural abnormalities were noted with impulsivity and aggressivity. Clastic attacks were reported by his family. Brain MRI and EEG were normal. An ECG and cardiac echography were also normal. β Glucosidase² was diminished in leucocytes (0.45 Units; normal 6.5–10.5 Units) and in cutaneous fibroblasts (23 Units; normal 80–370 Units). The haemogram was normal except for a thrombocytopenia with 71 000 cells/mm³. Acid phosphatases were increased (10.0 Units; normal 2.2–8.14 Units). Chitotriosidase when tested after 4 years of treatment, was still clearly increased (1012 Units; normal mean 20 Units).

The healthy parents, of Italian origin, were not consanguineous. They were tested for β glucosidase in leucocytes²; the concentrations were 4.1 Units for the father and 3.0 Units for the mother. The brother and sister refused testing.

Genomic DNA was analysed and partially sequenced. The patient gave informed consent according to bioethics in French Law and the Declaration of Helsinki. The presence of the L444P and D409H mutations was detected exactly as described in Boot *et al.*³ The NciI restriction enzyme was used for the mutation L444P and the Styl restriction

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.*³. 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