LETTERS TO THE EDITOR

Hashimoto's encephalopathy responding to plasmapheresis

A 47 year old man presented to the emergency department of our hospital. He was born in Uruguay, but had lived in Australia for many years and had not travelled overseas recently. He had no relevant medical history or record of illicit drug use. He had a 2 week history of a coarse, postural tremor of the upper limbs and an unsteady gait and was brought to hospital after an unwitnessed fall at home. On arrival he was alert but "irritable"; shortly thereafter he had a generalised seizure, which was treated with intravenous diazepam and phenytoin. Several hours later he had failed to regain consciousness: he was breathing spontaneously, with roving eyes, absent oculocephalic reflexes, generalised hypertonia and hyperreflexia, bilateral extensor plantar responses, was afebrile, and had no neck stiffness. He was intubated for airway management and had a normal precontrast and postcontrast cerebral CT. A lumbar puncture disclosed normal CSF pressure (15 cm H₂O), with a high protein (1.34 g/l) but normal cell count and glucose. Angiography of the vertebral system was normal. Intravenous heparin was started, and later intravenous acyclovir. After extubation, he had ongoing cognitive impairment and remained generally hyperreflexic with extensor plantar responses. His admission was characterised by a fluctuating, but slowly improving, delirium. He had short term memory deficits, visual and auditory hallucinations, and paranoid delusions. His upper limb tremor persisted and he had a second generalised seizure. His EEG was diffusely slow without epileptiform activity; this later improved. C-reactive protein was 58 mg/l but other investigations were normal or negative, including routine haematology and biochemistry, erythrocyte sedimentation rate, ANA, ANCA, HIV, and syphilis serology, carotid Doppler studies, brain MRI (precontrast and postcontrast), transoesophageal echocardiography, and CSF culture (including herpes simplex virus polymerase chain reaction). By discharge, his mental function had improved and he was taking clonazepam, phenytoin, carbamazepine, and haloperidol.

He presented again 3 weeks later with worsening generalised tremulousness. He was oriented but distractible. His CSF pressure was raised (21 cm H₂O) and protein was again high (1.06 g/l). Serum B12, folate, and TSH concentrations were normal and anticardiolipin antibodies were negative. His mental state fluctuated dramatically—from coherent, to agitated, to stuporose—often over a 24 hour period; his command of English paralleled his mental state. Despite being euthyroid, his antimicrosomal and antithyroglobulin antibody titres were markedly raised (figure, point A). A diagnosis of Hashimoto's encephalopathy was made and treatment with intravenous methylprednisolone was commenced, followed by oral prednisolone and azathioprine. His level of consciousness improved, as did his memory,

Fig. 1 Titres of antithyroid antibodies over a 6 month period. Treatment with corticosteroids and azathioprine was started at diagnosis (A). Plasmapheresis was performed at B and C.

and he was able to perform simple arithmetic. He was discharged from hospital, but 4 weeks later he had not returned to his premorbid level of functioning, with an ongoing tremor and difficulties feeding and dressing himself. Additional treatment was considered necessary, and the patient had a course of plasmapheresis (four exchanges, total 26.8 litres), with the rationale being to remove the presumed pathogenic humoral antibody. The volume of plasma exchanged per treatment was 1.5 times to twice the total plasma volume, and the number of exchanges was consistent with the treatment of other autoimmune neurological disorders.

His condition improved after the first plasma exchange, and by the end of treatment he was able to dress and feed himself and converse in English. He was able to return to part time work as a cleaner. This clinical improvement was accompanied by a further decline in antibody concentrations (figure, point B). He remained well, with slowly rising antibody titres, but when another seizure occurred plasmapheresis (three exchanges, total 21.0 litres) again resulted in a decline in antibody concentrations (figure, point C) and clinical improvement. He continued taking prednisolone and azathioprine throughout this time. He remained euthyroid and had no goitre.

The patient later had a further relapse, associated with generalised seizures. A trial of intravenous gammaglobulin was without effect and his condition again improved promptly with plasmapheresis. When last seen in the outpatient clinic he was clinically well, had no further seizures, and was taking prednisolone, azathioprine, sodium valproate, topiramate, and warfarin. He was building a barbecue at home and his wife thought he was as well as he had ever been. Two days later he was found dead at home by his wife. Initial postmortem examination failed to find a definite cause of death and further pathological investigations are proceeding.

After the initial report by Brain *et al* in 1966,¹ there have been several other individual case reports and series of patients with neurological syndromes associated with high titres of antithyroid antibodies. Our patient followed the typical course described in other cases of Hashimoto's encephalopathy, with tremor and seizures, fluctuating encephalopathy, high CSF protein, and a diffusely abnormal EEG.²⁻⁴ Although abnormalities in brain MRI have been described,^{3,5} other patients have had normal MRI,^{3,4} as did our patient. The unique feature of the present case was the patient's clinical and serological improvement with plasmapheresis, a treatment that has not been previously described in connection with this condition. The pathogenesis of Hashimoto's encephalopathy remains unclear. Several theories have been proposed, including a generalised abnormal-

ity of the immune system, cerebral vasculitis, recurrent demyelination, or a toxic effect of thyrotropin releasing hormone on the CNS.⁴ It is clear, however, that an abnormality of thyroid function itself cannot explain this condition, as many patients described in the literature are euthyroid either at the time of presentation or relapse. An autoimmune basis is suggested by the high concentrations of antithyroid antibodies and improvement with immunosuppressive therapy. The precise role of antithyroid antibodies is also unclear: if they are to be implicated as pathogenic, then it is surprising that more cases of encephalopathy are not seen in patients with Hashimoto's thyroiditis. It is possible that the antithyroid antibodies in Hashimoto's encephalopathy are a surrogate marker for other, as yet unknown, antibodies that cross the blood-brain barrier and initiate an autoimmune encephalopathy. Various immunosuppressive treatments have been used in this condition, including corticosteroids, azathioprine, cyclophosphamide, and intravenous immunoglobulin.^{2,4,5}

This patient's clinical course demonstrates that the response to corticosteroids may be incomplete and that additional clinical and serological improvement can be achieved with the use of plasmapheresis. It is unclear whether the patient's death was related to his underlying neurological condition. If it was, then it is a further indication of the unpredictable course and outcome of Hashimoto's encephalopathy.

We thank Dr R Lindeman for his assistance with plasmapheresis.

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Meningoencephalitis after streptokinase treatment

The mechanisms underlying allergic reactions to streptokinase treatment can be divided into three major groups: immediate IgE mediated (type I), immune complex deposition (type III), and antiorgan antibody mediated (type II). Apart from cerebral haemorrhage the only previously reported neurological complication of streptokinase therapy is the Guillain-Barré syndrome.¹ We present a case of meningoencephalitis after streptokinase therapy.

A 52 year old man presented with classic features of an acute anterior myocardial infarction. Treatment with oral aspirin and intravenous streptokinase was initiated. Fif-

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