LETTERS TO THE EDITOR

Encephalopathy associated with intravenous immunoglobulin treatment for Guillain-Barré syndrome

The use of intravenous infusions of immunoglobulin in the treatment of Guillain-Barré syndrome has become widespread. However, this treatment is not without morbidity. We describe an acute encephalopathy occurring in a patient receiving intravenous immunoglobulin infusions for Guillain-Barré syndrome.

A 55 year old woman was admitted with a four week history of malaise and occasional rigors and a one day history of pleuritic chest pain. She had a raised white cell count of $12.5 \times 10^9/l$, a lymphocyte count of $7.20 \times 10^9/l$, and a monocyte count of $1.32 \times 10^9/l$. Many atypical lymphocytes were seen on the blood film. Liver enzymes (IU/l) were slightly raised (aspartate transaminase 81, normal 10-34; alanine transaminase 135, normal 7-33; γ -glutamyl transpeptidase 90; normal 7-49). A chest radiograph and abdominal ultrasound were normal. Five days after admission the patient complained of low back pain and three days later she developed progressive weakness of her limbs and tingling in her hands. There was a right sided facial weakness, moderate limb weakness, and a slight reduction in proprioception in the feet but no other sensory loss. Deep tendon reflexes were absent and plantar responses were flexor. Cerebrospinal fluid contained 2 white cells/mm³ and had a protein content of 1.2 g/l. A diagnosis of Guillain-Barré syndrome was made. Electrophysiological examination confirmed a sensorimotor neuropathy with slowing of motor and sensory conduction.

Weakness progressed over the next 24 hours and she became unable to stand. A five day course of intravenous immunoglobulin at 0.4 g/kg per day was started. The patient's weight was estimated at 55 kg and intravenous immunoglobulin (Venoglobulin, Alpha Therapeutic UK Ltd) was given at a dose of 22 g/day.

At the end of the first day of immunoglobulin infusion the patient complained of the development of visual loss over 30 minutes. She reported that she could see only shadows. On examination she was unable to count fingers but could perceive movement. Neurological examination was otherwise unchanged, in particular fundoscopy and pupil reactions were normal. Pulse, blood pressure, arterial blood gases, urea, electrolytes, and blood glucose were also normal. Serum total protein concentration was 83 g/l with an albumin content of 41 g/l and globulin content of 42 g/l. The erythrocyte sedimentation rate was 52 mm in the first hour. Haemoglobin was normal but lymphocytosis persisted (total white cell count $8.5 \times 10^9/l$, 55% lymphocytes) and the platelet count was slightly increased ($568 \times 10^9/l$). No visual evoked potentials could be obtained, with either pattern reversal or flash stimuli. The next day immunoglobulin infu-

sion was continued. In the evening the patient became confused and disoriented. She was able to see movement only in the left visual field. A few hours later she had two generalised tonic clonic seizures a few minutes apart. She was cyanosed during these attacks, but recovered rapidly and subsequently maintained normal arterial blood gases on air. Brain CT was normal. Infusion of immunoglobulin was stopped and an intravenous loading dose of phenytoin (750 mg) and dexamethasone (4 mg six hourly) was given. An EEG recorded several hours after the convulsions showed widespread, symmetric slow wave activity.

The next day the patient was alert and oriented and the following day her vision had recovered almost to normal. Brain MRI performed two days after the immunoglobulin infusions were discontinued showed only a small area of increased signal in the white matter of the left occipital lobe on T2 weighted images. Recovery began a few days later. A second EEG recorded 18 days after the first was essentially normal.

The cause of the encephalopathy in this case is uncertain. No episode of hypotension was recorded nor any period of respiratory failure. No metabolic cause was identified. It is difficult to be certain whether the unidentified infection assumed to have caused the Guillain-Barré syndrome also caused the encephalopathy or whether the intravenous immunoglobulin was responsible. A postinfectious encephalitis could have developed in addition to Guillain-Barré syndrome, and postinfectious encephalitis may respond rapidly to steroids, particularly in children.^{1,2} However, recovery began almost immediately after the immunoglobulin infusion was discontinued and MRI two days later showed little abnormality.²

If the intravenous immunoglobulin was the cause of the encephalopathy, one possible mechanism is a transient hyperviscosity syndrome associated with rapid intravenous infusion of large doses of immunoglobulin.³ Reported neurological manifestations in patients with a hyperviscosity syndrome secondary to Waldenström's macroglobulinaemia include hemianopsia, confusion, and convulsions.^{6,7} Vasospasm is another explanation, suggested in a recent report of a patient who developed a similar reversible encephalopathy during intravenous immunoglobulin treatment for Guillain-Barré syndrome. Transcranial ultrasound showed increased flow rates in the middle cerebral and basilar arteries, which returned to normal as the patient recovered.⁷ There are two published cases of cerebral infarction associated with immunoglobulin infusion,^{8,9} but frank infarction did not occur in the patient reported here. The manufacturers of the preparation received by our patient are not aware of any case of encephalopathy developing in a patient given this preparation. The committee on safety of medicines, however, has received three reports of convulsions and one of an encephalopathy associated with immunoglobulin usage (Committee on Safety of Medicines, personal communication).

We suggest that a reversible encephalopathy may be a rare side effect of intravenous immunoglobulin treatment.

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- 1 Pasternak JF, De Vivo DC, Prensky AL. Steroid-responsive encephalomyelitis in childhood. *Neurology* 1980;30:481-6.
- 2 Dunn V, Bale JF, Zimmermann RA, Perdue Z, Bell WE. MRI in children with post-infectious encephalomyelitis. *Magnetic Resonance Imaging* 1986;4:25-32.
- 3 Dalakas MC. High-dose intravenous immunoglobulin and serum viscosity: risk of precipitating thromboembolic events. *Neurology* 1994;44:223-6.
- 4 Wuhrmann F. Über das Coma paraproteinaemicum bei Myelomen und Makroglobulinämien. *Schweiz med Wochenschrift* 1956;86:623-5.
- 5 Logothetis J, Siverstein P, Coe J. Neurologic aspects of Waldenström's macroglobulinaemia. *Arch Neurol* 1960;5:564-73.
- 6 Cohen Capt RJ, Bohannon RA, Wallerstein RO. Waldenström's macroglobulinaemia. A study of 10 cases. *Am J Med* 1966;41:274-8.
- 7 Voltz R, van Rosen F, Yousry T, Beck J, Hohlfeld R. Reversible encephalopathy with cerebral vasospasm in a patient with Guillain-Barré syndrome treated with intravenous immunoglobulin. *J Neurol* 1995 (suppl 2):S92.
- 8 Silbert PL, Knezevic WV, Bridge DT. Cerebral infarction complicating intravenous immunoglobulin therapy for polyneuritis cranialis. *Neurology* 1992;42:257-8.
- 9 Steg RE, Lefkowitz DM. Cerebral infarction following intravenous immunoglobulin therapy for myasthenia gravis. *Neurology* 1994; 44:1180-1.

Coexistence of type I familial amyloid polyneuropathy and spinocerebellar ataxia type 1. Clinical and genetic studies of a Japanese family

Type I familial amyloid polyneuropathy (FAP) is the most common form of hereditary generalised amyloidosis with an autosomal dominant pattern of inheritance.¹ A variant transthyretin (TTR) with a single substitution of a methionine residue for valine at position 30 (Met 30TTR) is a serum amyloid precursor, and this variant protein is produced by one base change in the TTR gene located on chromosome 18.² Spinocerebellar ataxia type 1 (SCA-1) is also an autosomal dominant neurological disorder showing symptoms and signs of progressive degeneration of the cerebellum, brainstem, and spinal cord.³ A recent study has shown that the expansion of a CAG trinucleotide repeat on chromosome 6 is responsible for the development of SCA-1.⁴ We described this unusual type I FAP family with CNS dysfunction elsewhere,¹ but the pathogenesis of the CNS disorder in this kindred was not clear. We present here clinical and molecular biological evidence that type I FAP and SCA-1 coexist in this family and that some of its members are affected by both diseases.

At this time 14 members spanning three generations have undergone clinical examinations (figure). The neurological manifestations are summarised in the table. Briefly, five showed clinical features of type I FAP with histological evidence of amyloid deposition and six had CNS dysfunctions, such as cerebellar ataxia and pyramidal tract signs. Of these six patients, two (II-5 and III-2) had only slowly progressive unsteady gait and dysarthria which started in their late 50s. One (III-4) experienced occasional instability after abrupt standing or turning. The other three (III-1, III-6, and III-7) showed symptoms of both type I FAP and CNS dysfunction. Among these three the representative patient, III-7, showed dysarthria, ataxic gait, and hyperreflexia of all the limbs at the age of 40. Subsequently, dysaesthesia in the legs and bowel dysfunction developed.

Family pedigree and results of gene analyses. The number of some unexamined family members is shown in ($\diamond$). Although several family members have been added, this family pedigree originally is the same as that of family K in the previous report.¹ ■: showing both type I FAP and SCA-1 symptoms; ▨: showing type I FAP symptoms; ▩: showing SCA-1 symptoms; ◐: said to have both type I FAP and SCA-1 symptoms; ◑: said to have SCA-1 symptoms. DNA testing of an individual, III-5, indicated by ($\diamond$) shows no abnormalities for the SCA-1 or TTR gene. It is apparent that patient III-7 with type I FAP symptoms and CNS dysfunction had a mutated TTR gene and an SCA-1 candidate gene.

Finally, he required a wheelchair due to worsened ataxic gait, and also had polyneuropathy with various autonomic symptoms. He died at the age of 51. The remaining six members (III-5, IV-1, IV-4, IV-5, IV-6, and IV-7) had no symptoms or signs suggestive of type I FAP or a CNS disorder.

Informed consent was obtained from all the members before testing. Genomic DNA was isolated from peripheral blood leucocytes collected from 12 of the 14 family members examined, using standard procedures. The polymerase chain reaction

(PCR) for allele-specific enzymatic amplification of genomic DNA was used. For the Met 30 TTR gene abnormality, a 368 base pair subsequence of the TTR gene, including exon 2, was amplified using two kinds of oligonucleotide primers as described previously.⁵ The amplified DNA was digested with endonuclease Bal I (TaKaRa Shuzo Co Ltd), and the resulting DNA fragments were electrophoresed through a 3% Nusieve 3:1 agarose gel (FMC BioProducts). To investigate the SCA-1 candidate alleles, we analysed the size of the PCR amplified frag-

ments: PCR reactions were performed with one pair of primers (CAG-a/CAG-b) as reported by Orr *et al*, under the modified conditions of their method.⁴ The PCR products were run on 3% Nusieve 3:1 agarose gels, and allele sizes were determined by comparing the migration relative to a 1 kb DNA Ladder (Gibco BRL, Life Technologies, Inc). Furthermore, the amplified fragments were subcloned to pCR vectors with a TA cloning system (Invitrogen Co, San Diego, CA). DNA was sequenced with an ABI 373A DNA sequencer (Applied Biosystems, Inc) using the dideoxy-termination method.

On restriction fragment length polymorphism analysis of the TTR gene, the DNA derived from patients III-7, III-8, and IV-2 showed two extra bands, a G $\rightarrow$ A transversion in the first base of codon 30, indicating a methionine for valine substitution at the protein level (figure).⁵ In all the members tested, the SCA-1 gene region was successfully amplified by PCR. The samples obtained from four patients (II-5, III-2, III-4, and III-7) and an asymptomatic family member (IV-6) showed expanded PCR fragments as well as fragments with normal lengths (figure). DNA sequencing of the PCR products in patient III-7 showed that one normal allele contained 27 CAG repeat units, whereas an abnormal one contained 47 (data not shown).

The peripheral somatic and autonomic nerve disorders seen in our patients satisfy the criteria for type I FAP. The most remarkable feature of the present family with this disease is the involvement of the CNS associated with cerebellar signs of dysarthria, incoordination of the limbs, ataxic gait, and pyramidal tract signs. In type I FAP, amyloid deposition in the CNS is usually restricted to the leptomeningeal vessels and pia-arachnoid membranes, sparing the brain and spinal cord parenchyma. As some members of this kindred had only a CNS disorder, the possibility that type I FAP and hereditary spinocerebellar degeneration coexist has been considered.¹ The results of our present study clearly support this hypothesis and show that the CNS disorder in the members of this family is SCA-1, a form of hereditary spinocerebellar degeneration. There were neither clinical nor genetic findings suggestive of the cosegregation of type I FAP and SCA-1 in this kindred; therefore, patients III-1, III-6, and III-7 are considered to have inherited the two diseases independently. SCA-1 is a unique type of dominantly inherited spinocerebellar ataxia which often shows oculomotor paresis, amyotrophy, extrapyramidal signs, and mild dementia. The clinical phenotype of this disease, however, seems to vary among families.³ In our patient III-7 with a double gene mutation for type I FAP and SCA-1, severe manifestation of type I FAP overshadowed the signs and symptoms of SCA-1 at the advanced stage. The other three patients (II-5, III-2, and III-4) with a single gene abnormality for SCA-1 lacked the clinical characteristics of this disease mentioned above. The diagnosis of SCA-1 for our patients, therefore, could only be made by direct detection of the mutation.

We thank Dr H Sasaki of Hokkaido University School of Medicine for his excellent comments on our study.

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Clinical summaries

Patient	II-5	III-1	III-2	III-4	III-6	III-7	III-8	IV-2
Age	67	55	65	58	51	51	52	39
Duration of illness (y)	10	17	12	unclear	11	11	12	10
	alive	dead	alive	alive	dead	dead	dead	alive
Type I FAP signs:								
Polyneuropathy	-	+	-	-	+	+	+	+
Autonomic failure	-	+	-	-	+	+	+	+
Cardiopathy	-	+	-	-	+	+	+	+
Nephropathy	-	+	-	-	+	-	-	+
SCA-1 signs:								
Dysarthria	+	-	+	+	+	+	-	-
Limb dysmetria	+	+	+	+	+	+	-	-
Gait ataxia	+	+	+	-	+	+	-	-
Hyperreflexia	+	+	+	+	+	+	+	-
Babinski sign	+	+	-	+	+	+	-	-

DNA analyses were not done on patients III-1 and III-6.

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- Ikeda S, Hanyu N, Hongo M, *et al.* Hereditary generalised amyloidosis with polyneuropathy. Clinicopathological study of 65 Japanese patients. *Brain* 1987;110:315–37.
- Sasaki H, Sakaki Y, Matsuo H, *et al.* Diagnosis of familial amyloidotic polyneuropathy by recombinant DNA technique. *Biochem Biophys Res Commun* 1984;125:636–42.
- Zoghbi HY, Pollack MS, Lyons LA, *et al.* Spinocerebellar ataxia: variable age of onset and linkage to human leukocyte antigen in a large kindred. *Ann Neurol* 1988;23:580–4.
- Orr HT, Chung M-Y, Banfi S, *et al.* Expansion of an unstable trinucleotide CAG repeat in spinocerebellar ataxia type 1. *Nature Genet* 1993;4:221–6.
- Nakazato M, Ikeda S, Shiomi K, *et al.* Identification of a novel transthyretin variant (Val¹⁰ → Leu) associated with familial amyloidotic polyneuropathy. *FEBS Lett* 1992;306:206–8.

Debrisoquine hydroxylase polymorphism in Leber's hereditary optic neuropathy

Leber's hereditary optic neuropathy (LHON) causes severe visual loss, most commonly in young men. The primary genetic defect is a mutation in mitochondrial DNA (mtDNA) at positions 11 778, 14 484, or 3460 base pairs (bp) in nearly all families in the United Kingdom.¹ However, in most cases, both patients and their unaffected relatives from families with LHON have very high amounts of mutant mtDNA (> 95%); other factors must therefore determine the development of visual failure. A number of findings suggest that there may be an environmental precipitant to the development of LHON. Firstly, there is no evidence of correlation between age of onset in index cases and affected siblings in families with LHON.¹ Secondly, some reports have suggested that the proportion of patients with LHON who drink alcohol and who smoke is unusually high; this is particularly pronounced in those patients with the 3460 and 14 484 bp mutations.² Thirdly, other case reports have postulated that LHON can be triggered by various metabolic and toxic precipitants, including diabetes, B12 deficiency, and exposure to toxins.

Cytochrome P-450 mono-oxygenases metabolise several endogenous compounds and environmental chemicals and individual variations in cytochrome P-450 expression might, therefore, influence susceptibility to LHON. Impaired debrisoquine metabolism is found in 5–10% of the white population. It is an autosomal recessive trait caused by mutations in the *CYP2D6* gene, which determines cytochrome P-450 activity in the liver and other tissues. Genotypic analyses have been used to identify a G to A transition at the intron 3/exon 4 junction (allele B), a base pair deletion in exon 5 (allele A), and (rarely) a deletion of the entire gene, which collectively account for 90% of poor metabolisers who are either homozygous for one or compound heterozygotes for two of

Distribution of *CYP2D6* alleles and genotypes in patients with LHON and controls

	LHON	Controls
Allele:	No of chromosomes	
Wild type (W)	70	226
G → A transition (B)	29	62
Base pair deletion (A)	3	2
Total	102	290
χ^2 (B v W)	2.06 (P > 0.10)	
Genotype*:	No of subjects	
WW/WW	24	96
AW/WW	3	2
WW/BW	19	32
WW/BB (PMs)	5	15
Total	51	145
%PMs	9.8	10.0
χ^2 (PMs v not)	0.012 (P > 0.50)	

*For example, AW/WW is heterozygous for the mutant A allele and homozygous normal (W = wild type) for the B allele. PM = poor metaboliser.

these mutations. Reports on the incidence of poor metabolisers in Parkinson's disease using pharmacokinetic assays have provided conflicting results, but genotypic analyses have found an excess of poor metaboliser genotypes.³

We investigated the frequency of these alleles in index cases of 51 families with LHON. Forty two had the 11 778 bp, four the 3460 bp, and five the 14 484 bp mutation; 32 were male, and 19 were female. Control blood samples were from 145 unrelated healthy subjects of similar ethnic and geographical backgrounds. Controls were only roughly matched for age and sex because these do not influence the distribution of *CYP2D6* genotypes. DNA was prepared from leucocytes by standard methods. The *CYP2D6* G to A transition and base pair deletion were analysed in two separate polymerase chain reactions using, respectively, oligonucleotide primer pairs C + D and E + F as previously described.³ Genotypes and allele frequencies in patients and controls were compared by χ^2 analysis with Yates' correction for 2 × 2 tables.

There was no excess of mutant *CYP2D6* alleles in unrelated LHON index patients compared with unrelated controls; nor was there an excess of poor metabolisers (table). It is therefore unlikely that impaired debrisoquine metabolism is responsible for the development of LHON in patients with a pathogenic mtDNA mutation. Apart from exposure to or impaired metabolism of environmental toxins, there are other possible explanations for the development of blindness in LHON. Firstly, the excess of affected males has led to suggestions that an X linked visual loss susceptibility locus may be involved.⁴ Secondly, some features of LHON are surprising for a genetic condition and an autoimmune component has been suggested. This is supported by the finding that, in rodents, mtDNA encoded peptides can act as transplantation antigens.⁵

We thank the Medical Research Council and the Deutsche Forschungsgemeinschaft for financial support.

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- Harding AE, Sweeney MG, Govan GG, Riordan-Eva P. Pedigree analysis in Leber's

hereditary optic neuropathy families with a pathogenic mtDNA mutation. *Am J Hum Genet* 1995;57:77–86.

- Riordan-Eva P, Sanders MD, Govan GG, Sweeney MG, Da Costa J, Harding AE. The clinical features of Leber's hereditary optic neuropathy defined by the presence of a pathogenic mitochondrial DNA mutation. *Brain* 1995;118:319–37.
- Smith CAD, Gough AC, Leigh PN, *et al.* Debrisoquine hydroxylase polymorphism and susceptibility to Parkinson's disease. *Lancet* 1992;339:1375–7.
- Bu X, Rotter JL. X chromosome-linked and mitochondrial gene control of Leber hereditary optic neuropathy: evidence from segregation analysis for dependence on X chromosome inactivation. *Proc Natl Acad Sci USA* 1991;88:8198–202.
- Loveland BE, Wang CR, Yonekawa H, Hermel E, Fischer-Lindahl K. Maternally transmitted histocompatibility antigen of mice: a hydrophobic peptide of a mitochondrially encoded protein. *Cell* 1990;60:971–80.

Pure sensory stroke caused by cortical infarction associated with the secondary somatosensory area

Pure sensory stroke, described as a distinct clinical entity in 1965 by Fisher,¹ denotes a hemisensory disturbance without other neurological deficits. Although pure sensory stroke is usually due to a thalamic lesion, it could be also caused by lesions involving any portion of the common human sensory pathway from the postcentral gyrus, known as the primary sensory area (SI), to the medulla.² We report a patient with pure sensory stroke resulting from a cortical infarction on the inner bank of the parietal operculum, which is known as the secondary somatosensory area (SII).

A 44 year old, right handed man with a history of cigarette smoking was admitted because of sudden decrease of touch and pain sensation in his right hemibody. On admission, neurological examination disclosed normal motor function and reflexes. There was a moderate hypaesthesia for light touch, pain, and temperature senses on the right side including the face, oral cavity, arm, trunk, and leg. Discriminative touch, joint, and vibration sensation as well as stereognosis and graphaesthesia were preserved on the right side. Cranial nerve functions including taste sense were also within normal limits. There were no neuropsychological signs such as aphasia, impairment of calculating ability, or disturbance of right-left discrimination. Magnetic resonance imaging taken four days after the onset showed a cortical infarction located within the inner bank of the left parietal operculum (figure). The common sensory pathway from the postcentral gyrus to the medulla, especially the thalamus, was normal on MRI. Results of routine laboratory examinations and vasculitis screening were unremarkable. A chest radiograph, ECG, echocardiogram, and carotid Doppler ultrasound examination were normal. Short latency somatosensory evoked potentials produced by stimulation of the median nerve were evaluated seven days after the onset. Both the latency and amplitude of any points including N20 were almost equal on both sides. The central conduction time (N13 to N20) had also no laterality. Cerebral angiograms, including the left middle cerebral artery, taken on day 20 showed no abnormality. At discharge, 27 days after the onset, a slight decrease in pain and touch sensation persisted in his right side.