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 × 10⁹/l, a lymphocyte count of 7.20 × 10⁹/l, and a monocyte count of 1.32 × 10⁹/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-glutaryl transpeptidase 90; normal). 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 back. There was a slight 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. In 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. Electromyography showed 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 (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 and that 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 × 10⁹/l, 55% lymphocytes) and the platelet count was slightly increased (568 × 10⁹/l). No visual evoked potentials could be obtained, with either pattern reversal or flash stimuli. The next day immunoglobulin infusion was continued. In the evening the patient became confused and disorientated. She was able to see 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 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 returned 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. The patient had hypertension recorded on her toes and no 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 change.

If the intravenous immunoglobulin was the cause of the encephalopathy, one possible mechanism is a transient hyperviscosity syndrome. In one case, an intravenous infusion of large doses of immunoglobulin was reported.3 Neurological manifestations in patients with a hyperviscosity syndrome secondary to Waldenstrom’s macroglobulinaemia include neuroaxial inflammation and convulsions.4,5 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.6 There are two published cases of cerebral vasospasm associated with immunoglobulin infusion,7,8 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 use (Committee on Safety of Medicines, personal communication).

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

K HARKNESS
S T HOWELL
G A B DAVIES-JONES
Department of Neurology,
Royal Hallamshire Hospital,
Glossop Road, Sheffield, S10 2JF, UK

Correspondence to: Dr Howell.

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 polyneuropathy in humans. The disorder has an autosomal dominant pattern of inheritance.1 A variant transthyretin (TTR) with a single substitution of a methione 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 Spino-cerebellar ataxia type 1 (SCA-1) is also an autosomal dominant neurological disorder showing symptoms and signs of degeneration of the cerebellum, brainstem, and spinal cord.3 A recent study has shown that the expansion of a CAG trinucleotide repeat on chromosome 6p is responsible for the development of SCA-1.4 We described this unusual type I FAP family with CNS dysfunction elsewhere,5 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 examination (figure). The neurological manifestations are summarised in the table. Briefly, five showed clinical features of type I FAP with histological evidence of deposition and six had CNS dysfunctions, such as cerebellar ataxia and pyramidal tract signs. Of these six patients, two (II-5 and II-2) had only slowly progressive unsteady gait and dysarthria without any evidence of dysautonomia. One (III-4) experienced occasional instability after abrupt standing or turning. The other three (III-1, III-6, and III-7) showed reversal of both type 1 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.
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 of the members before testing. Genomic DNA was isolated from peripheral blood leukocytes 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. 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 fragments: 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. 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→A transversion in the first base of codon 30, indicating a methionine for valine substitution at the protein level (figure). In all the members tested, the SCA-1 gene region was successfully amplified by PCR. The samples obtained from four patients (II-5, II-7, 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, atactic 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.

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. 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, ataxia, extrapyramidal signs, and mild dementia. The clinical phenotype of this disease, however, seems to vary among families. In our patient, we found 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.

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SHU-ICHI IKEDA
NOBUO YANAGISAWA,
Department of Medicine (Neurology), Shinshu University School of Medicine
Matsumoto 390, Japan
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) in the tRNA(Ser) portion 11778 (A to G), or 3460 base pairs (bp) in nearly all families in the United Kingdom. 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 component 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. 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. Other 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 may influence susceptibility to LHON. Impaired expression of cytochrome P-450 2D6 metabolite is found in 5-10% of the white population. It is an autosomal recessive trait caused by mutations in the CYPD26 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 (alleles 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 these mutations. Reports on the incidence of poor metabolisers in Parkinson’s disease using pharmacokinetic assays have provided conflicting results: patients with known mutations have found an excess of poor metaboliser genotypes.

We investigated the frequency of these alleles in index cases of 51 families with LHON. Forty patients by leucocytes by standard method. The CYPD26 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. Genotypes and allele frequencies in patients and controls were compared by \( \chi^2 \) analysis with Yates’ correction for 2 × 2 tables.

There was no excess of mutant CYPD26 alleles in index cases of LHON families 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 increased risk 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. 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.

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R M CHALMERS
O BANDMANN
E HARDING
University Department of Clinical Neurology (Neuromuscular Section), Institute of Neurology, Queen Square, London, UK

Correspondence to: Dr RM Chalmers, University Department of Clinical Neurology, Institute of Neurology, Queen Square, London WC1N 3BG, UK.


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, denotes a homisensory disturbance without other neuro- logical deficits. Although pure sensory stroke usually due to the carotid territory, 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 cortex, to the thalamus and mediulla. 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.

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 hypeaesthesia for light touch, pain, and temperature senses on the contralateral face, trunk, and limbs. Discriminative touch, joint, and vibration sensation as well as stereognosis and graphesthesia were preserved on the right side. Cranial nerve function, including taste sensation, was within the 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 several 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 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.

S Ikeda, N Yanagisawa, N Hanyu, K Furihata and T Kobayashi

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