The use of botulinum toxin to treat "striatal" toes

Botulinum toxin is well accepted as a powerful tool to treat strabismus, focal dystonia, and hemifacial spasm.¹ As a peripheral symptomatic treatment, it can be used to alleviate common extrapyramidal signs that are usually resistant to anti-parkinsonian medications.^{2,3} We have recently used botulinum toxin in three patients with dystonic up-going toe in Parkinson's disease or generalised dystonia. All three patients showed pronounced improvement.

Two patients, 60 and 63 years old, with idiopathic Parkinson's disease, who had been taking levodopa for 12 and 15 years experienced moderate dyskinesias as well as foot dystonia. The most pronounced symptom of the foot dystonia was a disabling spontaneous up-going toe that affected their gait and caused pain. The toes were extended spontaneously during "off" as well as "on" periods and were unresponsive to medical treatment.

The third patient was a 21-year-old woman with generalised dystonia that affected both arms and the right foot. An up-going toe was one of her most disturbing symptoms. Trihexyphenidyl (Artane; 25 mg/day) together with clonazepam (3 mg/day) gave her some relief, but had no effect on the toe. The extensor hallucis longus muscle of all three patients was injected with 50–70 u botulinum toxin type A (Botox®, Allergan, Irvine, CA, USA) with 80% to 90% subjective and objective improvement. The toes no longer extended spontaneously; moderate weakness of the extensor hallucis longus muscle was seen, but gait was unaffected.

Spontaneous extension of the toe is a very common and annoying symptom experienced by many patients with pyramidal as well as extrapyramidal disorders. It is highly resistant to drugs and until recently we could only offer soft or open shoes. Botulinum toxin is a well accepted treatment for focal dystonia⁴ but it has never been reported as an alternative treatment for spontaneous extension of the toe.

We highly recommend the use of botulinum toxin as a simple and effective symptomatic treatment for dystonic toe extension.

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Direct evidence for limited clonality of antibodies to glutamic acid decarboxylase (GAD) in stiff man syndrome using baculovirus expressed GAD

Stiff man syndrome is a rare disorder of the CNS characterised by rigidity of the body musculature probably as a result of an

Figure (A) ELISA plates were coated with cytosolic extracts (at about 1 µg/ml total protein) from Sf9 cells infected with either recombinant baculovirus (GAD) or wild-type virus negative control ("wt control"), reacted with serum from the stiff man patients (diluted 1/100) and the bound anti-GAD antibodies detected with mouse monoclonal antibodies (anti-γ (HP-6017), anti-μ (MB-11), anti-κ (KP-53), or anti-λ (HP-6054); all from Sigma) followed by alkaline phosphatase-conjugated goat anti-mouse IgG (Sigma). (B) ELISA plates were coated directly with serum from the patients with stiff man syndrome (diluted 1/50 000) and reacted with the monoclonal antibodies followed by the conjugate as in the top panel.

impairment in γ-aminobutyric acid (GABA)-ergic transmission. Glutamic acid decarboxylase (GAD), the rate-limiting enzyme in the synthesis of GABA, has been described in a number of molecular sizes and forms.¹ Since its molecular cloning there is general acceptance that there are two separate genes encoding two isoforms (molecular weights 65 000 and 67 000). The association of stiff man syndrome with insulin-dependent diabetes mellitus suggests an autoimmune aetiology² and antibodies to GAD are found in up to 60% of patients with the syndrome.² The presence of increased concentrations of IgG within the CSF and an oligoclonal pattern of CSF IgG on isoelectric focusing are regarded as supporting this hypothesis. Just as in multiple sclerosis or its animal model experimental allergic encephalitis,³ however, there is little evidence that these oligoclonal IgGs are directed against pathologically important CNS antigens. We present here direct evidence for antibody production of limited clonality against the large isoform of human GAD (termed GAD₆₇) in two patients with stiff man syndrome.

Clinical details of both patients have been given previously.⁴ Patient 1 has stiff man syndrome, diabetes mellitus, and pernicious anaemia and patient 2 has stiff man syndrome only. Serum from each of these patients was obtained by plasma exchange.⁴ Both were used in the studies of Solimena *et al.*⁵ and are positive for anti-GAD activity by immunocytochemistry, but negative by immunoblotting, suggesting that their autoantibodies react only with native GAD. Human GAD₆₇ was cloned from a brain cDNA library as previously described,^{6,7} and recombinant baculovirus was used to express the protein in Sf9 insect cells. The

product was recognised by standard antibodies against GAD₆₇ and was also immunoprecipitated by serum samples from the two patients (data not shown). The availability of this recombinant material allowed the development of a facile quantitative immunoassay for detecting and characterising autoantibodies against native GAD₆₇. In this report, we have used this assay to characterise the type of light chain of these autoantibodies.

Enzyme linked immunosorbent assay (ELISA) plates were coated with this recombinant material and used to analyse the class and light chain type of the GAD antibodies in serum from the two patients (figure, top panel).

IgG anti-GAD antibodies were clearly detected in both patients, although patient 1 had more; the possibility of IgM antibodies was also suggested but not certain. The anti-GAD antibodies all contained κ light chains, however, and no antibodies with λ chains were detectable. To confirm that the assay conditions used would detect each of the individual immunoglobulin chains with similar sensitivity, the ELISA was repeated without any recombinant protein but using instead serum from the two patients coated directly on to the plates (figure, B). This showed that the assay was in fact somewhat more sensitive for λ than for κ chains and more sensitive for IgM than for IgG. Our data, therefore, provide direct evidence for a clonally restricted response to GAD in stiff man syndrome and support the autoimmune hypothesis of its aetiology.

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Non-ischaemic causes of transient ischaemic attacks and minor strokes

The indications for a CT scan in patients with transient ischaemic attacks or minor strokes are still debated.¹