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-ischæmic 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

A recent report from the UK-TIA Study Group² presented 11 cases of intracranial tumours among 2449 patients with transient ischaemic attacks or minor strokes. Occasional cases of small cerebral haematomas have been found in patients with minor strokes,³ but only exceptionally in patients with transient ischaemic attacks.⁴ In a CT scan study of 284 cases with transient ischaemic attacks⁵ five patients had a mass lesion; none a brain haematoma.

We present the results of a prospective CT scan study of 175 patients (63 with transient ischaemic attacks and 112 with minor deficits lasting longer than 24 hours) recruited in the emergency rooms of two general hospitals. In every case, the CT scan (CX Tomoscan, Philips) was performed within the first week of the clinical event (with a mean delay of 13 (SD 24) hours). The mean age of the patients was 68 (8.5) years; 132 events were located in the carotid artery territory, 38 in the vertebrobasilar territory and five were of uncertain location. The CT scan was normal in 114 patients. Low density areas compatible with infarction were present in 56. Non-ischaemic causes of the presenting symptoms were found in three minor cases of stroke—namely, a brain tumour, compatible with an extensive hemispheric malignant glioma by MRI and biopsy features; a small occipital haematoma; and a medium sized basal ganglia haematoma (associated with an ipsilateral subdural haematoma). All three patients were over 60 and had at least one vascular risk factor. In one of the cases of transient ischaemic attack a mass located on the clivus (compatible by CT features with a meningioma) was considered to have caused cerebral symptoms through compression of the basilar artery. Also aetiologically related to the symptoms could have been a minor stroke case with a thrombosed middle cerebral artery bifurcation aneurysm, demonstrated by MRI angiography.

The number of cases in our study is insufficient to support definite conclusions. The yield of CT scan for the detection of non-ischaemic causes (such as cerebral and subdural haematoma and brain tumour) in minor strokes (cases with symptoms lasting longer than 24 hours) was 2.7% (95% CI 0 to 5.7) and in transient ischaemic attacks the yield was 1.6% (95% CI 0 to 4.7).

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Sumatriptan and giant cell arteritis

We have proposed a *unified theory* that suggests that migraine is essentially driven from the central nervous system and entrains the trigeminal innervation of the cranial vessels to form one of the clinical expressions of the disease.¹ The introduction into clinical practice of the novel antimigraine compound sumatriptan, a serotonin (5-HT) agonist, has provided a tool to understand further the underlying mechanisms of the disease. Its action as a vasoconstrictor and its inhibition of neurogenic inflammation in experimental animals has been cited by various groups as evidence for either the vascular or neurogenic inflammatory theories of migraine respectively. A patient was recently admitted to our institution with giant cell arteritis and headache not responsive to sumatriptan. Her lack of response casts some doubt on the neurogenic inflammatory theory of migraine.

The patient is a 68 year old woman who had a 10 day history of right sided temporal and frontal headache. The headache had spread from a small region above the eye to involve most of the right side of the head and she had noticed some increasing tenderness of the scalp muscles. The headache became more severe with time and had some pounding exacerbations but no associated features of migraine. Eight days into the illness she attended her general practitioner and was given sumatriptan (100 mg) orally as a single dose, which did not alter the headache. She had no other history, particularly of regular headaches, and there was no relevant family history. Physical examination was unremarkable except for tenderness of the temporal arteries bilaterally. The erythrocyte sedimentation rate (ESR) at this time was 110 mm/h. She was treated with high dose steroids with complete remission of the headache and general malaise and a drop in the ESR by the next day. A temporal artery biopsy showed pronounced inflammatory changes.

The patient had a classical presentation of temporal arteritis that responded to steroids and she has remained well on steroids. She had no response to sumatriptan despite some side effects from the drug, notably nausea and mild neck and arm discomfort typical of that reported in trials.² Practitioners should be watchful for secondary headache and in the elderly temporal arteritis must **always** be considered. Administration of a cranial vasoconstrictor to patients with inflamed narrowed vessels with the propensity to thrombose must be avoided absolutely. Sumatriptan is not a bedside test for migraine; it must not replace the careful history and should only be given to patients with a positive diagnosis in appropriate circumstances.

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Isolated lingual myoclonus associated with an Arnold-Chiari malformation

Reports on isolated rhythmic tongue movements are infrequent and may contribute to the understanding of rhythmic hyperkinesias in general. Isolated rhythmic movements of the tongue led to the diagnosis of an Arnold-Chiari malformation.

Case report

A 61-year-old man noted continuous jerking movements of the tongue for the first time 15 days before he was admitted to Sant Pau Hospital in 1984. The jerks, which were not preceded by any illness, persisted all day, were not accompanied by a clicking noise, and were not stopped or influenced by any action attempted by the patient. In 1974 he had a reactive mental depression that was treated with amitriptyline (75 mg/day) for nine months. No other medication was taken regularly in the nine years before the beginning of the abnormal tongue movements. There were no antecedents of head trauma or other relevant personal or family history. Neurological examination was normal apart from the lingual jerks. They consisted of continuous rhythmic 3 Hz, low amplitude, symmetrical contractions of both lateral edges of the tongue affecting mainly its middle and posterior parts and causing a midline depression of the tongue. The soft palate and other muscles innervated by the brainstem were not involved. The jerks persisted during sleep. Although he did not complain about phonation disturbances, speech was mildly affected. A forced palatalisation of some words was evident. He spontaneously produced vowel prolongation with the tongue pulled against the palate; when he was asked to let the tongue free in the mouth, most sounds had a quivering quality. Swallowing was normal. Protrusion, intrusion, passive depression, touch, or taps to the tongue did not influence the amplitude or the rhythm of the jerks. After hours of continuous activity, the movements would unexpectedly stop, only to start once again after a few minutes.

Routine blood analysis, surface EEG, cortical somatosensory evoked potentials, and brain stem auditory evoked responses were all normal. A CT scan showed a diffuse and symmetrical enlargement of the two lateral and third ventricles with mild periventricular oedema and a normal sized fourth ventricle. An Arnold-Chiari type I malformation was evident on an MRI study (figure).

After three days on 6 mg/day of clonazepam the movements were no longer continuous but occurred, at the same rate and amplitude, in random bursts lasting up to three minutes. These bursts totally disappeared in the second week. Over the next eight years, many attempts to discontinue clonazepam were followed by the re-emergence of the movements. During this period, other neurological and neuropsychological examinations, as well as repeated EEGs during and between the episodes,