showed strong immunoreactivity for the 14-3-3 family of proteins. Analysis of CSF additionally showed a herpes simplex virus-1 IgG titre of 1:10 (normal <1:10). The patient was diagnosed with probable Creutzfeldt-Jakob disease, but was treated with acyclovir for the possibility of herpes simplex virus encephalitis. Transient improvement in her mental status lasting several days was noted, but her symptoms subsequently worsened and she died five months after presentation.

Postmortem examination of the brain showed focal spongiform degeneration, neuronal loss, and gliosis limited almost exclusively to the striatum; most of the cerebral cortex showed no evidence of abnormality. Prion protein extraction from frozen brain tissue showed strong immunoreactivity for the abnormal isoform of prion protein as seen in Creutzfeldt-Jakob disease. Unlike classic Creutzfeldt-Jakob disease, there was also evidence of an encephalitis characterised by diffuse perivascular and leptomeningeal lymphocytic infiltrates and microglial nodule formation. Immunocytochemical stains were positive for herpes simplex virus. Although circumstantial, the presence of parenchymal inflammatory infiltrates with cells positive for herpes simplex virus immunocytochemistry was considered strongly suggestive of herpes simplex virus encephalitis.

Review of the literature disclosed no prior reports of the concurrence of neuropathologically verified Creutzfeldt-Jakob disease and herpes simplex virus encephalitis. Although this concurrence may be coincidental, the relation between Creutzfeldt-Jakob disease and herpes simplex virus has been speculated on in the literature, in particular whether Creutzfeldt-Jakob disease may stimulate recrudescence of latent herpes simplex virus harboured asymptotically in the CNS.² In retrospect, this patient's clinical course was typical of the subacute variety of Creutzfeldt-Jakob disease in which altered personality, sleep disturbance, ataxia, and myoclonus occur in the context of normal brain imaging and CSF studies.³ The presence of herpes simplex virus encephalitis in this patient was a secondary diagnostic consideration during her stay in hospital and its presence at necropsy was considered most consistent with stimulation by Creutzfeldt-Jakob disease of herpes simplex virus harboured latently in the CNS.

Concurrent Creutzfeldt-Jakob disease and herpes simplex virus encephalitis raise diagnostic as well as speculative issues. Traditionally, the diagnosis of Creutzfeldt-Jakob disease has been made on the basis of spongiform change, neuronal loss, gliosis, and the absence of an inflammatory reaction.⁴

However, as the present case shows, the presence of a virus associated inflammatory response on brain biopsy does not rule out the diagnosis of Creutzfeldt-Jakob disease. Conversely, a positive CSF assay for the 14-3-3 protein for Creutzfeldt-Jakob disease does not rule out the diagnosis of herpes simplex virus encephalitis.

This case illustrates the difficulty which may be encountered in the diagnosis of Creutzfeldt-Jakob disease on the basis of brain biopsy or CSF specimen. Definitive diagnosis of Creutzfeldt-Jakob disease is best accomplished by careful consideration of the results from various diagnostic tests including thorough postmortem examination.

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Botulinum toxin type A in the treatment of upper limb spasticity among patients with traumatic brain injury

We studied the efficacy and safety of botulinum toxin A (BTX-A) injections in patients affected by upper limb spasticity secondary to traumatic brain injury, in an open labelled trial.

Increased stretch reflexes, hypertonia, flexor spasms, and abnormal cocontraction are often associated with muscular contractures, causing many clinical manifestations in patients with traumatic brain injuries.

Botulinum toxin A (BTX-A) produces a dose related weakness of skeletal muscles by impairing the release of acetylcholine at the neuromuscular junction. Therapeutic intramuscular injections of BTX-A are a major

advance in the treatment of focal dystonia, and show promise in spasticity of varying aetiology.¹

The aim of this study was to evaluate the efficacy and safety of BTX-A treatment on disorders of muscular tone after traumatic brain injuries, in an early phase of rehabilitation, when retractions are still avoidable.

We examined six patients affected by severe traumatic brain injury (Glasgow coma scale <8). The mean age was 24.5 (range 18-42) years; spasticity had been present for a mean of 4.5 (range 4-6) months. One of the patients was in a vegetative state. The table shows the clinical data.

Upper limb muscles were injected with BTX-A (Botox[®], Allergan) in all six patients. In all, nine injections were carried out; three patients received only one injection (patients 2, 3, and 5), and the other three patients (1, 4, and 6) were reinjected after a variable lapse of time (1.5, 6, and 3.5 months later respectively). The mean dose of toxin injected for each treatment was 96 U. The toxin was injected by means of an EMG needle electrode guidance (Dantec 13R18), to improve the selectivity of treatment.

Target muscles for injections (table) were chosen on clinical judgement of muscle spasms or increased tone and then identified by EMG recording of active movements or stretch induced activity. Fixed muscular contractures and articular calcifications were assumed as criteria for exclusion from the trial; in doubtful cases, anaesthetic nerve block was performed before BTX-A treatment.

Each subject was assessed by a specialist in psychical medicine and a neurologist in a baseline evaluation and at fixed intervals after treatment (one week, one, three, six, and 12 months).

Outcome measurements were the modified Ashworth scale for grading muscle spasticity; joint angle measurements by means of a goniometer (range of movement); clinical evaluation of postural improvements, voluntary movements, and changes in limb function. The treated limbs were put in casts to prevent contractures after the injections; in some patients, additional medical treatment, such as lioresal, was given. The mean follow up was 10 (range 4-19) months.

The table shows the results. Improvements in modified Ashworth scale, joint range of movement, and clinical evaluation were found in all six patients. The modified Ashworth scale gain was one degree in four patients, two degrees in one patient, and three degrees in the other patients. Improvements in arm function for activities of daily living

Clinical data and results

Patient No	Sex	Age (y)	Injected muscles	BTX-A units	MAS		ROM	
					Before treatment	After treatment*	Pretreatment (degrees)	Post-treatment (degrees)†
1	M	19	Right B;BR B (1.5 months later)	50;50 70	3	2	Wrist: 20; fingers: 20	Wrist: 40; fingers: 45
2	M	18	Right FDS; FDP	50;50	2	1	Wrist: 0; fingers: 0	Wrist: 40; fingers: 20
3	M	42	Left FCU	100	3	2	Wrist: 0; fingers: 0	Wrist: 25; fingers: 25
4	M	25	Right FCU; FDS; FDP FCR; FDP (6 months later)	48;48 50;50	4	2	Wrist: 15; fingers: 15	Wrist: 50; fingers: 50
5	M	21	Left FCU; PT	50;50	3	0	Wrist: -15; fingers: 20	Wrist: 15; fingers: 30
6	M	22	Left FCR; FDP FCR; FDP (3.5 months later)	50;50 50;50	3	2	Wrist: 10; fingers: 20	Wrist: 20; fingers: 55

*Significant difference before and after treatment (Student's *t* test: *t* = 4.392; *p* = 0.007; †wrist: *t* = 6.047; *p* = 0.002; fingers: *t* = 7.181; *p* = 0.000). B = biceps muscle; BR = brachioradialis muscle; FDS = flexor digitorum sublimis muscle; FDP = flexor digitorum profundus muscle; FCR = flexor carpi radialis muscle; FCU = flexor carpi ulnaris muscle; PT = pronator teres muscle; m = months; MAS = modified Ashworth scale; ROM = range of movement.

were obtained in five of the six patients. In particular, in two patients (2 and 5) the reduction in spasticity led to a significant improvement in fine movements of the dominant hand, so that writing became possible. Reduced spasticity in one patient (4) enabled hand held utilisation of walking devices; in another two patients (3 and 6), it made for independence in dressing and eating. Clinical benefit started after two to three days and peaked in about three weeks. Three patients did not need a second injection; the other three patients were reinjected after varying times. Patient 1 had right biceps and brachioradialis muscle injection in the first session and a reinjection of the biceps muscle after 1.5 months; spasticity was reduced, mainly in the wrist and finger joints. The follow up of this patient was interrupted after four months. Patient 1 is still in a vegetative state. Three patients (1, 2, and 5) had pain arising from muscle spasms, which was relieved by BTX-A treatment.

These preliminary data show that BTX-A treatment is effective in reducing spasticity in selected patients with focal upper limb muscular tone disorders secondary to traumatic brain injuries. Spasticity, as measured by means of the modified Ashworth scale, was reduced and range of movement increased in five of the six patients. Greater facility in nursing care and reduced disability were found in all the subjects. The effects of a single injection were long lasting and only three patients needed a second injection. The treatment in the early phases of the muscular tone disorders seemed to be a critical factor. The pain secondary to muscle spasms was relieved by BTX-A treatment in our patients; the pain arising from capsular and synovial tissues, mainly at the elbow joint, was unaffected.

Previous studies have shown comparable results in spasticity secondary to stroke, multiple sclerosis, degenerative diseases, and cerebral palsy. Few reports are available for patients with traumatic brain injury, dealing only with isolated cases or small samples of patients with lower limb spasticity.²⁻³ To our knowledge, only one paper deals with a large population of patients with traumatic brain injuries⁴; most of these patients (12 out of 21) were chronically affected, (that is, spasticity had lasted for more than one year), and one of the acute patients had experienced a penetrating brain injury. The results obtained in the remaining eight acute patients were similar to ours.

In our patients, the changes were not strictly limited to the muscles injected; the treatment of proximal arm muscles invariably had a positive effect also on finger movement. A local toxin diffusion or an indirect permissive action could be hypothesised; however, action mechanisms other than the peripheral one for BTX-A cannot be ruled out.⁵

The treatment was completely safe and none of the patients complained of weakness due to the BTX-A injection.

Several points deserve further study: the choice of muscles, the number of injections, the dilution of the drug, and, in particular, the selection of patients. Furthermore, it is very important to define a clear goal for therapy for each patient. Double blind, placebo controlled, multicentre trials are warranted to provide answers for the aforementioned questions.

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CORRESPONDENCE

Erdheim-Chester disease and slowly progressive cerebellar dysfunction

In February 1995, Fukuzawa *et al* described a woman with Erdheim-Chester disease, a rare histiocytic disorder characterised by lipid laden cells infiltrating long bones, who presented with ataxia and diabetes insipidus.¹ They thought that this was the first reported case of Erdheim-Chester disease showing cerebellar symptoms and deep cerebellar lesions on MRI. We recently encountered a similar case, but on reviewing the literature we found that a few cases with ataxia and neurological signs had been reported previously. Erdheim and Chester's first case was thought to have had multiple sclerosis for seven years because of ataxia and ocular signs.² Subsequently a case was described in the German language by Kujat *et al*: a 62 year old man who presented with ataxia and bulbar symptoms.³ Brain MRI showed multiple brain stem, diencephalon, and cerebellar lesions. Another case was described by Smith *et al*: a 58 year old man with brain stem signs had a biopsy taken from the tibia which showed the characteristic lipid laden cells, and MRI of the brain showed multiple lesions.⁴

So, by contrast with the recognised pattern of skeletal involvement in Erdheim-Chester disease, the involvement of the CNS has variable presentation.

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Fuzakawa replies:

We appreciate the comments made by Bohlega. We agree that Erdheim-Chester disease can show variable CNS involvement,¹⁻³ and we also suspect that the involvement of the CNS may be relatively common during the entire clinical course of the disease. However, we had not found the case report in German by Kujat *et al*³ when we submitted our case report. In our article, we described a 59 year old woman with ECD who showed a four year clinical course of slowly progressive cerebellar symptoms, the clinical features of which suggested cerebellar degeneration and were different from those of previously reported cases of Erdheim-Chester disease showing ataxia.¹⁻⁴ The symptoms of diabetes insipidus had disappeared spontaneously when we first saw her, although they reappeared three years later. There was no definitive abnormality on CT, whereas MRI showed abnormal hyperintensity on T2 weighted studies in both dentate nuclear regions. Conversely, the brain MRIs of the previously reported patients with ECD who showed neurological signs disclosed multiple enhanced lesions in the CNS.²⁻⁴ We recently found another case report of a slowly progressive cerebellar syndrome associated with Erdheim-Chester disease, a 69 year old man presented with a one year history of progressive gait ataxia, dysarthria, dysphagia, fatigue, and weight loss.⁵ Unlike our patient, however, his brain MRI disclosed multiple white matter enhanced lesions in both cerebral hemispheres, pons, medulla, and brachium pontis. Furthermore, some cases with another form of histiocytosis—multifocal eosinophilic granuloma (MEG)—were reported to have presented as progressive cerebellar syndrome,⁶⁻⁸ and we previously reported a case with MEG showing progressive cerebellar and brainstem symptoms and multiple enhanced lesions on MRI.⁹ Therefore, these enhanced lesions on MRI may be a common finding of CNS infiltration of histiocytes. From the view of neuroimaging, our patient with ECD presented in this *Journal* is unique, although we could not clarify whether the MRI appearances were due to histiocytic infiltration. However, Erdheim-Chester disease should be included in the differential diagnosis of patients with otherwise unexplained slowly progressive cerebellar symptoms, and skeletal surveys are also indicated for these patients.

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