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High dose intravenous methylprednisolone in cluster headache

Bouts of cluster headache may be resistant to all the drugs usually effective, such as typical migraine preventing drugs, lithium, carbamazepine, valproate, and corticosteroids. Corticosteroids have been commonly used in cycles of 10–15 intravenous daily infusions of 50–100 mg prednisone. During a severe bout in a patient resistant to all treatments, we have tried high dose (500 to 1000 mg/day intravenously) methylprednisolone administration: single doses were found to be effective in blocking headache attacks for several days.

A 53 year old man began to have cluster headache at the age of 35. For several years he had about one cluster every two years, easily controlled by one or more of the commonly used drugs. In the past years, however, the clusters became increasingly resistant to all treatment. When aged 51 he had a cluster lasting more than 10 months, completely insensitive to the following drugs at the maximal doses he tolerated: 360 mg/day verapamil, 900 mg/day lithium (plasma concentrations 0.8–0.9 mEq/l), 4.2 mg/day methisergide, 20 mg/day flunarizine, 400 mg/day carbamazepine, 100 mg/day oral prednisone, and 300 mg/day indomethacin. After more than one year free from attacks, they reappeared with severe intensity, one to four a day, mainly during the night. The previously used drugs, as well as infusions of 100 mg/day prednisone for two weeks and hyperbaric O₂, alone and in association, were without effect. Relief was obtained only from sumatriptan at the onset of the attacks. After three months of ineffective attempts, we decided to administer 500 mg methylprednisolone intravenously (three hour infusion in saline) (figure, first slim arrow). Attacks stopped the same day of the infusion and the beneficial effect persisted, a single attack only reappearing six days later. Again 500 mg methylprednisolone was administered, giving relief for five days. We continued a schedule

Record of attacks and treatment schedule. Attacks stopped immediately and for several days after intravenous methylprednisolone infusion at a dose of 500 mg during the first two months and 1000 mg thereafter. Concomitant treatments (doses reported in the text) did not seem to modify the occurrence of the attacks.

of treatment based on a single 500 mg dose of methylprednisolone (figure, slim arrows) at the reappearance of a consistent attack, increasing the dose to 1000 mg (figure, thick arrow) from October. Methylprednisolone administration was associated with the H₂ receptor antagonist ranitidine. Concomitant treatments with (figure) 360 mg/day verapamil, 900 mg/day lithium carbonate, up to 200 mg/day lamotrigine, 300 mg/day indomethacin, 4.2 mg/day methisergide, and 1000 mg/day valproate did not prolong the periods free from attacks. Two successive methylprednisolone administrations at only three day intervals did not prolong the beneficial effect, which appeared to reduce its duration with time. Fortunately, the cluster vanished at the beginning of the 9th month from onset. No secondary effects of methylprednisolone treatment were seen.

In the past 10 years, the use of high dose steroids, mainly 500–1000 mg/day methylprednisolone intravenously for three to 10 days, has been proved to be effective in some neurological (for example, multiple sclerosis) and internal diseases of autoimmune origin. In these diseases the treatment has been found well tolerated, more effective than prolonged steroid therapy at lower doses, and devoid of significant adverse effects.

No role of the immune system has been so far proved in cluster headache. However, cycles of steroid therapy at medium doses have long been known to be among the most effective treatments.^{1–3} The only suggestion of a role for the immune system came from Martelletti and Giacobbo,⁴ who found an association of the HLA B21/DR5 antigen with responsiveness to prednisone therapy (our patient has HLA B7 B49 Dr2 Dr4 DR 53). Alternatively, steroids might suppress the release of vasoactive inflammatory agents—for example, stabilising mast cells.⁵

The present case suggests a possible beneficial effect of high dose intravenous steroids in cases of cluster headache resistant to usual steroid doses and to other drugs. In our opinion the possibility of a beneficial effect

can be tested with a single administration of 500–1000 mg methylprednisolone, which is almost devoid of risk.

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Concurrent herpes simplex virus encephalitis and Creutzfeldt-Jakob disease

Hsich *et al* recently described the 14–3–3 protein marker for Creutzfeldt-Jakob disease in which they noted a high number of positive assays (11 of 12) for the 14–3–3 protein in the CSF of patients with herpes simplex virus (HSV) encephalitis.¹ We report the case of a previously healthy 71 year old woman admitted to hospital with subacute changes in mental status who developed a rapidly progressive dementia characterised by personality change, insomnia, ataxia, and myoclonus. Brain MRI was unremarkable. Serial EEG was markedly abnormal due to the presence of diffuse slowing and continuous bilateral sharp waves with regular or irregular periodicity. Analysis of CSF at LCNSS, NIH

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 asymptomatically 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.