

## LETTERS TO THE EDITOR

### Headache and musculoskeletal symptoms

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**Keywords:** cervical problems, headache, migraine, musculoskeletal, pain

Received 8 March 2003

Accepted 22 May 2003

Dear Sir,

In an interesting recent paper in your journal Hagen *et al.* (2002) reported on the co-occurrence of headache and musculoskeletal symptoms in 51 050 adults. They reported that the prevalence of chronic headache was four times higher in individuals with musculoskeletal symptoms than those without (Hagen *et al.*, 2002). However, most important, they reported that individuals with neck pain were more likely to suffer from headaches as compared with those with musculoskeletal symptoms in other restricted areas (Hagen *et al.*, 2002).

I would like to familiarize the readership with some research which our group has recently published (Fishbain *et al.*, 2001) which resonates with the above results. In this study, 154 consecutive chronic headache patients with headaches interfering with function were identified in a pain facility population. These headaches were diagnostically evaluated according to IHS headache diagnostic criteria. The following results are notable: (i) the majority of headaches were related to a cervical injury; (ii) 83.7% of the headache patients had neck pain; (iii) migraine represented the most common diagnostic group (90.3%) with cervicogenic being second (33.8%); (iv) however,

there was much overlap between diagnostic groups so that 44.2% had more than one type of headache with cervicogenic having the greatest overlap (94.2%) and migraine second (68.3%); (v) the second most common headache precipitant was neck-position and the third being activity/exercise; (vi) the migraine and cervicogenic groups had a statistically significant greater number of neck-associated symptoms versus the remaining headache patients; (vii) of the total headache group, 74.6% complained that they had a tender point at the back of the neck with cervicogenic and migraine patients having the greatest frequency of these tender points; and (viii) the most common predictors of headache onset across diagnostic groups was severe headache beginning at the back of the neck or at a tender point in that region. Both of these studies then indicate that musculoskeletal neck-associated symptoms are common across headache diagnostic groups. As such, emphasis should be placed on developing IHS headache diagnoses which allow for the addition of musculoskeletal neck-associated symptoms; for example, migraine with neck-associated symptoms. Such flexibility would then allow the clinician to consider treatment aimed both at the migraine symptomatology and the neck-associated symptoms. Some of these ideas were outlined previously recently (Fishbain, 2002), but may not have disseminated yet to European clinicians.

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### Reply

We thank Dr Fishbain for his interest in our study of a large unselected population (Hagen *et al.*, 2002). The work by Fishbain *et al.* (2001), in contrast, was based on data derived from a specialized pain facility population. Despite this vital difference in study population, Dr Fishbain correctly noted several parallel findings; especially that neck pain is common across headache diagnoses, migraine included. Based on data from their study, Dr Fishbain suggests new IHS headache diagnoses with subdivisions according to neck-associated symptoms. We think such a development is premature in light of the current state of research in this field. Before introducing further splitting of the IHS headache diagnoses, we need justification from more studies in which headache patients are classified according to presence or absence of musculoskeletal symptoms. As stated in our article, such studies are needed to clarify the significance of musculoskeletal symptoms in the development of headache, and they may also contribute to the clarification of differences in treatment response.

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Sincerely,

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### Neurological findings in a case of coma secondary to *Datura stramonium* poisoning

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**Keywords:** atropine, coma, *Datura stramonium*, intoxication

Received 27 November 2002

Accepted 3 March 2003

### Introduction

*Datura stramonium* is a member of the belladonna alkaloid family. It contains mainly the alkaloid atropine, which enters the central nervous system (CNS),

interfering with cholinergic transmission. At high doses, atropine causes a stereotyped pattern of clinical manifestations, consisting of mydriasis, tachycardia, dry skin, flushing, urine retention, while CNS effects include restlessness, agitation, hallucinations and seizures, still larger doses results in coma (Brown and Taylor, 1996).

### Case report

We describe a case of *Datura* intoxication, dominated by neurological signs indicative of structural lesion of the brain.

A previously healthy 20-year-old male was admitted to our hospital in a state of unresponsiveness. At 37°C, the pulse rate was 150 beats/min and the blood pressure was 120/80 mmHg. The patient had no kind of respiratory abnormality and was rated 5 on the Glasgow coma scale.

Signs of meningeal irritation could not be elicited. The pupils of our patient were widely dilated and fixed, with no response to light. On touching the eyelashes the patient did not blink, but the response to corneal touch was intact. Additionally, the oculocephalic reflex was normal. A characteristic feature of the patient was his decorticate posture accompanied by paratonia. The plantar reflexes were extensor bilaterally, while grasp reflex could easily be elicited.

Common metabolic causes of coma were excluded. Brain computed tomography (CT) scan failed to detect any struc-

tural lesion, while the examination of the cerebrospinal fluid revealed no signs of CNS infection. Ambulatory electroencephalogram (EEG) showed no epileptiform activity.

The patient was treated with naloxone 0.4 mg intravenously without any improvement. At that time, we were informed that he had ingested seeds of the plant *Datura*. The intravenous injection of 2 mg of physostigmine relieved the patient from the comatose state. As the patient emerged from this state, he became confused but after 3 h he was fully responsive to stimuli and the neurological signs gradually disappeared. The patient remained hospitalized for 48 h, during which no further treatment was required. Clinical toxic screens using thin-layer and gas chromatography confirmed the presence of large amounts of atropine in successive urine samples.

### Discussion

Our case was significant, because the initial clinical picture with coma accompanied by attenuated corneal reflexes, decorticate posture and bilateral Babinski signs, could be attributed to destructive lesions of the cerebrum. However, the enlarged and unreactive pupils was the clinical point, which indicated that poisoning with anticholinergic drugs could have caused the comatose state. It is well known that bilateral mydriasis is a specific

feature of poisoning with these drugs and rarely occur in cases of anoxia, hypothermia and massive midbrain lesions (Adams, 1997). In fact, the normal breathing pattern of the patient and the intact oculocephalic reflexes practically excluded the possibility of such lesions. Finally, the decorticate rigidity, the Babinski signs and the abnormal corneal reflexes could be attributed to the suppression of neuronal activity, which occurs in deep coma of metabolic origin.

Interestingly, our case is similar in many aspects to the case reported by Oberndorfer *et al.* (2002). This could be explained assuming that, comatose patients because of *Datura* intoxication demonstrate a rather stereotyped pattern of neurological findings.

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### Hashimoto's encephalopathy: a treatable cause of mental impairment, stroke and seizures

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**Keywords:** Hashimoto's encephalopathy, mental impairment, status epilepticus, stroke

Received 10 January 2003

Accepted 5 June 2003

Dear Sir,

As average lifespan increases, so does the impact of diseases such as stroke and

dementia. The cost of these disorders is immense and defining treatable causes is, therefore, vital.

A 51-year-old woman presented to our department with increasing memory disturbance and unsteadiness that began after a fall 3 months earlier. Past medical history included hypothyroidism treated with thyroxin. Neurological examination revealed a mini-mental test score of 27/30. Haemoglobin, serum folate and cobalamin, liver transaminases, renal function, erythrocyte sedimentation rate and syphilis serology were normal. A cerebral magnetic resonance imaging (MRI) and electroencephalogram (EEG) were normal, cerebrospinal fluid (CSF) showed acellular fluid with elevated protein (0.82 g/l) and no oligoclonal bands. Serum thyroxin was normal (15.7 pmol/l), but serum thyroid-stimulating hormone (TSH) elevated (7.42 mIU/l). Her thyroxin treatment was increased from 0.1 to

0.15 mg/day. Her mental state remained unchanged, and 5 months later she presented in status epilepticus having first developed headache. The seizures did not respond to benzodiazepine treatment and she was intubated and treated with pentothal anaesthesia. After she awoke from anaesthesia, she had transient weakness of her left arm. Cerebral MRI was normal. EEG initially showed diffuse theta activity, which normalized before discharge. Serum thyroxin and TSH were normal, but antibodies against thyroid peroxidase were 644 IE/ml (normal < 250). The diagnosis of Hashimoto's encephalopathy was made and the patient treated with intravenous methylprednisolone 1 g followed by prednisolone 40 mg every other day.

Her mental state improved, but 1 month later she experienced a new episode of transient left-sided weakness involving her face, arm and leg that

resolved after 5 h. Doppler and MR examination were normal. The episode was considered to be a part of her autoimmune disease and the prednisolone treatment was maintained. After 6 months of treatment, prednisolone was gradually reduced and stopped.

Encephalopathy associated with Hashimoto's thyroiditis was first described in 1966 (Brain *et al.*, 1966). The clinical picture includes seizures, myoclonus, stroke-like episodes, intractable epilepsy, pseudodementia and impairment of consciousness (Shaw *et al.*, 1991). The majority of patients are women with either hypo-, euthyroid or with hyperthyroid status. The onset of symptoms may be abrupt or insidious (Kothbauer-Margreiter *et al.*, 1996). Cerebral blood flow, EEG and MRI findings may be normal or non-specifically disturbed (Peschen-Rosin *et al.*, 1999). Diagnosis depends on an awareness of the clinical syndrome, exclusion of other causes and the finding of thyroid autoantibodies, antimicrosomal antibodies in particular. Where doubt

exists, a trial of steroids may be appropriate. The serum concentration of thyroid autoantibodies does not predict clinical course or neurological manifestations (Shein *et al.*, 1986) and the aetiology and pathophysiological basis of this encephalopathy are unknown. An autoimmune cerebral vasculitis has been proposed as a possible pathogenic mechanism (Kothbauer-Margreiter *et al.*, 1996). The condition is thought to be underdiagnosed (Canton *et al.*, 2000).

Our patient presented with three different neurological conditions, responded completely to treatment and remains well at 24 months follow-up. As the prognosis of Hashimoto's encephalopathy is favourable and response to treatment good, the diagnosis should be considered early.

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#### Intrathecal antibody production against *Borrelia burgdorferi* in a patient with relapsing–remitting multiple sclerosis

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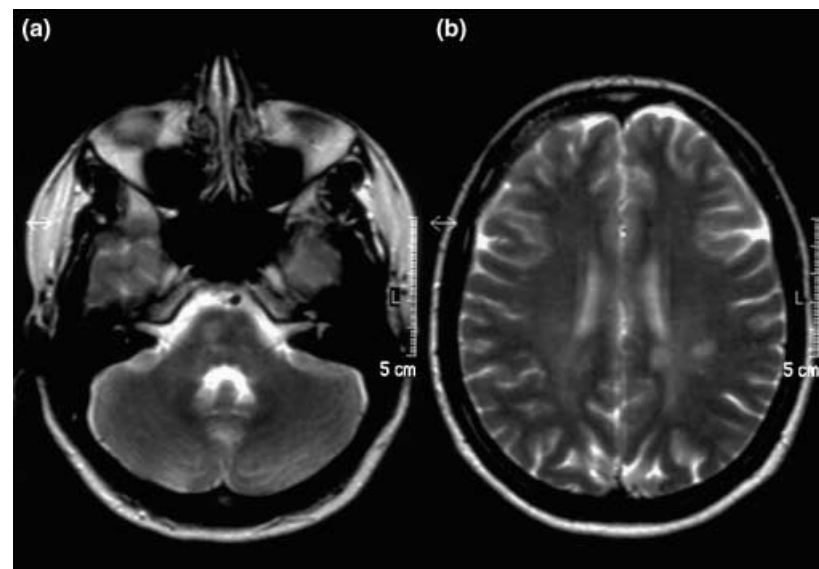
**Keywords:** intrathecal antibody production, multiple sclerosis, neuroborreliosis  
Received 17 March 2003  
Accepted 6 June 2003

Encephalomyelitis may be a manifestation of Lyme neuroborreliosis, mimicking a first episode of relapsing–remitting multiple sclerosis (RR MS) (Halperin *et al.*, 1996). Therefore, several studies have addressed the possibility of an association between Lyme borreliosis and MS. Only a minority of MS patients were found to be positive for serum *Borrelia burgdorferi* antibodies, and none of these patients had evidence of intrathecal synthesis of specific antibodies (Coyle *et al.*, 1993), the latter being a hallmark of

neuroborreliosis (Hammers-Berggren *et al.*, 1993). We report on a case with clinical RR MS and serologic evidence of transient intrathecal antibody production against *B. burgdorferi*.

A 38-year-old woman who had had optic neuritis 4 years ago presented with

subacute onset of vertigo and mild left-sided hemiparesis. T2-weighted MRI showed hyperintense lesions in the right pons and in the periventricular white matter (Fig. 1). The cerebrospinal fluid (CSF) revealed eight lymphocytes/ $\mu$ l, a normal protein content, an intrathecal



**Figure 1** Axial T2-weighted magnetic resonance imaging of the brain showing (a) hyperintense lesions in the right pons and (b) in the left periventricular white matter.

immunoglobulin G (IgG) synthesis (69% intrathecal fraction) and positive oligoclonal IgG bands. Antibodies to *B. burgdorferi* were determined by enzyme-linked immunosorbent assay (ELISA). IgG antibodies were positive in serum and CSF, which was confirmed by Western blot. IgM antibodies were not detectable. The IgG antibody index (AI) (Reiber *et al.*, 1998) was 14.5 (values > 1.4 indicate an intrathecal antibody synthesis). Serologic tests for *Treponema pallidum*, antinuclear antibodies, and rheumatoid factor were negative. The patient was treated with intravenous (i.v.) ceftriaxone 2 g/day for 21 days and i.v. prednisolone 500 mg/day for 5 days, and she recovered completely. Twelve months later, she developed urge incontinence and a reduced sensation for pain and temperature on the right leg. CSF again disclosed 11 lymphocytes/ $\mu$ l and an intrathecal IgG synthesis (54% intrathecal fraction) with oligoclonal bands. IgG antibodies to *B. burgdorferi* were still positive in serum and CSF. However, there was no intrathecal antibody production (AI 1.0). The analysis of virus-specific antibodies revealed an intrathecal IgG antibody synthesis against measles (AI 3.7), rubella (AI 1.5) and varicella-zoster virus (AI 11.3). RR MS was diagnosed and i.v. prednisolone 500 mg/day for 5 days was administered resulting in clinical improvement.

Previous case reports have discussed the problem of differential diagnosis in patients with clinical MS and positive Lyme serology (Karussis *et al.*, 1999). In our case, the relapsing clinical course and

MRI findings argue against a causative role of *B. burgdorferi*. In addition, CSF findings are not at all typical for neuroborreliosis. In neuroborreliosis, often a high cell count and a blood/CSF barrier dysfunction are found (Heller *et al.*, 1990). Furthermore, CSF analysis at the time of the third relapse disclosed an intrathecal antibody synthesis to three neurotropic viruses known as the 'MRZ reaction' in MS (Sindic *et al.*, 1994; Reiber *et al.*, 1998). Interestingly, the intrathecal immune response in MS is not only directed against viral antigens, e.g. 24% of MS patients had intrathecal antibody production against *Chlamydia pneumoniae* (Derfuss *et al.*, 2001). Therefore, the immune response to *B. burgdorferi* in our patient may be part of a bystander reaction similar to the MRZ reaction. Although, the intrathecal immune response in MS is stable over time (Derfuss *et al.*, 2001), the intrathecal anti-*Borrelia* antibody production in our patient was only transient. As regards the serologic diagnosis of *B. burgdorferi* infection, ELISA and immunoblot may be false positive (Brunner and Sigal, 2001). This cannot be excluded in our patient, although conditions frequently associated with false positive results (syphilis, systemic lupus erythematosus and rheumatoid arthritis) have been ruled out. We conclude that the diagnosis in the presented case is RR MS and we suggest to be very suspicious in a case of an MS-like presentation with positive Lyme serology with a CSF not compatible with a CNS infection by *B. burgdorferi*.

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## SIADH and seizure associated with immunoglobulin therapy

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**Keywords:** aseptic meningitis, hyponatremia, immunoglobulin therapy, seizure,

syndrome of inappropriate antidiuretic hormone

Received 26 January 2003

Accepted 1 June 2003

Dear Sir,

Intravenous immune globulin (IVIG) is widely used in neurologic disorders. Here, we report a case with syndrome of inappropriate antidiuretic hormone (SIADH) and seizure associated with IVIG therapy.

A 37-year-old man had paraparesis, hyporeflexia of the lower extremities, bilateral Babinski signs, a sensory level at T8, and a neurogenic bladder on May 17, 1998. His condition reached the nadir 24 h following onset. There were no significant findings in the routine tests but CSF study (Table 1). Magnetic resonance imaging (MRI) showed a non-compressive lesion

in the spinal cord from T2 to T5, with no significant findings in the brain. Connective tissue disease was excluded by serologic tests. Microbiologic studies did not identify any significant etiology. Intravenous methylprednisolone (1000 mg/day from days 3–7) was administered initially, but without response. Then, IVIG (GamimuneN; Bayer Co., IN, USA; buffer capacity 16.5 mEq/l, i.e. ~0.3 mEq/g protein; osmolarity 278 mOsm/l of solution) was administered at 400 mg/kg/day and infusion rate at 0.08 ml/kg/min during days 12–16. Headache, fever and chills, muscle pain, and chest discomfort were noted during, and usually lasted 60–90 min after each infusion. Fatigue, paresthesia, hypotension, and nausea occurred after the third day of IVIG, with the infusion rate < 0.04 ml/kg/min. Then,

**Table 1** Laboratory tests before and after immune globulin therapy

	Before IVIG	After IVIG	Normal ranges
<b>Serum</b>			
Na	136	112	135–145 mmol/l
Osmolality	Not done	259	280–296 mOsm/kg
Prolactin	Not done	14.4	0–10 ng/ml
ADH	Not done	15.6	1.0–13.3 pg/ml
<b>Urine</b>			
Osmolality	Not done	431	280–296 mmol/l
<b>CSF</b>			
Pressure	96	220	70–180 mm of water
Cell count (S/L)	18 (6/12)	102 (6/96)	0–5 mononuclear cells/ $\mu$ l
Glucose (CSF/serum)	54/110	62/104	CSF: 50–75 mg/dl
Protein	122	106	15–45 mg/dl
IgG index	0.74	1.26	< 0.7

IVIG, intravenous immune globulin; ADH, antidiuretic hormone; CSF, cerebrospinal fluid; S/L, segmented neutrophils/lymphocytes.

on the first day after completion of IVIG therapy, the patient had a generalized tonic-clonic seizure. Papilledema was not noted until after IVIG therapy. It was correlated with the rise in CSF pressure.

After IVIG therapy, hyponatremia and SIADH were noted (Table 1). A search did not show any etiology of meningitis. The brain MRI was still normal. The EEG showed diffuse slowing in the background without specific epileptic focus. Seizures occurred seven times during the first three days following IVIG therapy, and were later brought under control with valproate. The serum sodium improved 2 weeks

later, after water restriction. Aseptic meningitis was considered as the cause of SIADH and seizure. Although both IVIG (Dalakas, 1997) and methylprednisolone (Baumhefner *et al.*, 1989) can induce aseptic meningitis, the route of methylprednisolone is usually via the intrathecal pathway. Therefore, IVIG was inferred as the cause of aseptic meningitis.

Although the assay method might cause hyponatremia secondary to dilution after IVIG (Dalakas, 1997), the sodium concentration is usually above 130 mmol/l. Otherwise, aseptic meningitis does produce seizure in patients (4.7%)

(Inoue *et al.*, 1998). Hence, aseptic meningitis accounted for the SIADH and seizure in our case. Aseptic meningitis occurs in < 10% of patients treated with IVIG, and is unrelated to the commercial product, the infusion rate, or the underlying disease (Dalakas, 1997). One of the related mechanisms is immunologic hypersensitivity to the drug, most likely types III and IV (Jolles *et al.*, 2000). Another is the neurotoxicity of IVIG (Vriesendorp *et al.*, 1997). High-dose anti-GD2 IgG may contribute to the neurotoxicity through stimulation of normal lymphocytes with a subsequent release of cytokines.

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