LETTERS TO THE EDITOR

Carbamazepine in the treatment of generalised tonic clonic seizures in juvenile myoclonic epilepsy

Juvenile myoclonic epilepsy is characterised by bilateral myoclonic jerks on waking, and generalised tonic clonic seizures with onset in the mid-teens, which may be preceded by typical absences in 33% of patients.¹ Findings on EEG include bilateral spikes or multiple spike-slow wave discharges at 4-6 Hz with a normal background; about 30% of these patients show photosensitivity or focal abnormalities, or both.¹

A particularly good long-term prognosis exists if compliance with valproate, the drug of choice for the treatment of juvenile myoclonic epilepsy, continues.¹⁻⁴ In the 8-20% of patients in whom full control cannot be achieved with valproate treatment alone, low doses of the second-line anticonvulsant drugs clonazepam, clobazam, or phenobarbitone may be needed.¹⁻³ Carbamazepine is not indicated for juvenile myoclonic epilepsy, with some reports suggesting that it may actually exacerbate seizures.^{3,4} In view of this consensus it was of particular interest to us that in two patients with juvenile myoclonic epilepsy, generalised tonic clonic seizures but not absences or myoclonic jerks were controlled only after carbamazepine was added to valproate treatment.

CASE 1

This woman, aged 32 years, whose mother also has generalised tonic clonic seizures, has late onset congenital adrenal hyperplasia and juvenile myoclonic epilepsy with photosensitivity. Her first generalised tonic clonic seizure at the age of 14 years was induced by television; all others occurred on waking. Generalised tonic clonic seizures were well controlled by carbamazepine (400 mg/day, plasma concentration 34 $\mu\text{mol/l}$), only six having occurred in 13 years, but violent myoclonic jerks on waking and frequent, inconspicuous typical absences were resistant. Neurological examination was normal and EEG findings were consistent with juvenile myoclonic epilepsy and photosensitivity, but showed some inconsistent focal abnormalities. During her first pregnancy at the age of 29 years, the myoclonic jerks disappeared. Within a few days of the birth of a healthy son, they returned every morning after waking, and were violent enough to make her drop her baby. Six months later she had her first generalised tonic clonic seizure in three years. Juvenile myoclonic epilepsy was diagnosed and valproate (1 g/day) added. This fully controlled the myoclonic jerks and absences, and carbamazepine was withdrawn completely over two months. Three weeks later she had a second generalised tonic clonic seizure, associated with sleep deprivation and stress. Valproate was increased to 1.5 g/day but after two weeks a further three generalised tonic clonic seizures occurred at weekly intervals, prompting an increase in dose to 1.7 g/day. These seizures immediately preceded her second pregnancy. In spite of taking valproate at 2.0-2.2 g/day (plasma levels were consistently higher than 700 $\mu\text{mol/l}$) a

further three generalised tonic clonic seizures occurred at 21, 22, and 27 weeks' gestation, again when sleep-deprived. Carbamazepine (400 mg/day increasing to 600 mg/day) was then added. The remainder of the pregnancy was uneventful and no generalised tonic clonic seizures, myoclonic jerks, or absences have occurred for 29 months, despite decreasing the valproate dose to 1000 mg/day.

CASE 2

This 20 year old woman, had a febrile convulsion at the age of 3.5 years. Typical absences, myoclonic jerks, and generalised tonic clonic seizures occurred in her mid-teens with no particular circadian distribution. The seizures were spontaneous or precipitated by television, video games, anger and emotion, and sleep deprivation. Neurological examination and MRI were normal. Results of EEG support a diagnosis of juvenile myoclonic epilepsy with photosensitivity, but marked alternating focal abnormalities were also found in follow-up EEGs.

Valproate (1 g/day) controlled the generalised tonic clonic seizures initially but had little effect on the myoclonic jerks, and produced a large weight gain. Phenytoin made her hirsute and at a saliva concentration of 5.4 $\mu\text{mol/l}$ was of no benefit. At her first visit to us she was taking valproate (1200 mg/day; plasma levels >306 $\mu\text{mol/l}$), clonazepam (1 mg/day), and phenytoin (250 mg/day), and as a result of pre-examination stresses her myoclonus was worsening. A previous two week trial of carbamazepine (400 mg/day) alone had been unhelpful. Phenytoin was withdrawn slowly. With the combination of valproate (1500 mg/day) and clonazepam (1.5 mg/day) absences were minimised, myoclonic jerks were nocturnal only, but the generalised tonic clonic seizures persisted. Carbamazepine (1200 mg/day) was added to this regimen without side effects and no further generalised tonic clonic seizure has occurred in 15 months.

These cases of definite juvenile myoclonic epilepsy and photosensitivity show that carbamazepine combined with valproate was more effective than valproate either alone or with clonazepam in preventing generalised tonic clonic seizures. Carbamazepine alone did not prevent generalised tonic clonic seizures, myoclonic jerks, or absences in either patient and although valproate was efficacious against the latter seizure types, the combination of the two drugs was necessary for full generalised tonic clonic seizure control. Interestingly, the two patients had some focal abnormalities on EEG in addition to findings typical of juvenile myoclonic epilepsy. Valproate is the acknowledged drug of choice for this syndrome, producing a rapid and sustained reduction or abolition of generalised tonic clonic seizures, myoclonic jerks and absences in more than 80% of patients.¹⁻⁴ In those rare instances in which generalised tonic clonic seizures prove recalcitrant to treatment, however, and particularly if there is some evidence of focal discharges at EEG, the combination of valproate with carbamazepine may successfully abolish them. These patients exemplify the need for syndrome-related drug trials and for a consideration of possible pharmacodynamic interactions between various drugs used to treat epilepsy.

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Intracranial chordoma with a novel symptom

The case is described of a novel presentation of an adult with an intracranial chordoma. The onset was relatively acute with neck pain and lower cranial nerve involvement producing an unusual symptom related to head movement and posture. The tumour has followed an aggressive course in spite of radical surgery and radiotherapy.

A 40-year-old man presented with cervical and occipital pain which had persisted for four months. No neurological deficit was found and a diagnosis of cervical spondylosis was made. Plain radiographs of the craniovertebral junction and neck were normal.

Two months later he presented again, reporting that on flexing his neck or lying horizontal he could not move his tongue properly and was unable to speak. These symptoms resolved within 30 seconds of sitting up or raising his head. He was referred to the neurology department where wasting of his tongue, more marked on the right, with deviation of the median raphe to the right was noted. An inability to speak and to move his tongue on flexing the neck was shown but lingual sensation to touch and pin-prick was normal. The remainder of the neurological examination was normal and ear, nose, and throat assessment confirmed normal palatal movement and sensation.

After a few weeks his neck pain and the positional symptoms affecting his tongue resolved and were replaced by persistent dysarthria with difficulty in propelling saliva, food or fluid to the back of the mouth. There was no choking or nasal regurgitation. During this period he developed wasting of the extensor neck muscles, especially on the left side, and of the sternomastoids.

Enhanced CT and MRI showed a destructive mass lesion, thought to be a chordoma, extending from the clivus to the anterior margin of the foramen magnum. A transoral resection of the tumour was performed and complete clearance was felt to have been achieved. Histology showed the characteristic appearance of a chordoma: nests and chords of polyhedral tumour cells, often with vacuolated "bubbly" cytoplasm (physaliphorous cells) and uniform round nuclei, were surrounded by a plentiful mucinous matrix.

The patient made a good recovery after the operation, with some improvement of speech and swallowing. There was residual wasting and weakness of the tongue. Six months after the operation the bulk and power of the sternomastoids and neck extensor muscles had almost returned to normal.

Seven months after the operation the patient developed diplopia, his swallowing started to deteriorate again, and his voice became hoarse. At this time he was noted to have a partial left sixth nerve palsy and a left Horner's syndrome.

MRI showed a marked decrease in the bulk of the tumour from the original excision site, but extensive lateral extension along the floor of the skull base with encasement of the intrapetrous portion of the left internal carotid artery. Digital subtraction angiography with intravenous contrast showed a normal venous phase and the absence of vessel displacement or tumour circulation.

Using a posterolateral approach a further resection achieved a good macroscopic clearance apart from leaving some residual tumour in the cavernous sinus. The histology was identical to that of the sample taken during the first operation. Post-operatively there were left sided sixth and seventh cranial nerve palsies together with marked speech and swallowing difficulties. A feeding gastrostomy was required.

In spite of radiotherapy this neurological deficit has persisted and the left side of the patient's face has become numb. MRI one year after the second operation has shown extensive tumour recurrence affecting the clivus, extending anteriorly into the nasopharynx and posteriorly into the posterior fossa with compression of the medulla and cerebellum.

DISCUSSION

Skull base chordomas are rare tumours producing infiltrative destruction of bone. They tend to recur locally and have the potential to cause a variety of cranial nerve palsies at anatomically unrelated sites. The cranial nerve most often affected is the sixth, followed by the ninth and tenth.¹

Isolated hypoglossal lesions are uncommon from any cause. Chondroid chordomas may be the cause and exceptionally may arise within the hypoglossal canal.² Inability of the patient to speak and to move the tongue on neck flexion is an unusual symptom which, as far as we are aware, has not been described previously in relation to intracranial chordomas. It is reminiscent of the neck-tongue syndrome in which afferent fibres from the lingual nerve travelling via the hypoglossal nerve to the second (and possibly the third) cervical root are compressed at the craniocervical junction on head movement.³ The neck-tongue syndrome is usually a benign disorder not associated with serious intracranial pathology. It causes unilateral numbness of the tongue on head movement and patients may have the sensation that their tongue is being twisted sideways in their mouth. Dysarthria may accompany the hemiglossal sensory disturbance.⁴ Our patient had restricted tongue movement and an inability to speak without altered sensation, perhaps suggesting that on neck flexion the tumour compressed the hypoglossal nerve itself rather than the second and third cervical roots.

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Locked-in syndrome in fulminant demyelinating disease

The locked-in syndrome¹ is a state of paralysis of all limbs and the lower cranial nerves, with preserved consciousness, vertical eye movements, and blinking. The pathological damage is usually located in the basis pontis of the ventral pons, the most common cause being infarction. Rarer causes include pontine tumours, central pontine myelinolysis, pontine haemorrhage, and brain stem encephalitis. This report describes a fulminant first presentation of demyelinating disease with features of multiple sclerosis, which evolved within weeks into a fatal locked-in state. Pathological examination showed extensive demyelination of the ventral pons.

CASE HISTORY

A previously fit 50-year-old Spanish man developed slurred speech followed two days later by a mild weakness of his right arm and leg. Four days later he developed unsteadiness of his legs and two days later presented to this regional neuroscience centre. On examination he was dysarthric. Fundi, visual acuity, and fields were normal; his pupils were mid-point and briskly reactive. He had a left partial ptosis and diplopia in all directions of gaze, except the right lateral. There was mild pyramidal weakness of his right leg. His reflexes were brisk with extensor plantars and he had marked ataxia of the trunk and limbs.

Computed tomography showed a low density, non-enhancing area in the left rostral midbrain, with normal opacification of the basilar artery. His CSF was acellular, with normal protein and glucose; oligoclonal bands were absent. Routine haematological and biochemical tests, clotting studies, erythrocyte sedimentation rate, C reactive protein, and fasting lipids were normal. An autoantibody screen was negative. An ECG and chest radiograph were normal. A preliminary diagnosis of brain stem stroke-in-evolution was made, and he was anticoagulated intravenously with heparin. Subsequent vertebral angiography, however, was normal, and the heparin treatment was stopped. Visual evoked responses were bilaterally delayed. Despite the absence of oligoclonal bands in the CSF, the possibility of multiple sclerosis was considered, and high dose methylprednisolone was given for three days.

His initial response to steroids was good. The diplopia and ataxia improved. A right internuclear ophthalmoplegia was now apparent. Ten days after the end of the steroid treatment he developed complete transverse myelopathy with a sudden onset of flaccid paraplegia with areflexia and a sensory level to all modalities at T10. Myelography was normal and CSF protein, glucose, and cell count were also normal. Oligoclonal bands were again absent.

High dose steroids were restarted. MRI showed high signal lesions on T2-weighted images in the midbrain, cervical region, and parietal area, consistent with infarction or demyelination. One week later he developed weakness and sensory loss in the upper limbs, with acute aphonia and ventilatory failure requiring ventilation. He had a flaccid paresis of the arms with sensory disturbance to C5. Within 24 hours he had developed the locked-in syndrome with full consciousness, the only movements remaining being blinking and vertical eye move-

ments. He had a cardiac arrest and died 11 days after developing the locked-in syndrome.

PATHOLOGICAL EXAMINATION

Acute tracheobronchitis was found at necropsy. The brain was externally normal. No hemispheric or periventricular demyelinating lesions were seen. The midbrain and brain stem down to the lower medullary level were macroscopically abnormal. Externally, the pons and medulla were expanded and on dissection there was extensive discolouration and blurring of normal structures, with central granularity of texture. Sections stained with haematoxylin-eosin and luxol fast blue-cresyl violet showed sharply defined, irregular loss of myelin staining from the ventral half of the midbrain at the inferior collicular level (figure) to the ventral half of the pontine isthmus. Microscopic examination showed selective demyelination in the affected zone, which occupied the greater part of the pons and extended down into the medulla, the ventral two-thirds of which were affected. Axons were relatively spared and neurons and vessels were intact in the affected area; there was a marked cellular response affecting lymphocytes, macrophages, and astrocytes.

The spinal cord was almost entirely necrotic, with a loss of normal structure. Necrotising myelopathy affected all tissue elements. Ghost neurones were visible at some levels. Peripheral cord myelin was focally spared, as was myelin in the spinal nerve roots.

DISCUSSION

The case has been described of a patient with fulminant demyelination resulting in a fatal locked-in state, and with pathological evidence of extensive demyelination in the ventral pons.

Although the locked-in syndrome has been described previously in patients with multiple sclerosis,^{2,3} demyelination of the ventral portion of the brain stem was not present. Instead, demyelination was found in the internal capsule, cerebral peduncles, and tegmentum. Boor *et al*⁴ reported a patient with stepwise deterioration of lower brain stem dysfunction, similar to that described here, but without development of the locked-in state. The main clinical features of Boor *et al*'s patient were bulbar weakness together with the failure of automatic respiration, which was shown

Stained section of midbrain (Luxol fast blue-cresyl violet stain). Note area of myelin pallor in anterior half.