Letters

Myasthenic pseudo-internuclear ophthalmoplegia due to penicillamine

Sir: Myasthenia gravis is a well recognised complication of penicillamine treatment. We report a case where the patient presented with a pseudo-internuclear ophthalmoplegia.

A 55-year-old foreman engineer was referred to the Neurology Clinic with a 3 month history of diplopia most marked on lateral gaze to either side. He had suffered from rheumatoid arthritis for 20 years and had been receiving penicillamine 125 mg daily for the last 2 years. On examination the horizontal eye movements were as shown (fig a,b). There was nygastmus of the abducting eye on lateral gaze. Impairment of convergence and a mild bilateral ptosis were also noted. The rest of the neurological examination was unremarkable. On injection of 10 mg edrophonium intravenously the eye movements returned to normal (fig c,d). Rheumatoid factor and anti-acetylcholine receptor antibodies were strongly positive. Repetitive nerve stimulation at Erb's point showed a decremental response of the evoked muscle action potential from the deltoid muscle, reversed by intravenous edrophonium. A diagnosis of penicillamine induced myasthenia gravis was made. The penicillamine was discontinued and the patient started on pyridostigmine 30 mg tds. Three months later there was considerable resolution of his symptoms and signs and the pyridostigmine was stopped. After 6 months examination of the eye movements was completely normal. Repeat repetitive nerve stimulation testing and anti-acetylcholine receptor antibody assay were also normal.

True internuclear ophthalmoplegias are due to lesions in the medial longitudinal bundle, most commonly multiple sclerosis, whereas pseudo-internuclear ophthalmoplegias result from a peripheral conduction defect such as occurs in the Guillain-Barré syndrome or myasthenia.1 In the case reported here there was slight bilateral ptosis and paresis of convergence. However ptosis when mild and symmetrical may be difficult to detect and convergence may sometimes be impaired in a true internuclear ophthalmoplegia.2 Thus an edrophonium test is a valuable extension of the bedside examination to exclude myasthenia gravis even if a central lesion is suspected.

Most patients with penicillamine induced myasthenia gravis have rheumatoid arthritis associated with anti-acetylcholine receptor antibodies and an increased prevalence of HLA BW 35 and DR 1.3 The mechanism by which penicillamine induces myasthenia is incompletely understood. In vitro studies have shown that penicillamine may enhance the production of anti-acetylcholine receptor antibodies,4 possibly by modifying the receptor to produce an immunogenic form.5 After penicillamine withdrawal, the anti-acetylcholine receptor titre falls and the myasthenia gradually resolves.6

The clinical and electrophysiological features of penicillamine induced myasthenia gravis are indistinguishable from the primary disease. Ocular symptoms are common but, as far as we know, this is the first case reported presenting with a pseudo-internuclear ophthalmoplegia.

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Lithium-induced improvement of myotonia

Sir: Myotonia is a phenomenon of delayed muscle fibre relaxation associated with repetitive electrical depolarisations following a single induced muscle contraction.1,2 Myotonia is commonly found in the two inherited neuromuscular disorders, myotonic dystrophy (Steinert's disease) and myotonia congenita (Thomsen's disease). We have suggested that the myotonia of myotonic dystrophy results from adrenergic receptor dysfunction3 and that pharmacologic augmentation of receptor stimulation (such as with tricyclic antidepressant therapy) can reduce myotonia.4,5 In evaluations of neurotransmitter-modifying drugs in patients with myotonia, we had the opportunity to evaluate the effect of lithium carbonate treatment on myotonia in a man with myotonia congenita. We compared this effect to the changes caused by lithium administration in an animal model of myotonia.

A 37-year-old man with myotonia congenita complained that muscle stiffness interfered with his usual activities. Previous therapy with phenytoin, quinine, and procainamide had produced unpleasant side effects with no significant clinical improvement of the myotonia. He had difficulty making rapid movements in getting out of a car, standing up from a chair, or walking up and down stairs. On examination he had well-developed muscles with no evidence of weakness; myotonia was...
readily demonstrable in facial and limb muscles. A qualitative electromyographic study showed the typical waxing-and-waning discharges of myotonia. He was given lithium carbonate 300 mg tablets in a dose sufficient to achieve a lithium blood level of 1.5 mEq/L. At this dosage there was no change in his myotonic stiffness. His dosage was then slowly increased while monitoring adverse side effects. At a blood lithium level of 2.0 mEq/L, he noted greater ease in performing rapid alternating movements. When his blood level reached 2.3 mEq/L, he experienced cessation of stiffness and disappearance of clinical myotonia. He was able to move in and out of his car with ease, get up from a chair without difficulty, and outrun his teenager son. Prior to lithium treatment, starting from rest he could run the first lap of a measured distance in 50 seconds and the second lap in 25 seconds; starting from rest he could run up one flight of stairs in 55 seconds. With a lithium level of 2.3 mEq/L, starting from rest he ran the first lap of the measured distance in 35 seconds and the second lap in 20 seconds; he could run up one flight of stairs in 30 seconds. At a lithium level of 2.3 mEq/L, his only problem was excessive sedation which interfered with his employment and necessitated reduction of the dosage. Because blood lithium levels of less than 2.0 mEq/L produced no improvement of the myotonic symptoms and because of concern about the potential adverse renal effects of long-term high dose lithium administration, the lithium carbonate therapy was discontinued.

Animal study

We undertook preliminary studies of the effect of lithium upon Wistar Furth rats made myotonic by oral administration of a 5 mg/ml solution of 20, 25-diazacholesterol (DAC). Nine doses of 150 mg/kg body weight of the DAC was given to each animal. After the last dose of DAC, the animals showed clinical muscular stiffness and electrical myotonia. Twitch tension of the tibialis anterior muscle recorded isometrically using a Grass FTO3 force transducer and a Dynograph recorder during supramaximal stimulation of the sciatic nerve showed a delay in relaxation consistent with myotonia (fig). Repetitive sciatic nerve stimulation at 0.5 Hz caused a progressive decrement in twitch height. Recordings of twitch tension in DAC-treated animals after an 0.06% solution of lithium chloride was administered intravenously to achieve serum lithium levels of 12 mEq/L showed a 50% augmentation of twitch tension and the restoration of normal relaxation time (abolition of myotonia).

The acute effect of lithium administration to the myotonic animals had some similarity to the clinical effect of lithium therapy in the myotonic patient. We have no definite explanation for the lithium effect in either instance. Unlike the case of congenital myotonia in goats or of myotonia congenita in humans, a decrease in muscle fibre membrane chloride conductance is neither a necessary nor sufficient pre-requisite for the expression of DAC-induced myotonia. However, DAC treatment has been shown to alter membrane ion channel kinetics. DeCoursey, using the vametine-gap voltage clamp technique, has demonstrated a decreased rate of sodium channel inactivation in DAC-treated rat muscle. This decreased rate of sodium channel inactivation could increase the probability of repetitive discharge of action potentials. Using the kinetic parameters derived from the DAC-treated muscle fibres and a normal chloride channel conductance, DeCoursey could simulate repetitive myotonic discharges in a computer model. We have reason to believe that lithium ions may affect the kinetics of the sodium channel in skeletal muscle. Preliminary intracellular studies with DAC-treated muscle fibres bathed in normal Ringer's solution or lithium Ringer's solution (10 mM lithium chloride) demonstrate that lithium ions decrease the number of action potentials elicited in response to intracellular current pulses (200 nA, 25 ms duration). While the spike over-shoots remain the same, the spike thresholds appear to become less negative. Further studies with lithium may increase the understanding of the mechanisms of the myotonic discharges and may prove the usefulness of lithium in acceptable doses as an adjunctive therapy for patients with myotonic disorders.

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References

Pontine ataxic hemiparesis, a lateral penetrator syndrome?

Sir: Ataxic-hemiparesis due to a pontine lesion was first described in post mortem studies by Fisher. Since then, most studies using computed tomography have reported internal capsule lesions in ataxic hemiparesis. Only one previous case of brainstem infarct has been documented with computed tomography. We wish to describe a second case.

A 52-year-old Chinese female had a known history of diabetes mellitus and hypertension under treatment. She was admitted to hospital because of sudden onset of left sided weakness. There was no diplopia, vertigo, or other symptoms. On examination she had a blood pressure of 130/70 mm Hg. There was grade 3 power in the left upper limb, and grade 4 in the left lower limb. The reflexes were exaggerated on the left, Babinski’s sign was absent. Marked cerebellar incoordination, and dysdiadochokinesia was noted in the left upper and lower limbs. There was no cranial nerve abnormality, nor any sensory loss. Somatosensory evoked responses to median and tibial nerve stimulation was normal. CT scan showed a low density area in the right pons (fig). She improved progressively but 3 months later was still ataxic whilst having normal power and exaggerated tendon reflexes on the left side.

We have recently reported four cases of ataxic hemiparesis due to internal capsule and corona radiata infarction. These cases, as well as similar cases in the literature all had sensory impairment. In contrast, all ataxic hemiparesis cases due to brainstem lesions reported so far have had normal sensory findings. We postulated that the supratentorial cases could be separated from brainstem cases by the absence of cranial neuropathy, nystagmus, dysarthria, and the presence of sensory impairment. The present case of pontine infarct supports our previous contention in that there was no clinical evidence of sensory impairment and somatosensory evoked responses was normal. Clinical recognition of the difference may have more than casual interest, since ataxic-hemiparesis due to non-ischaemic lesions have all been situated in the brainstem.

Fisher had previously demonstrated three cases of ataxic hemiparesis associated with infarcts in the brainstem. All the infarcts were in the junction of the upper third and lower two-thirds of the basis pontis. Two of the cases had midline infarct cavities, and one had a more laterally situated infarct. The basilar artery was patent in all three cases, but a plaque was found in a branch artery in one case. Sakai et al reported a case with an infarct in the ventromedial aspect of thepons. Their case had also trigeminal weakness, suggesting that the lesion extended further laterally, and they thought a short circumferential branch rather than a median penetrating artery was likely to have been involved. The present case showed a lesion in the ventrolateral aspect of the pons.

Four cases of pontine haemorrhages causing ataxic hemiparesis also have been reported. These have all been small haematomas in the dorsolateral aspects of the pons. They did not exhibit features of lateral tegmental brainstem haemorrhage: all radiologically or pathologically confirmed cases had spinothalamic involvement, and frequently also eye movement disorders. Ataxia in lateral tegmental brainstem haemorrhage was also bilateral or contralateral to the weakness. The brainstem receives blood supply from paramedian arteries arising directly from the basilar artery, and a series of lateral penetrators from short circumferential branches of the basilar artery. In addition, branches from the long circumferential arteries supply parts of the lateral tegmentum. Both the pyramidal tract and medial lemniscus lie in the territory of the paramedian penetrators. It seems more likely therefore that the brainstem haemorrhage causing ataxic hemiparesis had been in the lateral penetrator territory. Fisher’s case 1, Sakai’s case and the current case, seem to have also lesions in the lateral penetrator rather than paramedian territory. Pontine ataxic hemiparesis, whether ischaemic or haemorrhagic in origin may simply be a pontine lateral penetrator territory syndrome.

Paramedian territory infarcts, unless limited, probably give rise to such significant hemiparesis that ataxia cannot be observed. Fisher’s two other cases may have been exceptional examples of such limited paramedian infarcts. However the acute ischaemia could have extended more laterally.

Fisher had speculated that in addition to involvement of the corticospinal tract, the pontine nuclei sending fibres to the opposite cerebellar hemisphere, or the crossing fibres from the opposite pontine nuclei, had to be involved to cause ataxia. It was unclear why the cerebellar signs were not bilateral. However, in his three cases, the infarcts were all described as extending only 5–7.5 mm in the anterior posterior direction. Our case had an infarct which was seen only on one CT slice. It is possible that crossing fibres from the pontine nuclei travel obliquely in the rostral caudal plane, so that a lesion limited in this plane, may affect only the pyramidal tract and pontine nuclei, and spare the contralateral crossing fibres, thus giving rise to homolateral ataxic hemiparesis. However the pontine nuclei are themselves aggregated in longitudinal columns in the rostral caudal direction, so that a small lesion may be expected also to affect the nuclei or their projections significantly. On the other hand, the corticopontine fibres descend with the corticospinal tracts, to terminate in the ipsilateral pontine nuclei. Ataxia could conceivably result from a critical lesion in the upper pons which interrupted both the corticopontine and corticospinal projections, without necessarily affecting the pontine nuclei or its projections.

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