LETTERS TO THE EDITOR

Recurrent spontaneous accessory neuropathy

Isolated spinal accessory nerve palsy of obscure or spontaneous origin is an uncommon but well recognised entity.1 We describe the first reported instance of recurrent spontaneous accessory palsy.

At the age of 22, the patient developed an aching discomfort in the right shoulder and neck. This resolved after a few days but after several weeks he became aware of weakness of shoulder elevation. Examination revealed wasting and weakness confined to the right trapezius muscle. Nerve conduction studies of the accessory nerve, recorded in the trapezius, revealed latencies of 4.3 ms on the right and 2.9 ms on the left (normal < 3.2 ms). Electromyography showed large motor unit potentials and reduced recruitment in the right trapezius only. After four to five months the condition improved and the size and strength of the right shoulder returned to normal.

He remained well and continued to work as a policeman until he was 31, when he again developed an ache in the right shoulder after exercising with five-pound dumb-bells. The ache persisted for two to three weeks but was never severe and did not interfere with his sleep. Naproxen provided some relief. About three weeks after the onset of pain, the patient began to notice weakness of his right shoulder and weakness of shoulder elevation. Two weeks later the pain had entirely resolved but he was now aware of the right shoulder hanging lower than the left. He had no sensation of weakness in the shoulder. The other limbs and spinal function remained normal.

Examination revealed a fit man with marked wasting of the right trapezius muscle and moderate weakness of shoulder elevation. There was right scapular winging of the trapezius type, which was present with the arm at rest and accentuated by lateral elevation of the arm. The right sternomastoid muscle was normal. No wasting or weakness was observed in the other right shoulder girdle muscles and the remaining cranial nerves and other limbs were normal. General examination was normal and there was no sign of injury or abnormality on the lateral side of the neck.

Cervical radiographs and myelography of the foramen magnum were normal. CT scan of the neck and skull base revealed no abnormality. The cerebrospinal fluid (CSF) was clear and colourless, with four lymphocytes and a protein of 0.34 g/l. Serum glucose, full blood count, sedimentation rate, C-reactive protein, antinuclear factor, and routine biochemistry were normal.

Nerve conduction studies of the accessory nerve, recording trapezius, revealed a considerable decreased amplitude of the compound muscle action potential on the right, but the distal latencies were similar and normal on both sides (right = 3.2 ms, left = 3.1 ms). Electromyography revealed fibrillation potentials and large motor unit potentials with reduced recruitment in the right trapezius, and normal findings in the serratus anterior, infraspinatus, deltoit, biceps, brachioradialis and extensor digitorum communis muscles.

Our patient experienced two similar episodes, separated by eight years, of shoulder ache followed by right trapezius weakness and wasting. On both occasions clinical and electromyographic examination found no abnormality except in the right trapezius, implying the presence of a lesion affecting the accessory nerve distal to the innervation of the sternomastoid. He appeared to make a complete recovery after the first episode, only to suffer a recurrence eight years later. Investigation has not shown an underlying cause and we therefore believe he is the first reported instance of a recurrent accessory nerve palsy.

Due to its complicated course, the accessory nerve may be damaged by a wide range of processes affecting the cervical spinal cord, the spinal canal, the foramen, and skull base, carotid sheath, or posterior triangle of the neck. The nerve is particularly vulnerable as it crosses the posterior triangle, where injury occurs most often following radical neck dissection, resulting in weakness and wasting of the trapezius. Spillane described three patients in 1949 who had clinical evidence of isolated accessory neuropathies, the cause of which was obscure.2 He made a complete recovery after a second episode coincided with light exercise with weights, these were small (5 pounds) and seem unlikely to have produced a stretch injury of the accessory nerve.

Pesticide toxicity and motor neuron disease

Pyrethrins are neurotoxins that kill insects by paralysis—"knock down". This is thought to be secondary to an effect on sodium channels in motor neurons. Mammals are spared from this effect as, unlike insects, they can metabolise pyrethrins in the hepatic microsomal system to non toxic compounds.1 We previously reported a case simulating motor neuron disease (MND) closely associated with over-exposure to permethrin and chlordane based insecticide.2 The chlordane component is metabolised to various compounds (including oxychlordane and epoxychlordane) via the cytochrome P450 enzyme system.3 However, permethrin and pyrethrin is metabolised by different routes (fig). Following esterase cleavage, two products are formed which are further metabolised then eliminated. In mammals,4 metabolite A is excreted in the urine as a glucuronide conjugate. Metabolite B undergoes oxidation and hydroxylation to yield mainly C and D, with other compounds. Conjugates of minor metabolites with glycine5, glutamic acid6 and taurine7 have been noted. However, the elimination of metabolites C and D in the rat is by sulphate conjugation8 which is the major metabolic pathway for permethrin.

This is of interest since we recently reported9 that MND patients have a defect in their ability to convert cytochrome to inorganic sulphate and also show a poor capacity to form the sulphate conjugate of paracetamol. In the light of these observations, the 4'-Hydroxy-3-phenoxyl benzyl alcohol (meta- bollite C) and/or 4'-Hydroxy-3-phenoxyl benzoic acid (metabolite D) may be responsible for the neurotoxicity that resulted in our patient suffering from his MND-type illness. Some environmental chemicals generally

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7. Pesticide toxicity and motor neuron disease.
thought of as harmless may therefore be toxic to a small proportion of the population who have an inability to metabolise them easily to safer compounds.

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(+)-PHNO: a new anti-Parkinsonian agent which does not induce chorea in MPTP-treated squirrel monkeys

Exciting advances in drug delivery technology to control fluctuations in response to anti-Parkinsonian therapy are under way. One recent development is a rate-controlled transdermal delivery system for the selective D3 agonist (+)-PHNO which was capable of maintaining stable plasma levels in the therapeutic range throughout a 24 hour period in primates. 1 The suitability of (+)-PHNO for rate-controlled administration through the skin is shown in Figure 1. A. In conventional anti-Parkinsonian agents, however, as well as "off"-swings, many Parkinsonian patients also have debilitating drug-induced dyskinesias, especially chorea. 2 The pathophysiology of this side effect is poorly understood. We now report that (+)-PHNO, unlike levodopa, does not induce chorea in MPTP-treated squirrel monkeys.

The subjects had previously served in experiments using transdermal application of (+)-PHNO 4 and had all received intermittent exposure to levodopa during the two years before this study (total exposure ranged from 70 to around 1500 mg/kg po for different animals). Locomotor activity and drug-induced choreoathetosis in each limb was scored continuously by direct observation every five minutes for up to three hours using a clinically-based rating scale of 0-4 according to frequency and severity. Dyskinesias in each limb were rated separately as follows: 0 = absent; 1 = occasional/mild; 2 = intermittent/ moderate; 3 = frequent/marked; 4 = continuous/severe. Dyskinesia was attributed to two treatments: (a) oral gavage at 5, 10, 15 or 20 mg/kg 1 h following treatment with double the respective dose of carbidopa. (+)-PHNO was examined at 0.625, 1.25, 2.5 or 5.0 μg/kg sc in the leg. Administration of levodopa caused a dose-dependent increase in locomotor activity accompanied by choreothetoid movements affecting the limbs, especially the legs. These reached a peak 40-60 minutes after treatment and were characterised by repetitive flexion/extension or circling movements of the hands, forearms, hindlegs and feet and gaiting of the pelvis. Buccolingual dyskinesias were not observed. Chorea appeared less severe at the highest dose of levodopa (20 mg/kg) due to the emergence of verticalisation or climbing behaviour between 90 and 165 minutes after treatment. In contrast, treatment with (+)-PHNO induced marked locomotor stimulation, but no chorea was observed in the limbs at any dose examined (see table). Unlike levodopa, lashing movements of the tail were observed following treatment with (+)-PHNO; the relevance of these movements for dyskinesias in humans is not clear.

The absence of chorea in MPTP-treated squirrel monkeys following acute administration of the D3-selective agonist (+)-PHNO agrees with a similar finding using chronic treatment with bromocriptine for five months in macaques. 5 Similarly, in stage I-II Parkinsonian patients, Stoaell et al 6 did not make any mention of dyskinesias following acute single dose oral treatment with (+)-PHNO. Interestingly, the less selective D4 agonist apomorphine has been reported to reduce choreas in Parkinsonian patients receiving levodopa therapy, 7 in Huntington's disease 8 and in neuroleptic-induced tardive dyskinesia. 9 However, it should be noted that dyskinesias have occasionally been observed after administration of (+)-PHNO both in primates 8 and in humans. 10 The reason for this discrepancy is not known, but may be related to the severity of Parkinsonism, duration of prior treatment with levodopa ("priming"), and type of dyskinesia (chorea or dystonia).

Our findings, and those of others, clearly indicate a difference between the effects of a nonselective, indirect agonist (levodopa) and D3-selective direct agonists in the genesis of choreas in the Parkinsonian brain. One interpretation of these findings is that stimulation of D3 receptors may induce chorea, D2 binding sites are particularly high in the medial pallidal segment, 11 an area implicated in the induction of chorea. 12 It is of interest that the direct nigropallidal dopamine pathway is relatively unaffected by the neurotoxin MPTP, 13 and this could provide a direct route for the production of chorea by levodopa.

We would predict that use of a directly acting selective D3 agonist such as (+)-PHNO via a sustained release preparation in de novo Parkinsonian patients might greatly reduce the incidence of both chorea and motor fluctuations whilst giving effective relief from akinesia.

We are extremely grateful to Professor C D Marsden for his evaluation of the drug-induced dyskinesias induced by levodopa and (+)-PHNO.

<table>
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<tr>
<th>Table</th>
<th>Induction of locomotor activity and chorea following treatment with levodopa or (+)-PHNO in MPTP-treated squirrel monkeys</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Levodopa (mg/kg po)</td>
</tr>
<tr>
<td>Vehicle 5 10 15 20</td>
<td>Score summed over 180 minutes</td>
</tr>
<tr>
<td>Locomotor activity</td>
<td>9 (10) 21 (6)* 34 (6)* 45 (8)* 31 (5)*</td>
</tr>
<tr>
<td>Chorea</td>
<td>0 4 (2) 64 (20)* 188 (28)* 156 (28)*</td>
</tr>
</tbody>
</table>

Values are expressed as the mean (1 SEM) for data obtained using seven animals.

*p < 0.01 compared to vehicle treatment, Dunnett's multiple comparison test.
Pesticide toxicity and motor neuron disease.

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