

Nerve conduction studies and electromyography were normal. Cranial MRI showed normal sinuses and multiple lesions in the periventricular white matter and brainstem consistent with demyelinated foci. Blood tests were negative for renal insufficiency, collagen vascular disease including Sjogren's syndrome, syphilis, HIV or HTLV-I infection, B12 deficiency, sarcoidosis, or thyroid disease. On the UPSIT, she identified 10 of 40 odours, indicating total bilateral anosmia. Over the next year, she developed relapsing and remitting sensory and motor manifestations typical of multiple sclerosis. Olfactory function remained poor.

To our knowledge, this is the first report of olfactory disturbances as the initial or most prominent manifestation of multiple sclerosis. Multiple sclerosis is an unusual cause of acquired smell dysfunction. Aging, chemical exposure, trauma, infection, local inflammatory conditions, sinus disease, and smoking are more common aetiologies.<sup>2</sup> The absence of pathological conditions known to cause olfactory loss, other than smoking in patient 1 and diabetes in patient 2, strongly suggests that the smell disturbances were due to multiple sclerosis in these patients. The fluctuation of olfactory function in parallel with multiple sclerosis disease activity, including improvement after corticosteroid treatment further supports the causal relation in patient 1. It is unlikely that the olfactory disturbances experienced by patient 2 resulted from her diabetes. Impaired olfactory function in diabetes typically manifests as increased olfactory thresholds rather than anosmia.<sup>2</sup> Also, it typically occurs in association with other diabetic complications.

Studies of olfactory function in multiple sclerosis have yielded conflicting results. Ansari<sup>3</sup> found no impairment in 40 patients with multiple sclerosis compared with 24 age and sex matched controls with other neurological diseases. This study employed nitrobenzene and amyl acetate as odorants, both of which are strong trigeminal stimulants the detection of which would not depend solely on the integrity of the olfactory pathways. With the UPSIT, Kesslak *et al*<sup>4</sup> found no difference in olfactory function in patients with multiple sclerosis compared with controls. In a previous study from our group employing the UPSIT,<sup>1</sup> two of 31 in patients with multiple sclerosis scored below normal with a disproportionate number in the low normal range, suggesting subtle olfactory deficits exist in some patients with multiple sclerosis. By contrast, in the study of Pinching,<sup>5</sup> 10 of 22 unselected patients with multiple sclerosis had quantitative olfactory loss and another five showed descriptive impairment. The disagreement between these studies may relate to the utilisation of different testing protocols and distinct patient populations.

Given the potential for demyelinating lesions to occur throughout the CNS in multiple sclerosis, one would expect olfactory symptoms to be a possible manifestation. Despite reports of impairment in olfactory function on formal testing, however, symptomatic loss of smell is very uncommon in multiple sclerosis. This rarity has several potential explanations. Firstly, changes in smell may be less noticeable to most patients than other neurological symptoms. Secondly, olfactory dysfunction may be confused with loss of taste. Thirdly,

physicians may attribute altered olfaction to other factors such as depression. Fourthly, pathological studies have suggested that the olfactory pathways are relatively spared in multiple sclerosis,<sup>3</sup> perhaps due to regional differences in myelin or myelin forming cells that alter the susceptibility to demyelination, lessen the physiological consequences of demyelination, or allow more efficient remyelination.

In summary, although it is not surprising that multiple sclerosis can produce abnormalities of olfactory function, symptomatic disturbances of smell are uncommon. In rare cases, olfactory impairment can be the presenting or most prominent manifestation of multiple sclerosis, and can be a troubling symptom in other patients. Multiple sclerosis should be considered in the differential diagnosis of acquired smell dysfunction.

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- Doty RL, Shaman P, Dann M. Development of the University of Pennsylvania smell identification test: a standardized microencapsulated test of olfactory function. *Physiol Behav* 1984;32:489-502.
- Getchell TV, Doty RL, Bartoshuk LM, Snow JB. *Smell and taste in health and disease*. New York: Raven Press, 1991.
- Ansari KA. Olfaction in multiple sclerosis. With a note on the discrepancy between optic and olfactory involvement. *Eur Neurol* 1976;14:138-45.
- Kesslak JP, Cotman CW, Chui HC, *et al*. Olfactory tests as possible probes for detecting and monitoring Alzheimer's disease. *Neurobiol Aging* 1988;9:399-403.
- Pinching AJ. Clinical testing of olfaction reassessed. *Brain* 1977;100:377-388.

#### Change in the concentrations of amino acids in cisternal CSF of patients with essential tremor

Essential tremor is the most frequent movement disorder in subjects over 40 years of age.<sup>1</sup> The disorder is inherited in an autosomally dominant manner and is slowly progressive over the years, leading to

disablement. The lack of any detectable neuropathological lesion<sup>2</sup> gives rise to the possibility that a change in neurotransmitter balance might play a part in the aetiology of essential tremor. There is an increased sensitivity of mouse neocortical slices to  $\gamma$ -aminobutyric acid (GABA) after chronic treatment with drugs improving tremor,<sup>3</sup> suggesting the importance of the inhibitory amino acid  $\gamma$ -GABA in the aetiology of essential tremor. We therefore analysed the amino acids in cisternal CSF of patients with essential tremor to determine whether there was any difference among concentrations of excitatory and inhibitory amino acids compared with controls.

The CSF of patients with essential tremor was taken by cisternal puncture after obtaining informed consent. The patients were undergoing neurological examination for other kinds of complaint, mostly headache, when inflammation and haemorrhage were excluded by cisternal puncture. The CSF of 19 cases whose samples were negative in respect of other diseases were included. The regional ethics committee approved the scientific analysis of CSF samples. Patients (7 women and 12 men) with essential tremor were new. They were not taking drugs. Their age was between 21 and 80 (mean 62 (SD 4.9)) years. The duration of disease was between one and 50 (mean 21 (SD 3.8)) years. Family history of disease was detected in 16 cases. Their hand tremor was characterised by postural and action tremor and they had difficulties in writing and dressing. Control subjects (10 men, five women aged 16 to 80 (mean 60 (6)) years) had no organic symptoms, but progressive headache, occasional unconsciousness of uncertain origin, and functional disorders needed more detailed neurological examination.

All CSF samples were centrifuged at 3000 g for 15 minutes at 0-4°C and the supernatant liquid was kept at -70°C.

The amino acids were measured by high performance liquid chromatography. This method generally offers sensitivities of 1 pmol for *o*-phthalaldehyde derivatives of amino acids. A Gilson liquid chromatographic system was used (two pumps, an autoinjector with sample loop size of 20  $\mu$ l and a fluorometer). Separation of amino acids was performed on a 5  $\mu$ m Ultrasphere C-18 column (150  $\times$  4.6 mm). Concentration was determined by a two point calibration curve internal standard method. The column was equilibrated with solvent A, which consisted of 22.5% methanol-acetonitrile (3.5:1 v/v) in 0.01 M potassium

Concentrations of amino acids (mmol/ml) in cisternal CSF of patients with essential tremor

Amino acids	Increased		Decreased		No change	
	C	T	C	T	C	T
Glutamate	10.18 (1.74)	17.25 (3.66)				
Aspartate			6.83 (1.42)	2.57 (0.44)**		
Serine			86.09 (24.2)	28.03 (3.0)*		
Glycine			17.53 (3.01)	10.76 (1.27)*		
Threonine			29.19 (2.34)	21.19 (2.68)*		
GABA					39.38 (5.22)	29.47 (3.03)
Asparagine					4.42 (0.37)	3.63 (0.37)
Glutamine					326.6 (67.3)	224.1 (27.4)
Arginine					23.52 (2.02)	21.24 (1.85)
Taurine					11.67 (2.38)	7.98 (0.81)
Alanine					33.97 (3.51)	27.36 (2.28)
Tyrosine					20.33 (1.92)	17.47 (2.18)
Phenylalanine					7.71 (0.65)	7.41 (0.64)

\**p* < 0.05; \*\**p* < 0.01. Data are given in mean (SEM). C = controls (n = 15); T = patients with essential tremor (n = 19).

phosphate buffer (pH 7.2). The mobile phase B consisted of 22.2% acetonitrile in methanol. The increments of buffer B in the gradient programme were 6.5%, 12.8%, 15.5%, 27.0%, 39.0%, 41.0%, and 59.5% at 5.5, 6.0, 13.0, 13.5, 14.0, 19.5, and 22.5 minutes, respectively. The analysis was carried out at a flow rate of 1.5 ml/min.

Before analysis 20 and 5 µl CSF samples were diluted with an internal standard of 20 and 95 µl α-aminoadipic acid (5 µM) respectively. The reagent mixture was prepared by dissolving 10 mg α-phthalaldehyde in 250 µl methanol and adding 50 µl 2-mercaptoethanol in 4.7 ml 1 M borate buffer (pH 10.5). Derivatives were made by mixing 63 µl α-phthalaldehyde with a 7 µl sample two minutes before injecting on to the column.

Statistical analysis was by unpaired *t* test and Mann Whitney U test. Data are given as means (SEM).

Although there were slight decreases in the concentrations of amino acids in patients with essential tremor there were no significant differences in most amino acids (table). The control values were similar to those found by others.<sup>4</sup>

Despite the great number of experimental studies dealing with the aetiology of tremor induced by harmalin, no human data exist yet that directly explain the generation of essential tremor.

The most surprising change in the concentrations of amino acids was that the concentration of serine and glycine was reduced. Glycine can be formed from serine by a reversible folate dependent reaction catalysed by the enzyme, serine trans-hydroxymethylase. Therefore it is concluded that the reduction in the concentration of glycine is a consequence of the decreased concentration of its major precursor, serine. The important role of glycine in decreased inhibition in the CNS has been demonstrated in the mutant spastic mouse.<sup>5</sup> The less severe phenotypes of these autosomal recessive inherited mice are characterised only by tremor of trunks and limbs, raising an interesting comparison with the similar features of essential tremor.<sup>5</sup>

Whereas the concentration of glutamate was not significantly changed, that of aspartate was significantly decreased ( $p < 0.01$ ). The climbing fibres of the cerebellum utilise excitatory amino acids as neurotransmitters<sup>6,7</sup> and an increase in the concentration of excitatory amino acids might have been expected if an overactivity of the inferior olive were involved in essential tremor. From experimental studies, however, the expected candidate for this neurotransmitter is glutamate.<sup>6,7</sup>

This is the first clinical study that draws attention to the possible role of glycine and it is concluded that the decreased concentration of glycine may be involved in essential tremor. Our findings also strengthen the hypothesis that this disease is of central origin.

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- 1 Rajput AH, Offord KP, Beard CM, Kurland LT. Essential tremor in Rochester, Minnesota: a 45-year study. *J Neurol Neurosurg Psychiatry* 1984;47:466-70.
- 2 Rajput AH, Rozdilsky B, Ang L, Rajput A. Clinicopathologic observations in essential tremor: reports six cases. *Neurology* 1991;41:1422-4.
- 3 Mály J, Stone TW. The effect of theophylline on essential tremor: the role of GABA. *Pharmacol Biochem Behav* 1991;39:345-51.
- 4 Gjessing LR, Gjesdahl P, Sjaastad O. The free amino acids in human cerebrospinal fluid. *J Neurochem* 1972;19:1807-8.
- 5 Becker CM. Disorders of the inhibitory glycine receptor: the spastic mouse. *FASEB J* 1990;4:2767-74.
- 6 Stone TW. Glutamate as the neurotransmitter of cerebellar cells in the rat: electrophysiological evidence. *Br J Pharmacol* 1979;66:291-6.
- 7 Barry J, Gombos G, Vizi ES. Release of (<sup>3</sup>H)L-Glutamate and (<sup>3</sup>H)L-Glutamine in rat cerebellum slices: a comparison of the effect of veratridine and electrical stimulation. *Biochem Res* 1989;14:1053-9.

### Persistent hemiballism in Parkinson's disease

Ballism has been regarded traditionally as a unique hyperkinetic movement disorder with clear anatomical localisation. In humans and other primates, lesions of the subthalamic nucleus cause contralateral hemiballism. This rather neglected small anatomical structure has lately attracted interest in connection with Parkinson's disease, as it has been shown in primates exposed to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), that the indirect motor loop from the striatum via the lateral segment of the globus pallidus and the subthalamic nucleus may be overactive, whereas the converse is true for the GABAergic projection from the globus pallidus to the thalamus.<sup>1</sup>

It is on this basis that experimental anatomical lesions of the subthalamic nucleus or neutralisation of its activity by high frequency electrical stimulation or by pharmacological agents such as N-methyl-D-aspartate (NMDA) antagonists, have been tried in Parkinson's disease or the MPTP models. Such lesions can reverse parkinsonian symptoms in the contralateral limbs.

In patients with Parkinson's disease, lesions in the subthalamic nucleus can reverse parkinsonism contralaterally.<sup>2</sup> We recently treated a patient with Parkinson's disease in whom a lesion in the subthalamic nucleus was expressed by sustained violent hemiballism. The patient was a 60 year old right handed man. His history showed arterial hypertension and non-insulin dependent diabetes mellitus, both controlled pharmacologically. He had gait disturbances and recurrent falls. When examined by a neurologist, hypomimia, symmetric limb rigidity that increased on contralateral activation, and a short step gait were noted. He had no tremor and showed a mild central left facial weakness accompanied by mild pyramidal signs. Treatment with levodopa and carbidopa and selegiline was beneficial.

About one year later, sudden involuntary violent ballistic movements of the left limbs appeared. On examination, there was rigid limb tone on the right whereas on the left the tone was normal. Tendon reflexes were brisker on the left and the plantar response was extensor. CT showed a haemorrhage in



Figure Unenhanced CT performed about six hours after the appearance of left hemiballism. Note the haemorrhage in the right subthalamus.

the right subthalamic nucleus (figure).

The ballistic movements continued despite withdrawal of antiparkinsonian drugs. Increasing doses of haloperidol up to 30 mg/day were not beneficial but aggravated the parkinsonian symptoms, mainly bradykinesia. Clonazepam was added at a dose of 1 mg thrice daily, which minimally reduced the hemiballism but had to be withdrawn because of intolerable somnolence.

Three months after the event, the patient still had hemiballistic movements, although somewhat attenuated. At this time the muscle tone in the left limbs was still normal, by contrast with the rigidity on the right.

The co-occurrence of Parkinson's disease and a lesion in the subthalamic nucleus in the same patient is a coincidental event of low probability, and confirms that destruction of the subthalamic nucleus in a patient with Parkinson's disease can reverse parkinsonian symptoms in the contralateral limbs as suggested by studies in primates.<sup>3,4</sup>

The persistence of hemiballism for several weeks is unusual. If hemiballism occurs after iatrogenic subthalamic nucleus destruction in monkeys treated with MPTP, it is usually of short duration. Aziz *et al*, however, in a study of the alleviating effect of lesions of the subthalamic nucleus in parkinsonian monkeys, mentioned one animal in whom hemiballism persisted for at least 16 weeks.<sup>4</sup> This finding, together with ours, implies that the occurrence, severity, and persistence of hemiballism should be carefully studied before the use of subthalamotomy by iatrogenic anatomical destruction becomes a therapeutic option in Parkinson's disease.

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- 1 Mitchell JJ, Clarke CE, Boyce S, *et al*. Neural mechanisms underlying parkinsonian symptoms based upon uptake of 2-deoxyglucose in monkeys exposed to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *Neuroscience* 1989; 32:213-26.