Table 1  Water deprivation test after treatment with hydrocortisone, thyroxine, and carbamazepine

| | Fluid balance (l) | Urine osmolality (mmol) | Plasma osmolality (mmol) |
|---|---|---|---|
| 0 hours | 0 | 114 | 288 |
| 8 hours | −1·8 | 231 | 299 |
| After DDAV (2·0 g im) | | 587 | 290 |

DDAV = diamine-D-arginine-vasopressin; im = intramuscularly.

but three months later at follow up still had no perception of light in her right eye, with a pale optic disc. She had normal vision in her left eye, and full ocular movements.

One month later she re-presented with a two day history of headache, nausea, vomiting, and urinary and faecal incontinence. She had a fever of 39·2°C, a blood pressure of 92/48 mmHg, and a pulse of 98 beats/min. General examination showed mild diffuse lower abdominal tenderness. She was drowsy, but obeyed first order commands, and was localising pain, with mild nuchal rigidity, photophobia, and a pale right disc with a right afferent pupillary defect. Eye movements were normal other than a partial right sixth nerve palsy. She showed left sided hyperreflexia and a left extensor plantar response. CT of the brain showed a small anterior collection in the sphenoid sinus and a small area of low attenuation in the right medial frontal region unchanged from the previous scan. The pituitary was normal in size and position. Her CSF had a protein concentration of 47 mg/l, a glucose concentration of 3·5 mM (blood sugar 3·8 mM), and 10 lymphocytes/mm.[3] Serum electrolytes were mildly abnormal (sodium 142 mM, potassium 3·8 mM, chloride 113 mM, bicarbonate 22 mM, urea 6·3 mM, and creatinine 134 μM). She was treated empirically with cephotaxime, metronidazole, and benzylpenicillin and improved over 24 hours although no organism was identified. She then gave a history of amenorrhoea from the time of her original admission. Electrolytes were now abnormal (sodium 151 mM, potassium 3·5 mM, chloride 116 mM, bicarbonate 25 mM, urea 2·3 mM, and creatinine 85 μM). A diagnosis of Addisonian crisis was made and she was treated with hydrocortisone (100 mg six hourly) and over the next 36 hours improved considerably with her blood pressure rising to 120/70 mmHg. Cortisol concentration measured before starting treatment with hydrocortisone was abnormally low at 71 nM. Her serum osmolality was then 296 mmol with a urinary osmolality of 105 mmol indicating diabetes insipidus, later confirmed with a water deprivation test (table 1). She was also biochemically hypothyroid, with a TRH test showing a subnormal TSH and prolactin response to TRH (table 2). Growth hormone was undetectable and LH (2·0 mU/l)

and FSH (4·0 mU/l) both subnormal. These results were interpreted as indicating panhypopituitarism. She was therefore treated with a combination of hydrocortisone, thyroxine, and desmopressin in replacement dosages. Oestradiol valerate was later added. Her blood pressure returned to 102/60 mmHg with no postural drop. Cranial MRI performed on recovery failed to show any abnormality in the region of the hypothalamus.

Anterior hypopituitarism after cavernous sinus thrombosis is thought to follow ischaemia related to venous thrombosis extending from the cavernous sinus to the hypophysial portal vessels, the sole blood supply of the anterior lobe.[4] Inflammatory involvement of the carotid artery may underlie the seizures and focal areas of cerebral infarction sometimes seen, as in our case, and may have also produced the posterior hypopituitarism by causing hypothalamic infarction, although this could not be detected on cranial MR images.[5] Our experience and that of others[3-5] is that hormonal deficiency may present catastrophically and that hypopituitarism should be actively searched for in all patients and may be an additional factor in the high mortality from cavernous sinus thrombosis.

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## Olfactory disturbances as the initial or most prominent symptom of multiple sclerosis

Although common in the general population, symptomatic olfactory disturbances are rare in multiple sclerosis.[1 2] When present, they are typically found in longstanding disease with other neurological manifestations. We report two patients with olfactory disturbances as the initial or most prominent symptom of multiple sclerosis.

Patient 1, a previously healthy, 36 year old woman acutely developed parosmias six months before evaluation. She perceived many items, particularly food, as smelling of gasoline. As a result, she developed an aversion to food and a 20 lb weight loss. Three months later, she noted persistent fatigue. Her doctor suspected depression, but a psychiatric evaluation and neuropsychological testing showed no evidence of an affective disorder or cognitive dysfunction. Subsequently, she developed left sided weakness and difficulty walking, prompting evaluation at the University of Pennsylvania. Her medical history was unremarkable apart from her smoking 20 cigarettes daily for 10 years. Neurological examination showed Lhermitte's phenomenon, bilateral optic disc pallor with normal visual acuity, mild spastic left hemiparesis, diffuse hyperreflexia, and bilateral Babinski signs. Cranial MRI showed multiple lesions consistent with demyelinating foci in the hemispheric white matter, brainstem, and cerebellum. There was no sinus disease. The cerebrospinal fluid contained 7 white cells/mm^{3} (all lymphocytes), 0·5 g/l protein 68 mg/100 ml glucose, raised IgG, and oligoclonal bands. Blood tests was negative for collagen vascular disease including Sjogren's syndrome, syphilis, HIV, and HTLV-I infection, B12 deficiency, sarcoidosis, and thyroid disease. Olfactory testing was performed with the University of Pennsylvania smell identification test (UPSIT), a widely used, standardised, microencapsulated, 40 odour, 4 item forced choice test.[1] On an abbreviated study, she identified 11 of 15 odours, equivalent to scoring below the 10th percentile for age matched women who smoked. The patient requested that testing be terminated because the test items smelled like gasoline. Methylprednisolone treatment (1 g intravenously each day for five days), produced rapid improvement in her left hemiparesis and olfactory symptoms. On a full length UPSIT two weeks later, she identified 35 of 40 items, including 14 of the 15 previously tested, corresponding to the 70th percentile.

Patient 2, a 48 year old woman was referred to the University of Pennsylvania for evaluation of possible multiple sclerosis. Twenty years earlier, she had developed urinary frequency, which resolved spontaneously over two months. After an uneventful pregnancy two years later, she developed bilateral, sequential optic neuritis. At age 48, she noted an acute loss of smell, prompting her to seek medical attention. She denied other neurological symptoms apart from decreased vision. Medical history was significant for adult onset diabetes mellitus, well controlled with insulin. Examination showed bilateral optic disc pallor with visual acuities of 20/100 OD and 20/40 OS, mild ocular ataxia, and bilateral Babinski signs. There was no evidence of retinopathy or peripheral neuropathy.

Table 2  TRH test

| Time after TRH | Prolactin (mU/l) | TSH (mU/l) | T4 (nM) | T3 (nM) |
|---|---|---|---|---|
| 0 min | <20 | 0·35 | 30 | 0·3 |
| 20 min | <20 | 0·45 | | |
| 60 min | <20 | 0·53 | | |
| Reference ranges | 350 | 0·4–5·0 | 50–144 | 0·9–2·7 |

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.[2] 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.[2] Also, it typically occurs in association with other diabetic complications.

Studies of olfactory function in multiple sclerosis have yielded conflicting results. Ansari[3] 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[4] found no difference in olfactory function in patients with multiple sclerosis compared with controls. In a previous study from our group employing the UPSIT,[1] 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,[5] 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,[3] 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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## 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.[1] 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[2] 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 γ-aminobutyric acid (GABA) after chronic treatment with drugs improving tremor,[3] suggesting the importance of the inhibitory amino acid γ-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 μl and a fluorometer). Separation of amino acids was performed on a 5 μm Ultrasphere C-18 column (150 × 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).