Neurofibromatosis 1 and multiple sclerosis

R E Ferner, R A C Hughes, M R Johnson

Abstract
Neurofibromatosis 1 is a common autosomal dominant disease that principally involves the skin and peripheral nervous system. The gene for the disorder has been located on chromosome 17q11-2 and there are three embedded genes within the neurofibrosis gene. One of these genes codes for oligodendrocyte-myelin glycoprotein, is found in the CNS during myelination, and may have a role in myelination formation.

The case histories of five patients, including two siblings, who have both neurofibromatosis 1 and multiple sclerosis are reported. All five had the primary progressive form of multiple sclerosis, which forms only 15% of multiple sclerosis in population surveys. The coincidence of neurofibromatosis 1 and multiple sclerosis might be due to a mutation in the embedded oligodendrocyte-myelin glycoprotein gene.

Methods
We sought information from neurologists with large series of patients with multiple sclerosis and from geneticists with neurofibromatosis clinics. Three patients were referred to our regional neurofibromatosis clinic of 200 patients; one patient, a sibling of one of these patients, had died and one patient was diagnosed at the Wessex regional neurological centre. All patients were seen by one of us except for case 2, whose case records were made available. All the patients fulfilled the diagnostic criteria for neurofibromatosis 1.

Case histories
CASE 1
A 44 year old housewife was diagnosed as having neurofibromatosis 1 when she was a teenager, on the basis of a family history, café au lait spots, axillary freckling, and multiple cutaneous neurofibromas. She presented in 1992, at 42 years of age with a two year history of progressive painful tingling in the hands and feet, and a six month history of right sided weakness and shaking of the right arm at rest. Her maternal grandmother, mother, and sister all had neurofibromatosis 1. Her mother had died of carcinoma of the stomach and her sister had died of a combination of bronchopneumonia, cerebrovascular disease, and multiple sclerosis (see case 2).

On examination she had the cutaneous...
Neurofibromatosis 1 and multiple sclerosis

stigmata of neurofibromatosis 1. The right disc was pale and corrected visual acuity was 6/18 on the right and 6/6–1 on the left. Tone was mildly increased in the right arm with a rest tremor and there was a mild intention tremor of both arms. She had a mild right sided hemiparesis with hyperreflexia and extensor plantar response.

A myelogram showed no evidence of intraspinal neurofibromatosis. Electrophoresis showed that the CSF gammaglobulin distribution was oligoclonal and this pattern was not present in the serum. Visual evoked responses were delayed bilaterally. T2 weighted brain MRI showed multiple areas of altered signal in the white matter of both cerebral hemispheres, predominantly in the centrum semi-ovale and periventricular regions (fig 1). Some of the lesions showed enhancement after contrast with gadolinium-dimeglumine-triamine-pentacetic acid (Gd-DTPA).

She was treated with a course of intravenous methylprednisolone without obvious improvement in her symptoms. Her walking gradually deteriorated and by 1993 she was only able to walk 100 metres unaided.

CASE 2
The sister of case 1 was born in 1942. She developed café au lait spots at six months and cutaneous neurofibromas as a teenager. In her teens she required surgery for kyphoscoliosis and a plexiform neurofibroma of the left chest wall. At the age of 23 years she noticed progressive weakness of the right leg and unsteadiness of gait. Three years later she experienced weakness and incoordination of the upper limbs and urinary frequency and urgency.

She was examined at another neurological centre in 1980. The cutaneous lesions of neurofibromatosis 1 were noted and she had a severe kyphoscoliosis. Her intellectual function was impaired with poor short term recall and general knowledge. Visual acuity was 6/6 bilaterally but she had bilateral optic atrophy and impairment of colour vision. There was a bilateral internuclear ophthalmoplegia and sustained nystagmus was evident on vertical gaze. There was pronounced disequilibrium, limb ataxia, more noticeable on the left, and a moderate spastic paraparesis.

A myelogram showed numerous small neurofibromas arising from the nerve roots in the cervical region but there was no significant cord compression. Brain CT showed several areas of low density in a periventricular distribution. Both visual evoked responses and somatosensory evoked responses were significantly delayed. Electrophoresis showed an oligoclonal distribution of gammaglobulin in the CSF, but not in the serum, and the CSF IgG concentration was 30% of the total protein. A diagnosis of neurofibromatosis 1 and multiple sclerosis was made and the patient was transferred to a rehabilitation centre.

At the age of 42 she had a haemorrhage into the right posterior limb of the internal capsule. She became increasingly disabled and died aged 46 from bronchopneumonia.

CASE 3
A 32 year old waitress had been born in this country but was of Asian origin. She developed café au lait spots as a baby and cutaneous neurofibromas when she was a teenager. There was no family history of neurofibromatosis 1.

According to her own report she had had learning difficulties at school and was experiencing problems in performing simple calculations in her job as a waitress. She had a six year history of progressive weakness and stiffness of her legs. On examination in 1989 she had multiple café au lait patches, cutaneous neurofibromas, and axillary freckling. Her intellect was impaired with a full scale IQ of 68. She had bilateral optic atrophy. There was a moderate ataxic spastic paraparesis, more pronounced on the right, with hyperreflexia and extensor plantar responses. Visual evoked responses were delayed bilaterally. T2 weighted MRI of the spinal cord did not show any evidence of cord compression. Brain MRI showed multiple, predominantly periventricular, lesions in both cerebral hemispheres. Oligoclonal bands were detected by CSF electrophoresis and were not present on serum electrophoresis. Normal white cell enzymes excluded a leukodystrophy and autoantibodies were negative.

She was treated with a course of intravenous methylprednisolone without benefit. Her walking continued to deteriorate over a five year follow up period and by 1994 she required a stick to walk about 100 metres.

CASE 4
A retired solicitor was born in 1926. There was no family history of neurofibromatosis 1. She developed café au lait patches and axillary freckling as a child and cutaneous neurofibromas during her teens. At the age of 42 in 1968, she experienced progressive slowness and stiffness of her walking and by 1981

Figure 1 Case 1; T2 weighted axial MRI (SE TR 2000/TE 80) of the brain. There are multiple high signal lesions in the centrum semi-ovale.
years his walking deteriorated and he had to give up his job as a storeman. A diagnosis of multiple sclerosis was made in 1980 when he developed a bilateral internuclear ophthalmoplegia and delayed visual evoked responses. He did not respond to treatment with intravenous methylprednisolone. His condition continued to worsen gradually, and by 1993 he was only able to walk a few steps with the aid of a Zimmer frame. T2 weighted brain MRI in 1993 showed areas of increased signal in the white matter of both cerebral hemispheres in the centrum semi-ovale, periventricular white matter, cerebral peduncles, and pons.

**Discussion**

These five patients with neurofibromatosis 1 all developed the primary progressive form of multiple sclerosis. This form of multiple sclerosis usually occurs in only 15% of patients with demyelination and is associated with relatively few lesions on brain MRI.\(^1\)\(^2\) T2 weighted brain MRI in four patients and CT on the fifth showed multiple areas of altered signal in the white matter of both cerebral hemispheres consistent with demyelination. The lesions in these patients were in the white matter rather than in the basal ganglia, the site of predilection for abnormalities associated with neurofibromatosis 1.\(^3\) The lesions in patients with neurofibromatosis 1, which are probably hamartomas, are not associated with overt neurological symptoms or signs and occur predominantly in children.\(^4\)

Visual evoked responses were delayed in all patients and this was not due to optic nerve gliomas, which were excluded by the brain scans. In the three patients in which the test was performed, CSF electrophoresis showed an oligoclonal gammaglobulin distribution that was not found on serum electrophoresis. Spinal MRI or myelography excluded neurofibromas as a cause of the progressive gait disturbance. One patient died of an unrelated cerebral haemorrhage and postmortem examination confirmed the diagnosis of multiple sclerosis by showing chronic plaques of demyelination throughout the brain and cervical cord.

Although multiple sclerosis is a common disease with a prevalence of at least 1 in 1000 in south east England,\(^1\) its occurrence in five patients with neurofibromatosis 1 merits closer inspection. Our patients may simply have both neurofibromatosis 1 and primary progressive multiple sclerosis as an unfortunate consequence of chance. However, OMgp has been identified as one of the embedded genes in the neurofibrosis 1 gene and may function as a cell adhesion molecule in the myelin of the CNS. Hence, it is reasonable to speculate that patients with neurofibromatosis 1 and demyelinating disease may have a mutation involving the area of the embedded OMgp gene, which produces this particular clinical phenotype. Molecular studies are under way to test this hypothesis.
We are grateful to Dr C Clarke for permitting us to review the case records of case 2, Dr T Cox for the MRIs, Dr P Kennedy for referring case 5, and Dr S Hodgson for advice.


Neurofibromatosis 1 and multiple sclerosis.

R E Ferner, R A Hughes and M R Johnson

*J Neural Neurosurg Psychiatry* 1995 58: 582-585
doi: 10.1136/jnnp.58.5.582

Updated information and services can be found at:
http://jnnp.bmj.com/content/58/5/582

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/