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Neurofibromatosis 1 and multiple sclerosis

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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 myelin 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.

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Neurofibromatosis 1 is a common autosomal disorder with a minimum prevalence of 1 in 5000 and a spontaneous mutation rate of about 50%.[1] The disease principally involves the skin and peripheral nervous system, but the complications may affect any of the body systems. The neurological manifestations of neurofibromatosis 1 range from usually mild intellectual impairment and optic nerve and parenchymal gliomas to epilepsy and macrocephaly.[2 3]

The gene for neurofibromatosis 1 is located on chromosome 17q11·2 and spans about 300 kilobases of genomic DNA.[4 5] Three genes, EVI2A, EVI2B, and oligodendrocyte-myelin glycoprotein (OMgp), are embedded in an intron of the neurofibromatosis 1 gene and are transcribed on the opposite strand to it.[4 6] The function of these genes is uncertain, but so far there is no evidence that altered expression of these genes in patients with neurofibromatosis 1 results in clinical heterogeneity.

Oligodendrocyte-myelin glycoprotein is a membrane glycoprotein that was initially identified as a peanut agglutinin binding protein appearing in the human CNS at the time of myelination.[7] It can be detected immunohistochemically in CNS myelin and on the surface of cultured oligodendrocytes. It is not found on Schwann cells, in peripheral nervous system myelin, or in any other tissue outside the CNS. The glycoprotein is anchored to the outer leaflet of the membrane through a glycosylphosphatidyl inositol lipid molecule, as is the cell surface form of the neural cell adhesion molecule, N-CAM.[8] Structurally, OMgp has the potential to function as an adhesion molecule and could contribute to the interactions between the plasma membranes of oligodendrocytes and axons required for myelination.[7]

There have been anecdotal reports of patients with both neurofibromatosis 1 and multiple sclerosis, but in the past the association was considered to be coincidental.[1 9] The recent advances described, however, provide a theoretical link between these conditions. We report five patients, including two siblings, with neurofibromatosis 1 and multiple sclerosis.

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.[10]

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

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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 semiovale 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.

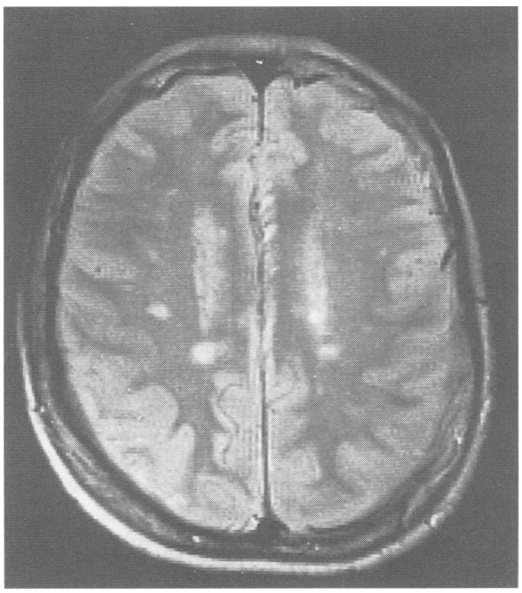

Figure 1 Case 1; T2 weighted axial MRI (SE TR 2000/TE 80) of the brain. There are multiple high signal lesions in the centrum semi-ovale.

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

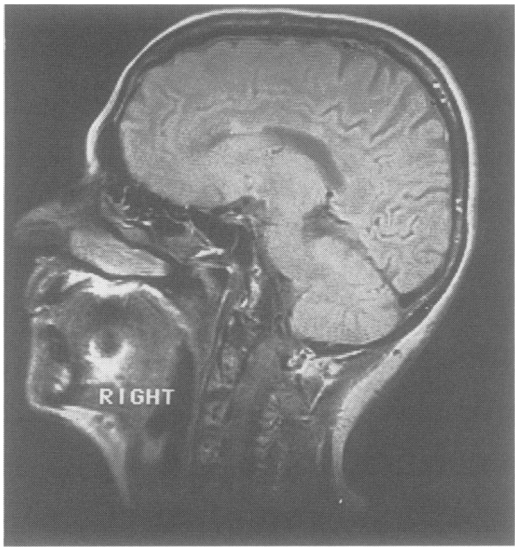

Figure 2 Case 4; T2 weighted sagittal MRI (SE TR 2000/TE 80) of the brain. There are multiple high signal lesions in the corpus callosum.

required two sticks to walk outside her home. On examination in that year she had multiple café au lait patches and numerous sessile dermal neurofibromas. There was a moderate tetraparesis with hyperreflexia and extensor plantar responses. Investigations including a brain CT, myelography and EMG showed no abnormality. By 1986 she had deteriorated further and required a wheelchair. She also complained of urinary urgency. Visual evoked responses were delayed bilaterally. T2 weighted brain and spinal cord MRI showed multiple high signal lesions in the white matter of both cerebral hemispheres, particularly in the periventricular region and also in the pons and cerebellar hemispheres (fig 2). High signal was also seen in the lower part of the medulla, extending down to the upper cervical cord.

Her condition remained stable until December 1988 when she developed a sudden headache, drowsiness, and neck stiffness. Brain CT showed subarachnoid blood and she died a few hours later.

Postmortem examination showed an aneurysm of the middle cerebral artery and multiple demyelinated plaques in the white matter of the cerebral hemispheres, pons, corpus callosum, cerebellar hemispheres, and optic nerves.

CASE 5

A 65 year old single man had been diagnosed as having neurofibromatosis 1 at the age of 35 years, on the basis of café au lait spots and multiple cutaneous neurofibromas. There was no family history of neurofibromatosis 1.

In 1974 he developed progressive gait disturbance. Six months later neurological examination showed pale optic discs, nystagmus on right lateral gaze, and an ataxic, spastic hemiparesis. Brain CT was normal and CSF examination showed normal protein concentration of which IgG constituted 7%. Electrophoresis of CSF was not performed. A test for antinuclear factor was negative. Over the next six 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.[11 12] 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.[9] 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.[9]

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,[13] 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.

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