LETTERS TO THE EDITOR

The thermolabile variant of 5,10-methylenetetrahydrofolate reductase is not associated with Parkinson's disease

Oxidative damage has been suggested as a potential mechanism for both atherosclerosis and neurodegenerative disorders such as Parkinson's disease.1 One report has noted a 2-5-fold increased risk of cardiovascular disease among patients with Parkinson's disease,2 suggesting that a common genetic variant may contribute to both diseases. One such candidate genetic factor, the ApoE-e4 allele, is found at a raised frequency in those with cardiovascular disease and Alzheimer's disease, but was recently shown not to be raised in patients with Parkinson's disease.3

Homocysteine is a pro-oxidant that acts via the copper catalysed, oxygen dependent, production of hydrogen peroxide. Moderately raised concentrations of the amino acid homocysteine (mild hyperhomocysteinaemia) confer a twofold to threefold risk of vascular disease. In a significant proportion of cases mild hyperhomocysteinaemia arises from the interaction of the homozygous thermolabile (tt) genotype of 5,10-methylenetetrahydrofolate reductase (MTHFR) with suboptimal folate and B12 nutrition.4 The tt genotype has also been directly associated with cardiovascular disease.5 We therefore determined the prevalence of the tt genotype in patients with Parkinson's disease. Patients with a classic form of Parkinson's disease (n = 188) and matched controls (n = 184) were selected as described previously.6 Cases had initial symptoms before the age of 56 years, and were born after 1924. Controls were age and frequency matched by five-year bands, sex, and urban-rural indicator. Genotyping for the tt allele was performed by polymerase chain reaction and Hinf I digestion of genomic DNA extracted from whole blood.7 The tt genotype was present in 9.6% (n = 18) of the patients with Parkinson's disease and 7.1% (n = 13) of the controls. In the Parkinson's disease group the heterozygote frequency was 42.5% (n = 80) and the non-thermolable homozygote frequency was 47.9% (n = 90). The corresponding frequencies in the control group were 47.3% (n = 86) and 45.6% (n = 84) respectively. There was no significant difference in the frequency distribution of genotypes (χ2 = 1.26, 2df, P = 0.33) and the odds ratio for the tt genotype was 1.39 (95% confidence intervals 0.63–3.12).

These results clearly indicate that the tt genotype is not associated with Parkinson's disease and does not explain the finding that patients with Parkinson's disease are at increased risk of vascular disease. The fact that no association is found may indicate that the brain is protected from raised homocysteine concentrations by the preferential accumulation of folate in the CNS, where its concentration is three times that found in serum. Other genetic candidates should be examined for a potential role in oxidative damage, and the importance of common environmental factors such as dietary antioxidants considered.

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Refsum's disease: long term treatment preserves sensory nerve action potentials and motor function

Refsum's disease is a recessively transmitted disorder characterised by retinitis pigmentosa, polyneuropathy, and cerebellar ataxia associated with tissue storage of phytic acid.1 Nerve conduction studies in patients with Refsum's disease show abnormal motor nerve conduction velocity (NCV) with signs of chronic denervation.2 Sensory nerve action potentials are usually slightly prolonged and absent.3 We present a patient with Refsum's disease with preservation of SNAPs and motor functions after 20 years of continuous therapy with both diet restriction and plasmapheresis. Her initial clinical course has been reported.4

A 39 year old woman with retinitis pigmentosa and cataracts was admitted in 1976 with a four week history of paraesthesia and weakness. Physical examination showed exfoliative dermatitis, constricted visual fields, right ptosis, and facial diplegia. She had bilateral foot drop and decreased sensation distally. She was areflexic. The peroneal nerves were palpably enlarged at the fibular heads. Protein content of CSF was 210 mg/dl with normal cell count and glucose concentration. Nerve conduction studies showed normal reduced motor conduction velocity of the right peroneal nerve (21.1 m/s) and of the right median sensory conduction velocity (44.4 m/s). Sural nerve biopsy showed an increase in intramyelinic myelin. Serum phytic acid concentration was 6460 μM/L (normal < 34 μM/L). She was diagnosed with Refsum's disease and started on a low phytanate diet. She was reviewed within one month with a flaccid tetraparesis and a worsening in nerve conduction studies. A twice weekly plasma exchange programme was instituted. She improved in motor and sensory function. She continued to accumulate fully with forearm crutches and a short leg brace in three months. Six months after the initiation of plasma exchange, the phytic acid concentration declined to 340 μM/L.

Subsequently, she was maintained on plasmapheresis once every three to six weeks and low phytanate diet over the next 20 years. The phytic acid concentration after plasmapheresis remained less than 340 μM/L. Repeat nerve conduction studies on eight occasions showed the preservation of the right sural and superficial peroneal SNAPs.

On most recent examination in 1996, she had normal strength, sensation, and reflexes in the upper limbs. She had only slight weakness and reduced sensations. She could ambulate fully with ankle braces and a cane for longer distances. Nerve conduction studies showed: (1) the median nerve: slightly prolonged distal latency (left/right 4:2 ms/4:0 ms); normal NCV in the forearm segment and minimal F wave latency bilaterally; and no significant difference in the compound muscle action potential (CMAP) amplitudes from the distal (wrist) to the proximal (elbow) stimulation sites on either side. (2) The right peroneal nerves: absent CMAP recording from the extensor digitorum brevis muscle. (3) The right tibial nerve: absent CMAP recording from the abductor hallucis muscle. (4) Normal sensory nerve conduction in bilateral median and radial, right ulnar, and right superficial peroneal nerves. Nerve conduction velocities were normal. There was no acutaneous and chronic denervation in the distal muscles of the right lower limb including the anterior tibialis and gastrocnemius muscles but no denervation in the proximal muscles of the right lower limb (the vastus lateralis and biceps femoris muscles), the paraspinal muscle in the lumbarosacral region, or right first dorsal interosseus muscle. These findings are consistent with a predominantly motor axonal polyneuropathy.

Our patient is unusual as most patients previously reported had different degrees of concomitant sensorimotor polyneuropathy. The reasons why motor fibres are more affected in our patient are not clear. One possible explanation is that phytic acid is more soluble in motor nerve membranes than in sensory nerve membranes. The difference in solubility may be caused by the differences in the ganglioside compositions of motor and sensory nerves. Larger amounts of phytic acid may accumulate in motor fibres than in sensory fibres and cause more damage.

The beneficial effects of dietary treatment and plasmapheresis in Refsum's disease are consistent.6 The effectiveness of the treatment can be monitored by measurement of serum phytic acid concentrations. However, not all of the clinical findings in Refsum's disease are reversible.7 Rapidly developed weakness associated with an acute exacerbation often responds more rapidly and completely to treatment than a gradual onset polyneuropathy. The acute flaccid tetraparesis of our patient responded quickly to plasmapheresis. The weakness has persisted since and is mostly likely due to chronic polyneuropathy.

In conclusion, a predominantly motor axonal polyneuropathy may be seen in Refsum's disease and long term dietary
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