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-ε4 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 early onset Parkinson's disease (n = 188) and matched controls (n = 184) were selected as described previously.[3] 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.[4] 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-thermolabile homozygote frequency was 47·9% (n = 90). The corresponding frequencies in the control group were 47·3 % (n = 87) and 45·6% (n = 84) respectively. There was no significant difference in the frequency distribution of genotypes (χ^2 = 1·26, 2df, P = 0·53) 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 phytanic 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 (SNAPs) are usually absent.[2] We present a patient with Refsum's disease with preservation of SNAPs and motor functions after 20 years of continuous therapy with diet restriction and plasmapheresis. Her initial clinical course has been reported.[3,4]

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. Nerve conduction studies showed reduced motor conduction velocity of the right peroneal nerve (21·1 m/s) and of the right median sensory conduction velocity (34·4 m/s). Sural nerve biopsy showed an increase in connective tissue and loss of myelin. Serum phytanic 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 returned 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 functions. She could ambulate fully with forearm crutches and a short leg brace in three months. Six months after the initiation of plasma exchange, the phytanic 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 phytanic 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 sensation in the lower limbs distally. She walked around her house without any assistance but required ankle braces and a cane for longer distances. Nerve conduction studies showed: (1) *the median nerves*: 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 drop 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; reduced CMAP amplitude (1·3 mv) recording from the tibialis anterior muscle; and no significant drop in CMAP amplitudes from the distal (the fibula neck) to the proximal (knee) stimulation sites. (3) *The right tibial nerve:*, absent CMAP recording from the abductor hallucis muscle. (4) Normal sensory nerve conduction in bilateral median and radial, right sural, and right superficial peroneal nerves. Needle examination showed acute 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 lumbosacral region, or right first dorsal interosseus muscle. These findings were compatible with a predominantly motor axonal polyneuropathy.

Our patient is unusual as most patients previously reported had different degrees of demyelinating sensorimotor polyneuropathy.[2] The reasons why motor fibres are more affected in our patient are not clear. One possible explanation is that phytanic 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 ganglionside compositions of motor and sensory nerves.[5] Larger amounts of phytanic 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 established.[1] The effectiveness of the treatment can be monitored by measuring serum phytanic acid concentrations. However, not all of the clinical findings in Refsum's disease are reversible.[1] 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 in our patient responded quickly to plamapheresis. The weakness she has had since 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