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 in 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.1

Homocysteine is a pro-oxidant that acts via the copper catalyst, oxygen dependent, production of hydrogen peroxide. Moderately raised concentrations of the amino acid homocysteine (mild hyperhomocysteinemia) confer a twofold to threefold risk of vascular disease. In a significant proportion of cases mild hyperhomocysteinemia arises from the interaction of the homoyzous thermolable (tt) genotype of 5,10-methylene-tetrahydrofolate reductase (MTHFR) with suboptimal folate and B12 nutrition.3 The tt genotype has also been directly associated with cardiovascular disease.4 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.1 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.5 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 = 87) and 45.6% (n = 84) respectively. There was no significant difference in the frequency distribution of genotypes (χ² = 1.26; 2df; P = 0.53) and the odds ratio for the tt genotype was 1.39 (95% confidence interval: 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.

DOROTHY RAMSBOTTOM
Shinjuku General Hospital
Department of Neurology
Tokyo, Japan
DARWIN L HARMON
Glyne House
Kemptown
Brighton, UK
YAOV BEN-SHILO
State University of New York
DOWNSHALL
New York Medical College
Valhalla, NY, USA
GEOFFREY DAVEY-SMITH
Department of Neurology
University of Bristol, UK

Correspondence to: Professor AS Whitehead, Genetics Department, Trinity College, Dublin 2, Ireland.


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.4 Nerve conduction studies in patients with Refsum's disease show abnormal motor nerve conduction velocity (NCV) with signs of chronic denervation.5 Sensory nerve action potentials (SNAP) were usually normal or 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.1

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 anorexic and lost 10 kg. Her peripheral nerves were palpably enlarged at the cubital 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 nerve fibre diameter. Serum phytanic acid concentration was 6460 μM (normal < 34 μM/L). She was diagnosed with Refsum's disease and started on a low phytanic acid diet. Six months later, she was re-examined with one month with a flaccid tetraparesis and a worsening in nerve conduction studies. A twice weekly plasmapheresis programme was instituted. She improved in motor and sensory function, but experienced heavily fatigued 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 sensibility. She could ambulate fully with long 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 nerve: slightly prolonged distal latency (left/right 4.2-4.0 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 median nerve distal to the elbow in the median CMAP amplitude (1.3 mV) recording from the tibialis anterior muscle; and no significant drop in CMAP amplitudes from the distal (the fibula) to the proximal (knee) stimulation sites. (3) The right ulnar 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 EMG 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 lumbarosacral region, or right first dorsal interosseous muscle. These findings are consistent with 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 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 ganglioside compositions of motor and sensory nerves.1 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 especially clear.6 The effectiveness of the treatment can be monitored by measuring raised 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 of our patient responded quickly to plasmapheresis. The weakness she had since is mostly likely due to chronic polyneuropathy.

In conclusion, a predominately motor axonal polyneuropathy may be seen in Refsum's disease and long term dietary
treatment and plasmapheresis are effective in preserving sensory nerve potentials and motor function.

JAU-SHIN LOU
ROBERT SNYDER
ROBERT C GRIFFS
Department of Neurology,
University of Rochester Medical Center
Rochester, NY, USA

Correspondence to: Dr Jau-Shin Lou, University of Rochester Medical Center, Department of Neurology, Box 673, 601 Elmwood Avenue, Rochester, NY 14642, USA.


Contraversive visual tilt illusion associated with a cerebellar infarction

Visual tilt illusion consists of an abnormal perception of the environment, which seems to be rotated at a variable angle without any change of the other characteristics of the objects. It is sometimes associated with other postural and ocular tilt effects. It can be secondary to disturbances in the peripheral or central vestibular pathways. Previous reports suggest that cerebellar injuries could also cause it, but this has not been documented before. We report a case of visual tilt illusion probably associated with an isolated cerebellar lesion, studied both clinically and MRI.

A 56 year old man with hypertension and hypercholesterolaemia had a sudden attack of continuous vertigo not related to cephalic movements, with nausea and vomiting, and a deviation to the left while walking. When it disappeared, 48 hours later, he complained that he saw objects as if they were tilted to his right by 30° and they should be rotated anticlockwise—that is, to his left—so as to be perceived as vertical. He had a slight head and body tilt to his left that worsened when he was asked to close his eyes and stand upright. There was no skew deviation or other ocular motor disorders. Fundal photographs were not taken, so that ocular torsion could not be assessed. There were no other alterations on neurological examination. Two weeks later the patient was asymptomatic. Brain CT and MRI showed a right hemispheric cerebellar region, suggesting an ischaemic infarction (figure). No brainstem or cortical alterations were found.

Visual tilt illusion has been described in unilateral peripheral vestibular lesions; in brainstem injuries, typically in the Wallenberg syndrome, in other medullary and mesencephalic lesions, and in thalamic and parietoinsular cortex disorders.1 The most frequent conditions associated with visual tilt illusion are vascular lesions. As far as we know, there are no reports on documents of abnormal cerebellar injuries associated with the illusion.

Physiologically, the vestibular pathways make contact with the ocular motor system, the spinal cord, and the vestibular cortex, contributing to the stabilization of posture and perception of verticality and self motion. The tonic bilateral vestibular input builds up the actual central vestibular tone in the three major planes: horizontal or ’yaw’, sagittal or ’pitch’, and frontal or ’roll’. It seems that central pathways that mediate vestibular function in either of the three planes travel independently of each other, so that a specific lesion could cause a disorder restricted to one of them. The vestibular tone in the frontal or ’roll’ plane allows a correct perceptual, ocular, and postural alignment to the ’gravitational vertical’; an imbalance in this tone causes a lateral tilt with alteration in perception of verticality, head and body posture, misalignment of the visual axes, or ocular torsion. Patients perceive the surroundings and their body as if they were tilted in the opposite direction to what the CNS erroneously computes as being vertical and try to adjust the visual objects and posture to it. Dietrich and Brandt showed that an alteration in the perceived verticality is not just the sensory consequence of the rotation of the eyes, as they can appear separately and are not proportional in degree. Furthermore, it is possible that not all the effects of tilt occur in one patient, and the perceptual disorder itself is the most sensitive sign of a vestibular tone imbalance in the frontal plane. Brainstem structures that mediate the vestibular tone in the ’roll’ plane include the vestibular nuclei and the interstitial nucleus of Cajal—perhaps the most rostral structure related to the control of vertical and torsional head and eye position. Both are connected by the medial longitudinal fasciculus, which crosses the midline in the pons. Visual vertical tilt is, then, ipsiversive to peripheral or pontomedullary lesions and contraversive to pontomesencephalic lesions and, in both cases, is usually associated with other tilt effects; in most rostral lesions it may be either ipsiversive or contraversive and is usually isolated. The role of the vestibular cerebellar structures with respect to the control of subjective verticality is not well known at the moment. Our patient’s clinical findings suggest that he had an inclination of the internal representation of the gravitational vector to his left and he tried to adjust both visual objects and posture to what he perceived as being vertical. It would have been interesting to assess whether there was a contraversive tilt to define his clinical setting more exactly, but it makes no difference to interpretation as ocular torsion can be associated or not with perceptual or other tilt effects. Our patient showed a right hemispheric cerebellar ischaemic lesion, in a territory dependent on the posteroinferior cerebellar artery (PICA), with no mass effect and no brainstem or other alterations on MRI. His perceptual and postural tilt was contraversive to the lesion. It is possible that an additional subtle medullary lesion in the distribution of the PICA, not evident with clinical and imaging studies, produced the tilt effect. This is because, because the major infratentorial arteries supply both brainstem and cerebellum and it is very difficult to differentiate the effects of cerebellar and brainstem lesions. But the tilt should then be ipsiversive to the posteroinferior cerebellar artery, to the hypothetical lesion. Therefore it is not likely that an associated medullary ischaemia could cause the tilt effects in our patient. A mesencephalic injury could cause this clinical picture but there were no other MR alterations and there were associated postural tilt effects. In this patient, we think that cerebel lar dysfunction could be responsible for the tilt effects.

The present report confirms a previously hypothesised role of the cerebellar structures in the control of perception of verticality, and may contribute to a better knowledge of the pathophysiology and the topographic diagnosis of the central vestibular syndromes.

M BARÓN, JM GONZÁLEZ, M JIANG, M LOUSA
Servicio de Neurología, Hospital Ramón y Cajal, Universidad de Alcalá de Henares, Madrid, España

Correspondence to: Dr M Barón, Servicio de Neurología, Hospital Ramón y Cajal, Ctra de Colmenar, Km 9,100, 28034 Madrid, Spain.


Low striatal D2 receptor binding as assessed by [11C]IBZM SPECT in patients with writer’s cramp

Writer’s cramp is a form of idiopathic focal task specific dystonia. In accord with other studies on idiopathic and symptomatic dystonia, Tempel and Perlmutter suggested the presence of an abnormal striostriatal mesocortical drive in writer’s cramp. In view of the