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Debrisoquine hydroxylase polymorphism in Leber's hereditary optic neuropathy

Leber's hereditary optic neuropathy (LHON) causes severe visual loss, most commonly in young men. The primary genetic defect is a mutation in mitochondrial DNA (mtDNA) at positions 11 778, 14 484, or 3460 base pairs (bp) in nearly all families in the United Kingdom.¹ However, in most cases, both patients and their unaffected relatives from families with LHON have very high amounts of mutant mtDNA (> 95%); other factors must therefore determine the development of visual failure. A number of findings suggest that there may be an environmental precipitant to the development of LHON. Firstly, there is no evidence of correlation between age of onset in index cases and affected siblings in families with LHON.¹ Secondly, some reports have suggested that the proportion of patients with LHON who drink alcohol and who smoke is unusually high; this is particularly pronounced in those patients with the 3460 and 14 484 bp mutations.² Thirdly, other case reports have postulated that LHON can be triggered by various metabolic and toxic precipitants, including diabetes, B12 deficiency, and exposure to toxins.

Cytochrome P-450 mono-oxygenases metabolise several endogenous compounds and environmental chemicals and individual variations in cytochrome P-450 expression might, therefore, influence susceptibility to LHON. Impaired debrisoquine metabolism is found in 5–10% of the white population. It is an autosomal recessive trait caused by mutations in the *CYP2D6* gene, which determines cytochrome P-450 activity in the liver and other tissues. Genotypic analyses have been used to identify a G to A transition at the intron 3/exon 4 junction (allele B), a base pair deletion in exon 5 (allele A), and (rarely) a deletion of the entire gene, which collectively account for 90% of poor metabolisers who are either homozygous for one or compound heterozygotes for two of

Distribution of *CYP2D6* alleles and genotypes in patients with LHON and controls

	LHON	Controls
Allele:	No of chromosomes	
Wild type (W)	70	226
G → A transition (B)	29	62
Base pair deletion (A)	3	2
Total	102	290
χ^2 (B v W)	2.06 (P > 0.10)	
Genotype*:	No of subjects	
WW/WW	24	96
AW/WW	3	2
WW/BW	19	32
WW/BB (PMs)	5	15
Total	51	145
%PMs	9.8	10.0
χ^2 (PMs v not)	0.012 (P > 0.50)	

*For example, AW/WW is heterozygous for the mutant A allele and homozygous normal (W = wild type) for the B allele. PM = poor metaboliser.

these mutations. Reports on the incidence of poor metabolisers in Parkinson's disease using pharmacokinetic assays have provided conflicting results, but genotypic analyses have found an excess of poor metaboliser genotypes.³

We investigated the frequency of these alleles in index cases of 51 families with LHON. Forty two had the 11 778 bp, four the 3460 bp, and five the 14 484 bp mutation; 32 were male, and 19 were female. Control blood samples were from 145 unrelated healthy subjects of similar ethnic and geographical backgrounds. Controls were only roughly matched for age and sex because these do not influence the distribution of *CYP2D6* genotypes. DNA was prepared from leucocytes by standard methods. The *CYP2D6* G to A transition and base pair deletion were analysed in two separate polymerase chain reactions using, respectively, oligonucleotide primer pairs C + D and E + F as previously described.³ Genotypes and allele frequencies in patients and controls were compared by χ^2 analysis with Yates' correction for 2 × 2 tables.

There was no excess of mutant *CYP2D6* alleles in unrelated LHON index patients compared with unrelated controls; nor was there an excess of poor metabolisers (table). It is therefore unlikely that impaired debrisoquine metabolism is responsible for the development of LHON in patients with a pathogenic mtDNA mutation. Apart from exposure to or impaired metabolism of environmental toxins, there are other possible explanations for the development of blindness in LHON. Firstly, the excess of affected males has led to suggestions that an X linked visual loss susceptibility locus may be involved.⁴ Secondly, some features of LHON are surprising for a genetic condition and an autoimmune component has been suggested. This is supported by the finding that, in rodents, mtDNA encoded peptides can act as transplantation antigens.⁵

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Pure sensory stroke caused by cortical infarction associated with the secondary somatosensory area

Pure sensory stroke, described as a distinct clinical entity in 1965 by Fisher,¹ denotes a hemisensory disturbance without other neurological deficits. Although pure sensory stroke is usually due to a thalamic lesion, it could be also caused by lesions involving any portion of the common human sensory pathway from the postcentral gyrus, known as the primary sensory area (SI), to the medulla.² We report a patient with pure sensory stroke resulting from a cortical infarction on the inner bank of the parietal operculum, which is known as the secondary somatosensory area (SII).

A 44 year old, right handed man with a history of cigarette smoking was admitted because of sudden decrease of touch and pain sensation in his right hemibody. On admission, neurological examination disclosed normal motor function and reflexes. There was a moderate hypaesthesia for light touch, pain, and temperature senses on the right side including the face, oral cavity, arm, trunk, and leg. Discriminative touch, joint, and vibration sensation as well as stereognosis and graphaesthesia were preserved on the right side. Cranial nerve functions including taste sense were also within normal limits. There were no neuropsychological signs such as aphasia, impairment of calculating ability, or disturbance of right-left discrimination. Magnetic resonance imaging taken four days after the onset showed a cortical infarction located within the inner bank of the left parietal operculum (figure). The common sensory pathway from the postcentral gyrus to the medulla, especially the thalamus, was normal on MRI. Results of routine laboratory examinations and vasculitis screening were unremarkable. A chest radiograph, ECG, echocardiogram, and carotid Doppler ultrasound examination were normal. Short latency somatosensory evoked potentials produced by stimulation of the median nerve were evaluated seven days after the onset. Both the latency and amplitude of any points including N20 were almost equal on both sides. The central conduction time (N13 to N20) had also no laterality. Cerebral angiograms, including the left middle cerebral artery, taken on day 20 showed no abnormality. At discharge, 27 days after the onset, a slight decrease in pain and touch sensation persisted in his right side.

Coronal T2 weighted MRI showing a high signal intense at a cortical area in the inner bank of the left parietal operculum.

Two somatosensory projection areas, S I and S II, have been shown to exist in the brains of mammals of various species.³ S I, located in the postcentral gyrus, is especially concerned with the integration of sensory experience and with the discriminative qualities of sensation. S II has been mapped to the parietal operculum in many animal species,³ including humans.⁴ According to recent studies with monkeys, the cortical area defined as S II lies limited to the inner bank of the parietal operculum, which is smaller in size than previously considered.⁵ The organisation of S II in humans remains unclear, although it has been considered as a cortical locus for pain perception.³ Penfield and Jasper⁴ initially identified an S II in humans in the precentral and postcentral cortex—using reports of sensations after electrical stimulation near the sylvian fissure. They proposed that S II was located in the superior bank of the sylvian fissure and contributed to somatic sensation. They also reported that no sensory disturbances occurred in patients after ablating S II. Conversely, the parietal operculum and insula have been described as producing various sensory disturbances such as impairment of all sensory modalities, impaired cortical sensation, or decreased pain and temperature sensation.⁶ To the best of our knowledge, there are no prior studies describing cortical infarction of a limited area in the inner bank of the parietal operculum.

There have been reports of pure sensory stroke due to lesion along the common human sensory pathway including parietal cortical infarctions of S I.² This patient showed restricted sensory impairment in light touch, pain, and temperature senses of the entire right side and fulfilled the criteria of pure sensory stroke. This sensory dysfunction seems to have resulted from a circumscribed cortical infarction of the inner bank of the contralateral parietal operculum, presumably S II.

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Possible clinical overlap between postencephalitic parkinsonism and progressive supranuclear palsy

Encephalitis lethargica is a transmissible disease of the CNS which occurred as a pandemic between 1916 and 1928 and subsequently a few sporadic cases have been reported. Close neuropathological similarities exist between postencephalitic parkinsonism and progressive supranuclear palsy¹ although the clinical presentation is quite different. Our patient had encephalitis lethargica in childhood, developed parkinsonism and later, progressive neurological disability, including frequent falls, neck extension, and supranuclear down gaze palsy. Despite the similarities to progressive supranuclear palsy on clinical examination, the neuro-otological investigations showed some distinctive features.

In 1917, aged six years, the patient was diagnosed as having "sleepy sickness", from which he seemed to recover fully. In 1959, 42 years after his encephalitis lethargica, he began to have excessive sleepiness such that he might fall asleep while playing cards or when at work. At about the same time, he was also noted to have indistinct speech and a resting tremor of his right hand and oculogyric crises occurred. Three years later he developed swallowing difficulties and was noted to have pinpoint pupils with full extraocular movements, slow dysarthric speech, extrapyramidal signs in his limbs, and sluggish limb reflexes. His parkinsonism remained static until 1970 when he was started on a small dose of levodopa with benefit. In 1979, aged 68, he began to fall and developed troublesome blepharospasm, with impairment of extraocular movements. In 1981, he had a further oculogyric crisis, after an excessive dose of sinemet. In 1986, he was readmitted to the National Hospital for Neurology and Neurosurgery for further investigation. His postural reflexes were severely impaired. He was extremely slow to initiate gait, but once started he could walk fairly fluently and with only mildly reduced steps. A general poverty of facial expression and bradykinesia, together with a resting tremor of the lower jaw and right hand were noted. There was pronounced axial rigidity with neck extension, but power, coordination, and limb reflexes were normal, with the exception of absent ankle jerks and extensor plantar responses. Speech was slow and monotonous. The pupils were pinpoint, but circular in shape, and reacted briskly to both direct and consensual light. There was a mild bilateral ptosis. Pronounced blepharospasm triggered by glabellar tapping, together with increased facial jerks, were noted.

Neuro-otological examination disclosed smooth pursuit eye movements in the horizontal plane of about 30° to 40° to both right and left, but only 10° upwards and no downward pursuit from the midposition. Doll's head manoeuvres significantly improved both the horizontal and vertical eye movements, indicating supranuclear involvement. Volitional saccades were absent in the vertical plane, whereas slow, stepped saccades were elicited to about 40° right and left of the midposition. There was no convergence and no spontaneous or positional nystagmus. Optokinetic nystagmus showed a good response to clockwise and occasional beats on counterclockwise stimulation, but there was no response in the vertical plane. Horizontal eye movements were recorded with conventional DC electro-oculography. Hypometric, slow saccades were noted to both right and left. Pursuit was preserved, particularly at the lowest frequency (0.2 Hz; peak velocity 20°/s), but at higher frequencies and velocities, there was a symmetric large reduction of smooth pursuit function (gain 49% at 0.3 Hz and 30°/s; 35% at 0.4 Hz and 40°/s). Small, dysrhythmic, but preserved optokinetic responses were found on both clockwise (gain 82%) and counter clockwise (gain 77%) stimulation. Recordings included a search for spontaneous and lateral gaze evoked nystagmus, but neither were found in the presence or absence of optic fixation. Vestibulo-ocular function tests showed a deviation of the eyes in the opposite direction to the rotational stimulus, but no nystagmus was seen. Caloric testing showed large amplitude responses in the horizontal plane, with no enhancement of the response after removal of optic fixation. Bilateral irrigation at 20°C for 40 seconds resulted in three minutes of pronounced upbeat nystagmus, whereas bilateral irrigation at 44°C showed pronounced downbeat nystagmus lasting four minutes. Auditory brainstem evoked potentials showed waves of small amplitude with bilateral delay of wave III and V consistent with eighth nerve or intrinsic brainstem dysfunction. Brain CT showed sulcal widening and mild hydrocephalus consistent with cerebral atrophy. During the patient's admission sinemet was stopped, which did not lead to any appreciable deterioration in the degree of extrapyramidal dysfunction. In October 1987, aged 76, he developed a marked alteration in his affect in that whereas throughout his life he had always complained of many symptoms he rather underplayed his disabilities and was extremely anxious. He died the next year, aged 77. No postmortem examination was carried out.

Progressive supranuclear palsy primarily affects the saccadic system; vestibular and optokinetic stimuli typically produce a tonic drift of the eyes in the direction of the slow phase of the induced response with no saccadic intrusions to produce the characteristic nystagmic pattern. With progression of the disease, reflex eye movements become deranged as the ocular motor neurons themselves become involved. Various eye signs have been reported in encephalitis lethargica.² Symptoms and signs localised to abnormalities in the pons and midbrain, and characteristic of progressive supranuclear palsy, have been described in the acute stage of encephalitis lethargica, but, although various ocular palsies have been noted in postencephalitic parkinsonism, the characteristic progressive supranuclear eye move-