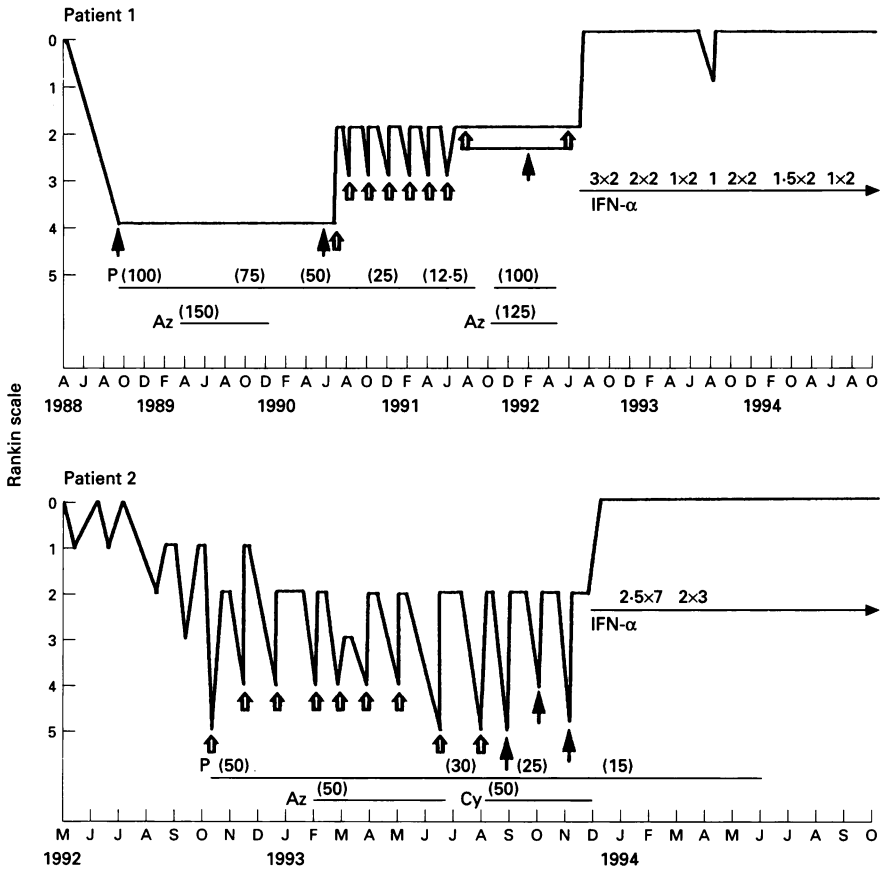

Clinical course of patients 1 and 2. ⇧ = high dosage intravenous immunoglobulins (HIG); ⇧⇧ = HIG maintenance; ⬆ = plasmapheresis; P = prednisone, (alternate day dosage (mm) in parentheses); A = azathioprine; Cy = cyclosporin (daily dosage in parentheses); IFN-α = interferon-α (weekly dosage in million IU).

temporary improvement during and after a flu like syndrome. In July 1992 solo treatment with interferon-α-2a (Roferon-A) at a dosage of 3 million international units (MIU) twice weekly was begun. On the third day after the first injection a dramatic improvement was seen and during 11 days the patient progressively recovered to normal. Serial nerve conduction studies showed progressive reduction of conduction blocks. Seven days after the reduction of interferon-α to 1 MIU/week, progressive weakness of distal muscles occurred that paralleled an increase in multiple conduction blocks. Reinstitution of interferon-α-2a treatment at a dosage of 2 MIU twice weekly, produced a complete recovery within six days. Again the dose of interferon was gradually reduced to 1 MIU twice weekly, without clinical changes.

Only minor adverse effects, such as fever and arthromyalgia, were seen during interferon treatment.

Patient 2 was a healthy 3 year old boy who developed a waddling gait and muscle pain in his legs 20 days after an upper respiratory tract infection. The patient had recovered spontaneously after 15 days. During the next three months he had another three episodes of leg weakness lasting 10–15 days. Brain and spinal cord MRI was normal; electrophysiological studies showed delayed motor conduction velocity with multiple conduction blocks in all the nerves tested and normal sensory conduction velocities. The CSF contained 96 mg/dl protein and 3 white blood cells/ml, but no oligoclonal bands.

During the fifth attack the child became unable to walk unaided and was admitted to our neurological department. He was treated with IVIg at a dose of 1 g/kg daily for two days and prednisone (at a dose of 50 mg every other day) and after three days he regained the ability to walk. Neurography showed disappearance of conduction blocks in two of three motor nerves. Twenty days later the boy had another relapse. Again treatment with IVIg improved motor symptoms in a few days. In the next 15 months he showed relapses every 13 to 20 days despite treatments with azathioprine and cyclosporin. All the episodes responded to IVIg. During three relapses the patient was treated with plasma exchange and showed improvement comparable with IVIg treatment. Treatment with interferon-α-2a (Roferon-A) (2·5 MUI/day)) was given. After this treatment the child regained normal strength within 15 days. The dose of interferon-α was reduced to 2 MIU twice a week after three months. The patient showed no relapses during the subsequent months and no adverse effects were seen. Neurography performed two months after interferon treatment showed improvement of motor conduction velocity in all nerves with pronounced reduction of conduction blocks.

On the basis of the research criteria for the diagnosis of CIDP[2] our patients were affected by "probable CIDP". Despite a good response to IVIg, these patients were still moderately disabled and frequent infusions were needed. In 1992 Engel *et al*[3] described a patient with long lasting CIDP unresponsive to corticosteroids, azathioprine, cyclosporin, plasma exchange, and IVIg, who showed pronounced improvement with interferon-α treatment. This finding led us to the use of interferon in our patients.

Interferon-α treatment resulted in a dramatic and long term recovery. We doubt that this response was fortuitous, because (*a*) both patients showed a pronounced improvement a few days after starting interferon-α and this result was never achieved with other treatments; (*b*) no relapse occurred during full dosage interferon-α treatment whereas before this the patients had had a relapsing course over a long period, despite immunosuppressive treatments; (*c*) patient 1 deteriorated on reducing interferon-α to 1 MIU a week and promptly responded to a higher dose, suggesting a dose-response effect.

The mechanism by which interferon induced an improvement in our patients is uncertain. Interferons exert complex immunomodulator effects and there is evidence that interferon-α may both improve or worsen autoimmune disease.[4] The recent finding that interferon-α may benefit patients affected by multiple sclerosis and that the production of lymphocyte interferon-γ is reduced by this treatment, suggests that interferons may play a central part in the pathogenesis of demyelination in both the central and the peripheral nervous system.[5]

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Kava and dopamine antagonism

Kava is a drink widely used for its calming and tranquilising properties by the native population in the islands of the south Pacific.[1] The beverage is prepared from the roots of the kava plant (*Piper methysticum*); Besides its widespread social use it is also a ceremonial drink, and heads of state have been reported to drink kava during welcome

ceremonies in Fiji.[1] Pharmacological preparations of kava are marketed in various European countries as mild anxiolytics (for example, Laitan or Kavasporal in Germany, Potter's antigian tablets in the United Kingdom, Viocava in Switzerland, Mosaro in Austria), and 547 000 units of preparations containing kava were sold in Germany during 1993. The basis of kava's action has been attributed to a group of α-pyrones (dihydrokawain, kawain, dihydromethysticin, methysticin, dihydroyangonin, yangonin) present in the root extract of the kava plant,[2] but little is known about the pharmacology of these various compounds.

We have recently seen four patients who developed clinical signs suggestive of central dopaminergic antagonism after exposure to various kava preparations.

Patient 1, a 28 year old man, had a history of three episodes of acute dystonic reactions and exposure to promethacin (50 mg in 1983) and fluspirilen injections (1·5 mg in 1983 and 1986) for treatment of anxiety. Each time biperiden (5 mg intravenously) had led to immediate and complete relief of symptoms. He denied further use of these drugs when he presented at our hospital with a recent history of an acute attack of involuntary neck extension with forceful upward deviation of his eyes, which had begun 90 minutes after the intake of the first dose of Laitan (100 mg kava extract) in 1993 and subsided spontaneously within about 40 minutes.

Patient 2, a 22 year old woman, was prescribed Laitan (100 mg kava extract) because of anxiety and nervousness. Four hours after the first morning dose she experienced involuntary oral and lingual dyskinesiae, tonic rotation of the head to the right, and painful twisting movements of the trunk. About 45 minutes later 2·5 mg biperiden was given intravenously, and the dystonic reaction immediately subsided. There was no history of any other drug exposure during the preceding months.

Patient 3, a 63 year old woman, experienced forceful involuntary oral and lingual dyskinesiae of sudden onset after taking Kavasporal forte (150 mg kava extract) three times daily for four days because of anxiety. She was seen in the emergency room about one hour later, and 5 mg biperiden given intravenously immediately stopped the dyskinesiae. The patient denied having taken any other medication during the preceding months.

Patient 4, a 76 year old lady, had first developed signs of idiopathic Parkinson's disease at the age of 59. After eight years of levodopa treatment motor fluctuations and dyskinesiae were becoming an increasing problem. When first seen she was taking 500 mg levodopa (plus 125 mg benserazide) per day and was experiencing motor oscillations between Hoehn and Yahr stage III when "on" and stage V when "off".

Kavasporal forte (150 mg kava extract) twice daily was prescribed by her general practitioner because of complaints of inner tension. Within 10 days she noted a pronounced increase in the duration and number of her daily "off" periods. She returned to her normal baseline pattern within two days of discontinuing Kavasporal forte.

These case histories suggest that the sedative effects of kava might result from dopamine antagonistic properties of the extracts from the *Piper methysticum* plant. This possibility is also supported by clinical findings of beneficial effects of kava on schizophrenic symptoms in Australian Aborigines.[3] Experimentally, kava extracts have been shown to antagonise stereotypies induced by apomorphine in mice.[4] We draw attention to the potential of extrapyramidal side effects of kava preparations and caution their use, particularly in elderly patients.

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Abnormal lactate after effort in healthy carriers of Leber's hereditary optic neuropathy

Leber's hereditary optic neuropathy (LHON) is a maternally inherited disorder associated with several point mutations in mitochondrial DNA (mtDNA). It preferentially affects neural structures and the heart conduction system. The reasons for such preferential clinical expression, although they may relate in part to the different degree of organ heteroplasmy, are still imperfectly known. Expression of the mitochondrial defect depends on each tissue's differing metabolic requirements, being manifest only when a certain metabolic threshold is reached. Functional stress may therefore be required for expression. Skeletal muscles are clinically spared in LHON: symptoms and signs of muscular involvement are never detected and muscle biopsies usually lack ragged red fibres, the hallmark of mitochondrial myopathies.[1] Abnormalities in the form of subsarcolemmal rims of enlarged mitochondria may, however, be found on electron microscopy together with electron dense and paracrystalline inclusions.[1] A partial defect of the complex I of the respiratory chain has also been found in the muscle[1] and platelets[2] of patients with LHON.

We have shown that phosphorus magnetic resonance spectroscopy (^{31}P-MRS) shows impaired recovery of phosphocreatine after exercise in the muscles of patients affected with LHON with the 11 778 mtDNA mutation, in the absence of resting abnormalities[3]; we also have evidence that the same occurs in asymptomatic carriers. We hereby report abnormalities of lactate production only after muscular effort in asymptomatic carriers of LHON.

We studied 28 asymptomatic members of two unrelated Italian families with LHON. Family 1, with 14 members examined, had the np 11 778 mtDNA mutation only. Family 2 had the primary np 11 778 mutation plus the np 13 708 and 4216 secondary mutations. In all cases, blood, urinary epithelium, and hair were examined for mtDNA mutations according to described methods.[3] Seven out of 14 members of family 1 and nine out of 14 of family 2 carried the mtDNA mutation(s). All carriers were virtually homoplasmic for the mtDNA mutations, except one person from family 1, with a 5–25% of wild type mtDNA. All members, carriers and non-carriers, were examined by us and found to be clinically normal.

Serum lactate was evaluated at rest and after standardised moderate exercise on a cycloergometer, according to the method of Nashef and Lane.[4] Venous samples were collected at rest, immediately after 15 minutes of pedalling an electronically braked bicycle ergometer under ECG monitoring at the predicted heart rate, and 15 minutes after the end of exercise. Samples were collected without stasis in sodium fluoride containers and the plasma was immediately separated, frozen, and analysed (Lactic acid, DIMENSION®). A Student's *t* test on unpaired data was used to compare the two groups: carriers *v* non-carriers of the mtDNA mutation(s). Serum lactate concentrations at rest were comparable in both carriers and non-carriers. Lactate was significantly increased immediately after exercise and 15 minutes after recovery from exercise in the carrier group (table). No significant differences were found between members of family 1 and family 2, whether carriers or non-carriers.

Our findings indicate that healthy carriers of 11 778 mtDNA mutations display abnormal lactate production only under conditions of muscular exercise. The lactate findings are thus in good agreement with our ^{31}P-MRS studies of muscle again showing normal resting conditions but delayed recovery of phosphocreatine after effort in affected patients[3] and asymptomatic LHON carriers alike. They imply that LHON should be considered a threshold character, and suggest that neurological dysfunction sets in when metabolic demands overcome the already impaired brain energy reserve. To explain the preferential involvement of neural structures, it is interesting to note that, whereas normal skeletal muscle operates at a resting rate of 16–19% of its maximal velocity of ATP biosynthesis (V/Vmax%), brain resting rate of ATP synthesis is normally 55%, rising to 59–63% in LHON, much nearer to its maximal energy capability, and thus also nearer to the theoretical threshold of energy failure. The reasons, however, for the preferential involvement of the optic nerve, although

Lactate concentrations (mean (SD)) mmol/l at rest, immediately after effort and 15 minutes after recovery in healthy carriers and non-carriers of LHON mtDNA mutation

	Rest	*After effort*	*Recovery*
Healthy carriers (n = 16)	0·99 (0·6)	2·63 (1·2)	1·62 (0·8)
		p<0·05	p<0·04
Non-carriers (n = 12)	0·90 (0·4)	1·76 (1·0)	1·11 (0·4)