Individual miotic responses for patients and controls.

two. The mean (SD) change in pupillary diameter (miosis) was 0.28 (0.6) mm for controls and 1.28 (0.7) mm for patients. Pupillary constriction of at least 0.5 mm was found in five control subjects, whereas 25 of the patients had pupillary constriction of at least 0.5 mm (figure; $p < 0.0001$). No difference was found between the two groups in postural fall in systolic blood pressure, although one control subject had a fall of 30 mm Hg and also a pupillary constriction of 3 mm. These results show increased sensitivity to pilocarpine in patients with Alzheimer's disease, and suggest cholinergic dysfunction somewhere in the parasympathetic pathway to the iris. The pupillary response to dilute parasympathetic agents is a useful method of studying the integrity of cholinergic neurons of the ciliary ganglion in conditions such as Adie's syndrome.⁴

Studies of supersensitivity of the iris to cholinergic agents have shown that it can also occur with preganglionic lesions,⁵ so that it is possible that a cholinergic abnormality of pupil innervation in Alzheimer's disease could be central and not at the ciliary ganglion. It is of interest that none of these patients had postural hypotension, which could have indicated autonomic failure. In the present study no evidence was forthcoming from control subjects that a parasympathetic dysfunction of the iris in Alzheimer's disease could be due to age.

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Rheumatic chorea and lupus anticoagulant

Two patients were diagnosed as Sydenham's chorea out of 322 patients seen in our movement disorder clinic in 1991-3. Both had lupus anticoagulant.

Patient 1 was a 15 year old girl who had had three attacks of generalised chorea within two years. The first attack occurred a month after a pharyngitis episode; it was the most severe and the longest, lasting five months. Because the choreoathetotic hyperkinetic movements were severe and only slightly improved by sodium valproate (1500 mg daily) and haloperidol (3 mg daily), corticosteroid treatment was required for two months (prednisone, initial dosage 40 mg daily). She had a history of asthma, which was treated with cromoglycate, and frequent episodes of pharyngitis. There was no other relevant personal or family history. Her physical examination was normal. Laboratory investigations showed an antistreptolysin-O titre between 300 and 621 Todd units (normal <250). Several determinations of activated partial thromboplastin time during the first attack of chorea showed prolonged values (57 sec; control 32.5 sec), not corrected by the addition of normal plasma. In the two subsequent relapses of chorea only a slight prolongation of the activated partial thromboplastin time was detected. Anticardiolipin IgG antibodies ranged between 6.9 and 19 U GPL/ml (normal, <15). Anticardiolipin IgM antibody concentrations were normal. Brain MRI showed a slight asymmetry of the frontal horns of the lateral ventricles, but there was neither change of signal nor gadolinium enhancement. Since February 1993, she has remained asymptomatic, just receiving prophylactic treatment with intramuscular penicillin.

Patient 2 was a 12 year old girl who presented with mild generalised chorea in July 1992. No other neurological or systemic abnormalities were seen. One year earlier she had had a pharyngitis episode followed by fever and migratory polyarthritides. There was a family history of rheumatic fever without chorea. Laboratory investigations showed antistreptolysin-O titres between 300 and 460 Todd units, and prolonged activated partial thromboplastin time (39 sec; control 30 sec) not corrected by the addition of normal plasma. Anticardiolipin antibody concentrations were normal. Brain MRI was normal. The patient was treated with sodium valproate (1000 mg daily) and prophylactic intramuscular penicillin, and the choreic movements disappeared within the next few months. Although an increased titre of antistreptolysin-O antibody is still present, subsequent coagulation studies have been normal.

Extensive investigations showed no other abnormalities in either case. Thus two patients with rheumatic chorea and prolonged activated partial thromboplastin time are reported. Although more specific coagulation tests¹ were not done, lupus anticoagulant is the most probable explanation for the increased activated partial thromboplastin time detected in both cases. In patient 1, a high titre of anticardiolipin IgG antibodies was also detected.

Rheumatic fever and systemic lupus erythematosus are two known causes of immunologically mediated chorea, and lupus anticoagulant seems to represent the

main biochemical abnormality responsible for chorea in systemic lupus erythematosus. Although lupus anticoagulant has been associated with chorea gravidarum,² and anticardiolipin antibodies with rheumatic fever,³ to our knowledge, lupus anticoagulant had not been reported in patients with rheumatic chorea.

Although little is known about the role of antiphospholipid antibodies, anticardiolipin antibodies seem to be unrelated to the rheumatic chorea pathogenesis.^{3,4} Different protein fractions responsible for lupus anticoagulant and anticardiolipin antibodies have however, been isolated.⁵ Therefore, the antineuronal antibodies responsible for rheumatic chorea could be more related to lupus anticoagulant than to anticardiolipin antibodies.

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Acute peripheral neuropathy, rhabdomyolysis, and severe lactic acidosis associated with 3243 A to G mitochondrial DNA mutation

Neuropathy can be a complication of progressive external ophthalmoplegia, but is rare in mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). We report here a case of mitochondrial cytopathy with these unusual manifestations.

The patient is a 33 year old woman who had a normal birth and early development. When she was aged 30, after the stillbirth of her first child, she developed spontaneously remitting myalgia of her thigh muscles. At the age of 32 she had intermittent headaches and nausea after physical work. At the age of 33, during her second pregnancy, she felt numbness in her toes and weakness in her legs, which spread to all four extremities over three weeks. She also developed facial weakness. Simultaneously, intrauterine fetal death occurred and abortion had to be induced. By that time she was too weak to walk. She was diagnosed as having Guillain-Barré syndrome and was given betamethasone (8 mg/day) for two days. This was not effective, and she was transferred to our hospital.

Examination on admission on 16 October 1991 showed average height and

weight, mild, diffuse upper limb weakness, and severe lower limb weakness. The weakness was predominantly distal and deep tendon reflexes were absent in all four limbs. All sensation modalities were impaired in her cheeks, trunk, and limbs, predominantly distal. She complained of dysaesthesia in her left cheek, forearms, and legs. She could barely stand with support. Mild myalgia was present in the thigh muscles. Laboratory tests showed a moderate increase in serum creatine kinase (496 IU/l) and a small increase in glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, and lactate dehydrogenase. On the second day in hospital, motor conduction velocity was normal in all limbs, but a low amplitude motor potential was noted in the tibial nerves. Sensory conduction velocity was normal in the median nerves, but sural nerve action potentials and F waves in the median and tibial nerves were absent. A conventional needle EMG showed that the interference pattern in limb muscles during maximal voluntary contraction was reduced but the motor unit potential was normal. There was no denervation potential at rest. Brain CT showed left frontal atrophy despite her normal intelligence. On the morning of the third day in hospital, she complained of nausea and dyspnoea with tachypnoea. Blood gas analysis showed severe metabolic acidosis (pH 7.01). Despite an intravenous infusion of 400 ml 7% sodium bicarbonate, her metabolic acidosis worsened (pH 6.97). She went into a state of shock in the evening and was given continuous haemodialysis for 52 hours. Two plasma exchanges were also given. During the next several days, her condition was critical, with multiple organ failure, including acute respiratory failure, acute renal failure, acute heart failure, and rhabdomyolysis. Even after her acute pulmonary oedema improved, she required mechanical ventilation for four months because of respiratory muscle weakness. The peak values of serum myoglobin and creatine kinase were 18 000 ng/ml and 20 800 U/l respectively at this time. Lactic acid and pyruvic acid had reached 294.4 mg/dl and 8.94 mg/dl, respectively by 10 hours after we first became aware of her acidosis. Her CSF protein and cell count were normal in three examinations carried out during the course of her illness.

Muscle biopsy from her left quadriceps femoris, taken on the seventh day in hospital, showed ragged-red fibres among necrotic fibres and scattered small angular fibres. No apparent grouping of fibre type was evident. A sural nerve biopsy three months after admission showed a severe decrease in myelinated fibres. Teased fibre preparations showed myelin ovoid formation and no demyelination.

Mitochondrial DNA analysis after amplification of the tRNA^{Leu(UUR)} gene region and digestion with ApaI¹ showed 3243 A to G point mutation in blood and muscle samples from the patient, as well as in blood samples from her mother, brothers, and sisters. The percentage of mutant was about 40 in her blood and 70 in the muscle sample. She was treated with 3.0 g of sodium succinate, 150 mg of coenzyme Q₁₀, and 30 mg of idebenon per day. One month after admission motor conduction velocity of the left tibial nerve was slightly reduced (38.0 m/s) and the amplitude was reduced to 200 μ V. Seven months after admission,

the motor conduction velocity had recovered to normal, with low amplitude motor potentials in the legs, but needle EMG showed polyphasic long duration motor unit potentials in her limb muscles. After 18 months, she was able to stand without support. Her reflexes were improved but the achilles tendon reflexes were still absent. Sensory disturbances also disappeared but painful dysaesthesia remained in her lower legs.

In this case, the diagnosis of MELAS was based on the history, the existence of lactic acidosis, ragged-red fibres, and mitochondrial DNA analysis. There were several new clinically important points in this patient with MELAS:

Firstly, she developed symptoms during her first and second pregnancies; therefore, gestation was possibly an aggravating factor for her.

Secondly, she had acute axonal neuropathy, which has rarely been reported with MELAS, although ophthalmoplegia plus or myoclonus epilepsy with ragged-red fibres has been reported to be associated with neuropathy.^{2,3} None of the patients with MELAS reported by Markesbery⁴ and Katsuragi *et al.*⁵ had major features of neuropathy such as sensory disturbance or muscle weakness.^{4,5}

Thirdly, rhabdomyolysis has not been reported in MELAS. Our patient certainly developed rhabdomyolysis after an episode of critical acidosis, because her serum creatine kinase on that morning was 506 U/l, and it rose to 20 800 U/l the next morning. Hypotension, acidosis itself, or two days of treatment with betamethasone followed by its withdrawal might cause rhabdomyolysis.

Fourthly, she developed critical lactic acidosis, which improved with continuous haemodialysis and plasma exchange. Therefore, haemodialysis or plasma exchange should be considered in severe lactic acidosis in MELAS. Finally, this case adds a new clinical manifestation associated with the 3243 A to G mutation in mitochondrial DNA.

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Papilloedema and visual failure in a patient with nocturnal hypoventilation

A morbidly obese woman treated for polymyositis developed symptoms of raised intracranial pressure and visual failure. Invasive CSF pressure monitoring showed normal pressures during the day, but transient episodes of raised intracranial pressure during sleep. These episodes were associated with hypoxia and hypercarbia, and suggest a possible aetiological relation between increased intracranial pressure, visual failure, and nocturnal hypoventilation.

A 45 year old woman was admitted for investigation of headaches, papilloedema, and progressive visual failure. She was morbidly obese (weight 126 kg, body mass index 52.7 kg/m²) and gave a history of recurrent deep vein thrombosis, pulmonary emboli, and polymyositis (treated with prednisolone and azathioprine). Examination showed bilateral papilloedema with visual acuities of 6/24 in the right eye, and just able to count fingers with the left. A lumbar puncture had only been successful in the sitting position; hence an accurate measurement of the CSF opening pressure had not been recorded. Biochemical and cytological analysis of the CSF was unremarkable, and CT of the head was normal. A clinical diagnosis of benign intracranial hypertension was made and a neuro-ophthalmological opinion sought. A left optic nerve fenestration was performed without improvement, and so detailed assessment of the intracranial pressure was requested. Access to CSF was achieved with a right frontal ventricular catheter connected to a subcutaneous reservoir. Continuous monitoring of intracranial pressure was undertaken from the reservoir (Camino optical transducer) through a fluid filled transcutaneous butterfly needle (21G). Radial arterial blood pressure, middle cerebral artery flow velocities by transcranial Doppler (Scimed), and continuous measurements of peripheral oxygen saturation by Multinex oximetry were also taken, and displayed graphically on a portable computer. The cerebral perfusion pressure (mean radial arterial blood pressure-mean intracranial pressure) and pulsatility of the middle cerebral artery flow velocity (FV) were calculated (pulsatility index PI = FV amplitude/FV mean) were calculated. Recordings were carried out during the night with the patient in her usual sleeping position (20 degrees head up) for up to 10 hours. Before sleep, baseline intracranial pressures of 5-15 mm Hg were recorded. Within one hour of sleep, cycles of high pressure waves (40-45 mm Hg) lasting 10-20 minutes were evident, occurring every 60-120 minutes and superimposed on higher background pressures of 15-25 mm Hg (fig 1). The intracranial pressure waves were accompanied by a fall in cerebral perfusion pressure to as low as 40 mm Hg, and were tightly coupled with increases of middle cerebral artery flow velocity and decreases in cerebrovascular resistance.

Respiratory function was evaluated further; arterial blood gases showed daytime hypoxia (mean PaO₂ = 9.1 kPa) with normocapnia (mean PCO₂ = 5.2 kPa). Overnight ventilation studies indicated a mean baseline arterial saturation of 88.2% and end tidal PCO₂ of 6.1 kPa. During the periods of raised intracranial pressure,