negative, as were CSF cultures and 14-3-3 protein. EEG initially recorded a generalised slowing. Subsequently, there were continuous spike and wave discharges consistent with generalised status epilepticus and, later, a burst-suppression pattern.

The cerebral cortex and hippocampus were normal. Profound abnormality of the subcortical white matter was reported, with widespread vacuolar change in the frontal and parietal lobes (fig 1D). Associated astrocytic hyperplasia was observed, but no atypia or inclusions (fig 1E). The thalami showed severe vacuolar change with intense astrocytic hyperplasia (fig 1F). The only other area of grey matter affected was the cerebellar dentate nucleus. The brainstem and cerebellar white matter were normal. No inflammation was seen. vCJD was excluded by negative prion protein immunohistochemistry and western blot. No plaques were seen. Histological examination of the small bowel showed partial villous atrophy consistent with coeliac disease.

Discussion

The question of a putative link between neurological disorders and coeliac disease is the subject of much debate. White matter abnormalities on MRI have been shown in patients with coeliac disease, but the pathology is limited.¹ Postmortem studies have shown several histological abnormalities, including cerebellar Purkinje cell loss and spongiform demyelination in posterior and lateral columns.² In our patient, there was extensive vacuolar change in the thalamus and subcortical white matter. One similar report in the literature describes a progressive leucoencephalopathy in association with coeliac disease. Brain biopsy in that case showed myelin pallor, accumulation of CD68-positive macrophages and preservation of axons.³

Other causes of vacuolar leucoencephalopathy were considered, including vCJD, HIV infection and glutaric acidemia, all of which were excluded by appropriate laboratory tests. Toxins and recreational drugs can cause similar changes, but careful inquiry and negative toxicology excluded these causes. The possibility that the changes were seizure related was also considered, but the neuropathology of refractory seizures is well documented and has never shown such spongiform myelinopathy. Furthermore, the hippocampus and cortex showed no evidence of structural injury. We ascribe this patient's leucoencephalopathy to coeliac disease for the following reasons: no other cause for spongiform white matter degeneration could be found; coeliac disease is known to be associated with white matter abnormalities; pathological studies have described spongiform demyelination in patients with coeliac disease; and there is striking resemblance to a previous report.³

The radiological findings late in the course of the illness raised the possibility of vCJD. The pulvinar sign, defined as "hyperintensity of the pulvinar relative to the signal intensity of the anterior putamen" is a highly accurate diagnostic sign for vCJD in the appropriate clinical setting.⁴ Bilateral thalamic hyperintensities have been described in other conditions and may be a source of diagnostic confusion. Our patient had a progressive disorder of >6 months duration, with early psychiatric symptoms (anxiety), ataxia, myoclonus and dementia. EEG did not show typical appearances of sporadic CJD, and MRI showed

bilateral pulvinar hyperintensities. Although his clinical presentation was atypical, we could not exclude the possibility of vCJD until after a neuropathological examination.

The pathogenesis of neurological complications in coeliac disease remains unknown. Dietary and immune-mediated mechanisms have been suggested, but conclusive evidence is lacking. Interestingly, raised CSF glycine may be associated with similar white matter disease.⁵ A relationship between intestinal malabsorption and disturbed amino acid metabolism could, in theory, result in the exposure of white matter to altered levels of amino acids, which may have been toxic. Further CSF was unfortunately not available to measure glycine levels in this patient.

The spectrum of neurological complications associated with coeliac disease continues to expand. We suggest that coeliac disease be considered in the differential diagnosis of leucoencephalopathy of unknown origin and that it may be a cause of a false positive pulvinar sign.

A M Ryan, J Ryan, M Wan-Ahmed

Department of Neurology, Cork University Hospital, Cork, Ireland

O Hardiman

Department of Neurology, National Institute for Neurology and Neurosurgery, Beaumont Hospital, Dublin, Ireland

M A Farrell

Department of Neuropathology, National Institute for Neurology and Neurosurgery, Beaumont Hospital, Dublin, Ireland

B McNamara

Department of Neurophysiology, Cork University Hospital, Cork, Ireland

B J Sweeney

Department of Neurology, Cork University Hospital, Cork, Ireland

Correspondence to: B J Sweeney, Department of Neurology, Cork University Hospital, Cork, Ireland; bsweeney@eircom.net

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Mitochondrial disease mimicking Charcot-Marie Tooth disease

Patient 1 was a 24-year-old woman with a 12-year history of a progressive sensorimotor peripheral neuropathy associated with pes cavus and bilateral foot drop. She had no family history of neuromuscular disease. At the age of 20 years she underwent nerve conduction studies (NCS), which showed absent motor and sensory responses in the lower limbs, with reduced upper limb motor conduction velocities (table). Upper limb sensory nerve action potentials (SNAP) were also absent. Interestingly, she had a lumbar puncture that showed no cells but a raised protein concentration of 1.56 mmol/l. A sural nerve biopsy showed active chronic axonal neuropathy with some segmental demyelination, not consistent with chronic inflammatory demyelinating polyneuropathy (CIDP). Her muscle biopsy showed neuropathic changes with a mild inflammatory infiltrate. Genetic testing for X-linked Charcot-Marie Tooth disease (CMT) 1A, 1B and X-linked was negative. Four years later, she developed an external ophthalmoplegia, increasing abdominal borborygmi, pain, nausea, vomiting and diarrhoea, associated with considerable weight loss. Urinary thymidine levels (92 µmol/mmol creatinine) and deoxyuridine (168 µmol/mmol creatinine) were markedly raised. DNA sequencing showed compound heterozygous mutations (G106T and del-G at nucleotide 1444) in the thymidine phosphorylase gene, confirming the diagnosis of mitochondrial myopathy, neuropathy and gastrointestinal encephalopathy (MNGIE) syndrome.

Patient 2 is a 38-year-old man who first noticed weakness and cramping of his legs at the age of 27 years. NCS carried out at the time of presentation showed mildly reduced motor amplitudes and slowed motor conduction velocities (table), worse in the lower limbs than in the upper limbs, suggestive of a demyelinating rather than axonal peripheral neuropathy. SNAPs were absent in the lower limbs, but were normal in the upper limbs. The diagnosis of CMT was made on the basis of the clinical and neurophysiological findings, but genetic testing did not confirm this diagnosis. At the age of 35 years, the patient began to develop cramping abdominal pains associated with a decrease in appetite, early satiety and marked weight loss. He recalled having prominent borborygmi throughout childhood. He is the third of four boys, whose parents are first cousins. His second eldest brother had diabetes and died at the age of 27 years from a "ruptured diverticulum". On examination, he was markedly cachectic, with bilateral pes cavus and clawed toes. He had an external ophthalmoplegia with bilateral ptosis, and facial, proximal and distal limb muscle weakness. He had low thymidine phosphorylase activity in the buffy coat, associated with an increased concentration of plasma thymidine (11.9 µmol/l) and deoxyuridine (6.7 µmol/l). DNA sequencing showed a homozygous 20 base-pair deletion in exon 10 of the thymidine phosphorylase gene, thus confirming the diagnosis of MNGIE syndrome.

Patient 3 is a 30-year-old man, with no family history of neuromuscular disease. At age 25 years, he presented with walking difficulties, muscle weakness and exercise intolerance. On examination, he had evidence of peripheral wasting, clawed toes and bilateral pes cavus. His upper and lower limb motor

Table Representative nerve conduction studies of patients 1–3

	Patient 1			Patient 2			Patient 3		
	Latency (ms)	Amplitude (mV)	C vel (m/s)	Latency	Amplitude	Velocity	Latency	Amplitude	Velocity
Motor nerve conduction studies									
Peroneal nerve ankle-EDB		Absent		7	1.6		7.1	0.7	
Peroneal nerve knee-EDB					0.5	27		0.7	19
Tibial nerve ankle-AH		Absent		7.3	2.2		6	8.2	
Tibial nerve knee-AH					1.9	25		4.9	21
Median nerve wrist-APB	6.4	8.4		5.7	5.6		5.2	12.4	
Median nerve elbow-APB		4.6	21		3.7	32		5.6	25
Sensory NCS									
Sural nerve		Absent			Absent			Absent	
Median nerve wrist-index		Absent		5.2	13			Absent	
Median nerve elbow-index				10.4	3	42			

AH, abductor hallucis; APB, abductor pollicis brevis; C vel, conduction velocity; EDB, extensor digitorum brevis; NCS, nerve conduction studies.

NCS studies showed relatively preserved motor amplitudes with reduced conduction velocities (table). Sensory responses were absent in both the upper and lower limbs. His symptoms progressed over 5 years and he developed an external ophthalmoplegia, bilateral ptosis, proximal limb weakness and mild limb ataxia. These new neurological signs prompted a needle muscle biopsy, which showed numerous COX negative ragged-red fibres on the combined cytochrome c oxidase succinate dehydrogenase stain, confirming the diagnosis of a mitochondrial myopathy. Unfortunately, DNA available was insufficient to perform a Southern blot to confirm an mtDNA genetic abnormality.

Discussion

Mitochondrial diseases can affect multiple organs, but have a predilection for organs with high-energy requirements such as the muscles or brain.¹ Thus they may present in a wide variety of ways, including myopathy, external ophthalmoplegia, diabetes mellitus, short stature or hearing loss. Although peripheral neuropathy is often a component of mitochondrial disease,^{2,3} it is rarely the presenting symptom. Previous reports have not emphasised the possible confusion between mitochondrial disease and CMT disease when peripheral neuropathy is the dominant feature.

Peripheral neuropathy in mitochondrial disease may occur in up to 50% of affected patients² but is often subclinical.³ In most studies, the axonal form predominates, although demyelinating forms have also been reported.^{3,4} The symptoms of MNGIE syndrome have also been reported to mimic those of CIDP.⁴ Over 30% of the patients seen in our neurogenetics clinic with genetically or biopsy-proved mitochondrial myopathy have a peripheral neuropathy on NCS, but <5% of these are demyelinating. The three patients discussed here are the only patients to initially present with the primary problem of a neuropathy, with distal weakness, pes cavus and clawed toes. The severity of sensorimotor peripheral neuropathy with slowed conduction velocities led clinicians to consider the possibility of CMT. On electrophysiological grounds alone, it would be difficult to distinguish CMT from mitochondrial disease, as both of these conditions have axonal and demyelinating forms. Clinical features distinguishing our patients from patients with CMT included external

ophthalmoplegia and bilateral partial ptosis. In the two patients with MNGIE syndrome, severe gastrointestinal involvement prompted further investigation. Although not specific for mitochondrial disease, these clinical features are exceedingly rare manifestations of CMT disease, and we note that recently there has been a case report of a Taiwanese family with probable CMT and ptosis.⁵ These ophthalmological and gastrointestinal clinical features were not initially present in our patients and thus it is important to follow up patients with undiagnosed peripheral neuropathies and negative genetic studies for CMT, particularly if the conduction velocities are slowed. On development of these features, a measurement of thymidine phosphorylase activity in the buffy coat and plasma thymidine levels for MNGIE syndrome, genetic studies and muscle biopsies confirmed the diagnosis of mitochondrial disease.

In conclusion, young patients with CMT-like peripheral neuropathies and negative CMT genetic studies should undergo close clinical follow-up. The development of any atypical clinical features, such as ptosis, external ophthalmoplegia or prominent gastrointestinal symptoms, should prompt consideration of the diagnosis of a mitochondrial cytopathy. In these cases, a muscle biopsy or relevant genetic studies should be carried out.

M Needham

Department of Neurology, Royal North Shore Hospital and University of Sydney, Sydney, New South Wales, Australia

J Duley

Chemical Pathology, Mater Health Services, Brisbane, Australia

S Hammond

Department of Neurology, Orange Base Hospital, Sydney, New South Wales, Australia

G.K. Herkes

Department of Neurology, Royal North Shore Hospital and University of Sydney, New South Wales, Australia

M Hirano

Department of Neurology, College of Physicians and Surgeons, Columbia University, New York City, New York, USA

C M Sue

Department of Neurology, Royal North Shore Hospital and University of Sydney, Sydney, New South Wales, Australia

Correspondence to: C M Sue, Department of Neurogenetics, Clinic 4, Royal North Shore Hospital, Reserve Rd, St Leonards, Sydney, New South Wales 2065, Australia; csue@med.usyd.edu.au

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Isolated shoulder palsy due to cortical infarction: localisation and electrophysiological correlates of recovery

Isolated pure motor involvement of the shoulder and arm muscles is extremely rare after stroke, and up to now has been documented by magnetic resonance imaging (MRI) in only one patient.¹

The corticospinal system is known to exert a greater influence over distal than proximal upper limb muscles, and the mechanisms that induce better recovery from stroke of proximal muscles are debated. The contribution of ipsilateral corticospinal fibres from the unaffected hemisphere, or of corticoreticulospinal projections, has been hypothesised.^{2,3}

A 65-year-old right-handed man awoke unable to abduct the right arm. Examination showed a strength of 0/5 (Medical Research