He became anxious and complained of migrainous headaches and abdominal pain. Soon after, he died after prolonged status epilepticus.

Lactate-ischaemia ergometry at age 20 was unremarkable. In serum, lactate and CK (244 U/l) were mildly elevated. In CSF, protein was elevated to 158–146 mg/dl, and lactate was normal. Liver enzymes, echocardiography and abdominal ultrasound were unremarkable. Electroneurography showed a sensor-axonal neuropathy. Visually evoked potentials (VEP) and vestibulogram were pathological; funduscopy and electroretinogram were normal. EEG was generally slowed with occipital 2–5/s theta/delta waves. MRI revealed mild frontoparietal leuкоencephalopathy, mild cerebellar atrophy and T2-hypointensities in the cerebellar peduncles (fig 1A). MR spectroscopy was normal. Muscle biopsy revealed no ragged red and/or COX negative fibres. Screening for mtDNA deletions in fibroblasts was negative.

Patient II.3, the 23-year-old sister, exhibited from 6 years progressively focal motor and generalised tonic-clonic seizures and generalised tonic-clonic seizures, delayed psychomotor development, sensori-axonal neuropathy and mild tetraparesis, and from 18 years a cerebellar syndrome. No external ophthalmoplegia occurred. For 4 years on primidone and valproate, no seizures and no hepatopathy were noted. At age 25, she developed refractory status epilepticus, remained comatose with intermittent focal seizures and developed intracranial pseudoobstruction short before death.

Blood tests revealed normal lactate and liver function. CSF analysis showed high protein (264 mg/dl) and VEP were prolonged. MRI showed very mild leuкоencephalopathy, infratentorial atrophy and T2-hyperintensities in the cerebellar hemispheres (arrow), and during status epilepticus transient cortical T2-hyperintensities in the frontal and parietal lobes with mild T2-hyperintensities in the cerebellar hemispheres (arrow). MRI revealed mild frontoparietal leuкоencephalopathy, mild cerebellar atrophy and T2-hypointensities in the cerebellar peduncles (fig 1A). MR spectroscopy was normal. Muscle biopsy revealed no ragged red and/or COX negative fibres. Screening for mtDNA deletions in fibroblasts was negative.

Both patients carried the POLG1 missense mutations, c.2284G>A (A62T) and c.2890C>T (R964C) compound heterozygously. The parents and the unaffected brother were heterozygous (fig 1B).

To validate pathogenicity, the two mutations were introduced in the equivalent position of MIP1 gene, the POLG1 orthologue of yeast Saccharomyces cerevisiae. MIP1 A665, corresponding to POLG1 A662, was converted to T665. MIP1 Q766, corresponding to POLG1 R964, was first converted to R766 (‘humanised’) and then to Q766. Petite (MIP1 2.2% (SD 0.2)) and erythro-mycin-resistant (Ery 24% (SD 0.2)) mutant (MIP1 1.6 (SD 0.4)x10^{-1}) frequencies served as a measure for mtDNA deletions and mtDNA point mutations respectively.

The MIP1 22% (SD 0.2)) and erythro-mycin-resistant (Ery 24% (SD 0.2)) mutant (MIP1 1.6 (SD 0.4)x10^{-1}) frequencies served as a measure for mtDNA deletions and mtDNA point mutations respectively.

The MIP1 22% (SD 0.2)) and erythro-mycin-resistant (Ery 24% (SD 0.2)) mutant (MIP1 1.6 (SD 0.4)x10^{-1}) frequencies served as a measure for mtDNA deletions and mtDNA point mutations respectively.

The MIP1 22% (SD 0.2)) and erythro-mycin-resistant (Ery 24% (SD 0.2)) mutant (MIP1 1.6 (SD 0.4)x10^{-1}) frequencies served as a measure for mtDNA deletions and mtDNA point mutations respectively.

The MIP1 22% (SD 0.2)) and erythro-mycin-resistant (Ery 24% (SD 0.2)) mutant (MIP1 1.6 (SD 0.4)x10^{-1}) frequencies served as a measure for mtDNA deletions and mtDNA point mutations respectively.

The MIP1 22% (SD 0.2)) and erythro-mycin-resistant (Ery 24% (SD 0.2)) mutant (MIP1 1.6 (SD 0.4)x10^{-1}) frequencies served as a measure for mtDNA deletions and mtDNA point mutations respectively.
seizures are focal and rare. Both patients eventually received coenzyme Q10 and creatine, but therapeutic effects remain uncertain.

Concerning MRI in POLG disease, there are reports of cerebrocortical and cerebellar atrophy, leuкоencephalopathy, cortical hyperintensities and focal lesions, partially reversible, in thalami, basal ganglia, occipital poles and in cerebellar hemispheres. Interestingly, both siblings displayed symmetrical cerebellar T2-hyperintensities. Leuкоencephalopathy was mild. Cerebellar atrophy was more prominent in the female, not correlating with severity of ataxia. Her transient precentral cortical T2-hyperintensities most likely represent postictal vasogenic oedema.

Carrier frequency studies suggest that the disease is underdiagnosed as having an A467T mutation frequency of 0.69% in British and 0.19% in German controls. Taken together, our cases highlight the importance of genetic testing for POLG disorders also in the absence of external ophthalmoplegia, typical muscle pathology, valproate toxicity and hepatic pathology.

S Stricker,1 H Prüss,1 R Horvath,2,3 E Baruffini,4 T Lodi,4 E Siebert,5 M Endres,1,6 R Zschenderlein,1 A Meisel1
1 Department of Neurology, Charité Universitätsmedizin Berlin, Berlin, Germany; 2 Friedrich-Baur-Institute, Ludwig-Maximilians-Universität Munich, Munich, Germany; 3 Mitochondrial Research Group, University of Newcastle, Newcastle, UK; 4 Department of Genetics, Biology of Microorganisms, Anthropology, Evolution, University of Parma, Parma, Italy; 5 Department of Neuroradiology, Charité Universitätsmedizin Berlin, Berlin, Germany; 6 Centrum für Schlaganfallorschung Berlin (CSB), Berlin, Germany

Correspondence to: Dr S Stricker, Charité Universitätsmedizin Berlin, Department of Neurology, Charitéplatz 1, 10117 Berlin, Germany; sarah.stricker@charite.de

Acknowledgements: We thank J Schäfer, Department of Neurology, University of Dresden, for the mtDNA testing in fibroblasts and discussion of the case, and S DiMauro, Neurological Institute of New York Columbia University, for discussion of the case.

Funding: Department of Neurology, Charité University Medicine Berlin, Helmholtz Gemeinschaft für Forschungseinrichtung. Telethon-Italy no GGP07019.

Competing interests: None.

Patient consent: Obtained from the patient’s family.

Provenance and peer review: Not commissioned; externally peer reviewed.

Received 22 October 2008
Revised 30 December 2008
Accepted 17 January 2009

doi:10.1136/jnnp.2008.166066

REFERENCES
A variable neurodegenerative phenotype with polymerase γ mutation

S Stricker, H Prüss, R Horvath, et al.

*J Neurol Neurosurg Psychiatry* 2009 80: 1181-1182
doi: 10.1136/jnnp.2008.166066

Updated information and services can be found at:
http://jnnp.bmj.com/content/80/10/1181.full.html

**References**

This article cites 5 articles, 2 of which can be accessed free at:
http://jnnp.bmj.com/content/80/10/1181.full.html#ref-list-1

**Article cited in:**
http://jnnp.bmj.com/content/80/10/1181.full.html#related-urls

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/