NOVEL POLG VARIANTS ASSOCIATED WITH LATE-ONSET DE NOVO STATUS EPILEPTICUS AND PROGRESSIVE ATAXIA

Mitochondrial disease is phenotypically and genetically heterogeneous with an estimated prevalence of 1 in 4,300.1 Mutations in the POLG gene, encoding the catalytic subunit of DNA polymerase gamma, are an important cause of mitochondrial disease. The spectrum of clinical manifestations in POLG-related mitochondrial disease is variable,2 with disease onset ranging from adulthood-onset dominant or recessive progressive external ophthalmoplegia (chronic progressive external ophthalmoplegia), ataxia-neuropathy spectrum, myoclonic epilepsy, myopathy, and sensory ataxia to childhood-onset Alpers syndrome, which is characterized by intractable seizures, psychomotor regression, and hepatic impairment. Epilepsy is a poor prognostic factor in regression, and hepatic impairment. Epilepsy is a poor prognostic factor in POLG mutations,3 and the onset of epilepsy often clusters in childhood (<5 years) and teenage.4 However, late-onset epileptic encephalopathy is uncommon.4,5 Herein, we describe a patient who died of de novo, late-onset refractory status epilepticus with the identification of 2 novel variants in the POLG gene.

Case report. A 69-year-old woman presented with an 8-year history of slowly progressive gait ataxia associated with dysarthria to the regional ataxia center. She also noted to have generalized myoclonic jerks for 9 months. There was no other medical history or relevant family history of any neurologic disorder. On examination, she had evidence of ophthalmoplegia in all directions of gaze. She was found to have prominent gait and lower limb ataxia. Myoclonus was demonstrable with outstretched arms. Reflexes were present and symmetrical. She was just able to walk with a stick and required 1 person’s assistance. Mitochondrial disease was suspected, and she underwent a muscle biopsy.

She was admitted acutely to the hospital following 2 episodes of generalized tonic-clonic seizures at age 71. She was treated with IV phenytoin and levetiracetam. Her management was rapidly escalated to the administration of general anesthesia due to convulsive status epilepticus. Laboratory investigations including routine biochemistry, autoantibodies, septic screens, and CSF analysis were unremarkable, except a slightly raised serum lactate level at 3.3 mmol/L (normal: <2.2 mmol/L). EEG showed encephalopathic changes. MRI head T2 and fluid attenuation and inversion recovery sequences revealed stroke-like lesions (figure, A), in addition to the previously documented changes in the clinic (figure, B). Epilepsia partialis continua, affecting the left face, arm, and leg, emerged on day 12 of admission. Her seizures were suprarefractory to treatment, despite receiving a combination of phenytoin, levetiracetam, clonazepam, propofol, midazolam, and pulse methylprednisolone. She died of worsening epileptic encephalopathy and multiorgan failure after 2 weeks of hospitalization.

This patient was tested negative for common mitochondrial DNA (mtDNA) point mutations, including m.3243A>G, m.8344A>G, and m.8993T>C/G. She was also tested negative for 3 common POLG mutations (p.Ala467Thr, p.Trp748Ser, and p.Gly848Ser). Her muscle biopsy revealed histochemical and molecular genetic evidence of mitochondrial dysfunction, including cytochrome c oxidase–deficient fibers (figure, C) and variable mtDNA deletions (figure, D). No pathogenic variant was identified in TWNK and RRM2B. Direct sequencing of the POLG gene (GenBank accession number NM_002693.2) identified 2 rare variants, c.1232T>A, p.(Arg574Gln), both affecting conserved amino acids and predicted to be damaging (figure, E). Familial segregation studies were not feasible, as she was the only child and both her parents were deceased.

Discussion. Our patient’s initial presentation of a progressive cerebellar ataxia plus other neurologic features including external ophthalmoplegia and myoclonus is highly suggestive of a mitochondrial etiology. Moreover, her neuroimaging findings of bilateral signal abnormalities in thalami, cerebellar dentate nuclei, and cerebellar atrophy have previously been reported in POLG-related mitochondrial disease.6 However, the development of fatal epileptic encephalopathy is rather surprising, given the insidious onset of her illness. Our case highlights the progressive nature of POLG-related mitochondrial disease, the overlap of clinical syndromes and
difficulty of predicting the trajectory of disease progression, and the management challenge of refractory mitochondrial epilepsy.4 The presence of focal onset motor status, together with the acute stroke-like lesions, is likely related to the neuronal energy failure6 of which inhibitory interneurons have been shown to be particularly vulnerable to mitochondrial dysfunction.7

We were unable to unequivocally conclude whether these 2 variants were in cis or in trans. We speculate that our patient had a late-onset recessive POLG disease, given that recessive POLG disease is more common than dominant presentations according to our experience and reported cases in the literature. Both variants are located in the linker domain of POLG, and we have recently showed that mutations (homozygous or compound heterozygous) in this region are associated with later disease presentation and longer survival compared with other domains within the POLG protein.4
We propose that POLG-related mitochondrial disease should be a differential diagnosis in cases of de novo status epilepticus, particularly with other clinical features such as ataxia and external ophthalmoplegia, irrespective of age. Full sequencing of POLG should be performed because more than 20% of patients do not carry 1 of the 3 common mutations, as exemplified by this case.

From the Wellcome Centre for Mitochondrial Research (Y.S.N., H.P., D.M.T., R.W.T.), Institute of Neuroscience, Newcastle University, Newcastle upon Tyne; and Sheffield Teaching Hospitals NHS Trust and University of Sheffield (N.H., M.H.), Royal Hallamshire Hospital, Sheffield, United Kingdom.

Author contributions: Y. S. Ng: analysis and interpretation of data and drafting and revising the manuscript. H. Powell: acquisition of data and genetic analysis and interpretation of data. N. Hoggard: acquisition, analysis, and interpretation of imaging data. D. M. Turnbull: interpretation of data and revising the manuscript. R. W. Taylor: study concept and design, analysis and interpretation of data, and revising the manuscript. M. Hadjivassiliou: study concept and design, analysis and interpretation of data, and revising the manuscript.

Acknowledgement: The clinical and diagnostic mitochondrial services in Newcastle upon Tyne is funded by the UK NHS Highly Specialised Service for Rare Mitochondrial Disorders of Adults and Children.

Study funding: No target funding reported.

Disclosure: Y. S. Ng holds an NIHR Clinical Lectureship and received funding from the MRC Centre for Neuromuscular Diseases for his doctoral study. H. Powell reports no disclosures. N. Hoggard has served on the editorial board of British Journal of Radiology and has received research support from the Medical Research Council. D. M. Turnbull is supported by the Wellcome Centre for Mitochondrial Research (203105/Z/16/Z) (newcastle-mitochondria.com), the MRC Centre for Translational Research in Neuromuscular Disease Mitochondrial Disease Patient Cohort (UK) (G080067/4), the Lily Foundation and the UK NIHR Biomedical Research Centre for Aging and Age-related disease awarded to the Newcastle upon Tyne Foundation Hospitals NHS Trust, and the UK NHS Highly Specialized “Rare Mitochondrial Disorders of Adults and Children” Service. M. Hadjivassiliou has served on the editorial board of Cerebellum & Ataxias and has been a member of the medical advisory boards of Auxxia UK and Coeliac UK. Go to Neurology.org for full disclosure forms. The Article Processing Charge was funded by the Wellcome Centre for Mitochondrial Research.

This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (CC BY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Received March 15, 2017. Accepted in final form June 30, 2017.

Correspondence to Dr. Hadjivassiliou: m.hadjivassiliou@sheffield.ac.uk

1. Gorman GS, Schaefer AM, Ng Y, et al. Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease. Ann Neurol 2015;77:753–759.

2. Cohen BH, Chinnery PF, Copeland WC. POLG-related disorders. In: Pagon RA, Adam MP, Ardinger HH, et al, editors. GeneReviews® [Internet]. Seattle: University of Washington, Seattle; 2010: 1993–2016. Available at: http://www.ncbi.nlm.nih.gov/books/NBK26471/. Accessed December 18, 2014.

3. Neeve VC, Samuels DC, Bindoff LA, et al. What is influencing the phenotype of the common homozygous polymerase- mutation p.Ala467Thr? Brain 2012;135:3614–3626.

4. Anagnostou ME, Ng YS, Taylor RW, McFarland R. Epilepsy due to mutations in the mitochondrial polymerase gamma (POLG) gene: a clinical and molecular genetic review. Epilepsia 2016;57:1531–1545.

5. Cheldi A, Ronchi D, Bordoni A, et al. POLGI1 mutations and stroke like episodes: a distinct clinical entity rather than an atypical MELAS syndrome. BMC Neurol 2013;13:8.

6. Tzoulis C, Neckelmann G, Mark SJ, et al. Localized cerebral energy failure in DNA polymerase gamma–associated encephalopathy syndromes. Brain 2010;133:1428–1437.

7. Lax NZ, Grady J, Laude A, et al. Extensive respiratory chain defects in inhibitory interneurones in patients with mitochondrial disease. Neuropathol Appl Neurobiol 2016; 42:180–193.