

TITLE:

Epilepsia partialis continua and bilateral cortical deafness in a previously well 77-year-old.

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Michael Li reports no disclosures.

Dr. Symmonds reports no disclosures.

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Dr. Hofer reports no disclosures.

Dr. Nithi reports no disclosures.

Professor Poulton reports no disclosures.

Dr. Sen reports no disclosures.

Case report

A 77-year-old woman was transferred from her local hospital with a history of episodic left-sided facial twitching and worsening bilateral hearing loss. A month prior to admission, she was seen in the emergency department after waking with new-onset left-sided facial twitching and facial droop. A stroke was excluded. However, the facial jerks persisted and increased in frequency after discharge. Associated features included deterioration in hearing, a loss of oral sensation and dysarthria. She was previously well, a retired competitive swimmer with no significant medical or family history.

Examination revealed repetitive jerks over the left face (especially affecting frontalis and orbicularis oculi – see Video 1) consistent with *epilepsia partialis continua* (EPC), marked bilateral deafness and left-sided upper motor neurone facial weakness. She was disinhibited and perseverant.

A broad range of diagnoses was considered including infectious, inflammatory, paraneoplastic, lymphomatous and autoimmune aetiologies. Blood tests, including serum lactate and extensive autoantibody testing, and serial lumbar punctures were unremarkable. Mildly impaired glucose tolerance was demonstrated. MRI (Figure 1) revealed extensive confluent areas of T2-hyperintensity and swelling involving cortex and white matter in the frontotemporal and insular regions bilaterally (right>left). Diffusion-weighted imaging did not show significant restricted diffusion and the intracranial arteries appeared normal on a time-of-flight magnetic resonance angiography sequence. EEG demonstrated excessive slow activity over the right hemisphere with frontal spikes and sharp wave discharges (Video 1).

The clinical presentation and imaging findings raised the possibility of an underlying mitochondrial disorder. Although serum genetic testing for common mutations was negative, muscle biopsy revealed increased cytochrome c oxidase (COX)-negative succinate

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dehydrogenase (SDH)-positive fibres consistent with mitochondrial cytopathy (Figure 1). Muscle DNA analysis found a very small proportion of mitochondrial DNA (mtDNA) with multiple deletions, however no pathogenic variants were identified in 21 genes of mtDNA maintenance. Furthermore, FGF-21 levels, which we have found are a useful biomarker for defects of mtDNA maintenance, were low.¹ Whole genome sequencing of muscle mtDNA identified a rare homoplasmic (i.e. present in all mtDNAs) variant (m6052A>G, (p.Asn50Ser)) in the *MT-COI* gene.

The patient commenced and up-titrated anti-epileptic medications (levetiracetam, clobazam and diazepam) to minimal effect. Prednisolone had been commenced at the referring hospital to treat a putative inflammatory cause, but yielded no response. Therefore, prednisolone was weaned, and carbamazepine commenced for EPC, which proved promptly beneficial. After discharge, her facial twitches resolved completely within a few months with no further seizure activity. Subsequent MRIs demonstrated stable atrophy over previously affected areas (Figure 1). After 36 months of follow-up, she has only mild bilateral hearing impairment and has returned to swimming.

Discussion

We report a previously well 77-year-old woman who developed subacute clinical manifestations of a likely mitochondrial cytopathy, namely EPC and bilateral cortical hearing loss. Notably, onset of mitochondrial disease over age 65 is exceedingly rare and described only in case reports.²

Epilepsy affects up to 23% of adult patients with a confirmed genetic diagnosis of mitochondrial disease. Among these patients, average age of seizure onset is 29 and focal seizures are most common.³ Almost one-third also experience EPC as part of their seizure phenotype.⁴ Seizure prevalence varies by genotype, suggesting preferential brain expression

of certain mtDNA mutations for unknown reasons.³ Hearing loss and cognitive impairments feature in mitochondrial syndromes, along with stroke-like episodes (as was seen here), movement disorders, impaired glucose tolerance and myopathies.⁵

In our case, while the clinical, radiological and histological features were highly suggestive of mitochondrial cytopathy, we could not establish a definitive molecular diagnosis. A rare homoplasmic variant was detected in *MT-COI*, which encodes the catalytic subunit of mitochondrial respiratory chain complex IV. Phenotypes of known complex IV defects range from pure myopathy to Leigh's syndrome.⁶ Homoplasmic mtDNA polymorphisms of uncertain significance such as this one are common, with pathogenicity being hard to determine unless heteroplasmy (where an individual harbours >1 type of mtDNA) is present.

We also found a low level of mtDNA deletions in our patient's skeletal muscle, but without the ptosis or external ophthalmoplegia that characterise patients with defective mtDNA maintenance. Aging itself is associated with somatic mtDNA mutations and this probably explains the accumulation of these deletions,⁶ though such changes are attenuated in active elderly people.⁷ Perhaps somatic deletions and/or a low level of other pathogenic mutations with heteroplasmy below our laboratory's threshold ($\approx 5\%$) explain the COX-negative fibres. In some cases, whole genome sequencing may identify an underlying cause.

This case highlights the breadth of presentations in which a mitochondrial aetiology is high on the differential diagnosis, and the associated diagnostic challenges, particularly in the elderly.

Acknowledgements

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Appendix 1: Author Contributions

Name	Location	Role	Contribution
Michael Li	John Radcliffe Hospital / University of Oxford, UK	Author	Wrote the manuscript
Dr. Mkael Symmonds	John Radcliffe Hospital / University of Oxford, UK	Author	Interpreted EEG data and commented on the manuscript
Dr. Pieter Pretorius	John Radcliffe Hospital / University of Oxford, UK	Author	Provided neuroradiological input and commented on the manuscript
Dr. Fintan Sheerin	John Radcliffe Hospital / University of Oxford, UK	Author	Provided neuroradiological input and commented on the manuscript
Dr. Monika Hofer	John Radcliffe Hospital / University of Oxford, UK	Author	Provided histopathological input and commented on the manuscript
Dr. Kannan Nithi	John Radcliffe Hospital / University of Oxford, UK	Author	Provided clinical care to the patient and commented on the manuscript
Professor Joanna Poulton	John Radcliffe Hospital / University of Oxford, UK	Author	Provided clinical care to the patient, provided expertise regarding mitochondrial analyses and commented on the manuscript
Dr. Arjune Sen	John Radcliffe Hospital / University of Oxford, UK	Author	Responsible for the care of the patient while at The John Radcliffe Hospital and commented on the manuscript.

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Figure legends and titles:

Figure 1: MRI scans and representative muscle biopsy photomicrographs from the patient.

(A) Axial T2-weighted and (B) coronal FLAIR (fluid-attenuated inversion recovery) MRI images at the time of presentation demonstrating extensive confluent areas of hyper-intense signal and swelling. These changes involved cortex and white matter within the right temporal lobe, frontal operculum and insula, with similar but more limited involvement of the left superior temporal gyrus and posterior insula. (C) Axial T2-weighted and (D) coronal FLAIR images from an MRI scan performed 2 years later, showing significant volume loss in previously affected areas with pronounced cortical damage and white matter gliosis. These changes are particularly evident in the right temporal lobe, frontal operculum and insula, with compensatory dilatation of the temporal horn of the right lateral ventricle. There is more subtle volume loss in corresponding regions in the left cerebral hemisphere. (E) Representative Haematoxylin & Eosin-stained frozen section of muscle biopsy depicting increased variability of muscle fibre diameters with smaller / atrophic variably angulated fibres. (F) Representative frozen section stained with combined cytochrome oxidase (COX) / succinate dehydrogenase (SDH) showing two scattered COX-negative SDH positive fibres (blue staining). Overall, there were increased numbers of COX-negative SDH positive fibres in this biopsy.

