Reviewer’s report

Title: Polg1 mutations and stroke like episodes: A distinct clinical entity rather by an atypical MELAS syndrome

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Reviewer: Marcus Deschauer

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The authors present an interesting patient with mitochondrial disease due to POLG1 mutations who suffered from stroke symptoms at age 74 and 78 years. A very late onset of stroke-like episodes is unusual for patients with POLG1 defects.

There are two major questions that should be answered by the authors:

1. Could the episodes be “normal” strokes in an older patient in co-incidence with mitochondrial disease? This is not discussed in the paper. Did the patient have vascular risk factors for cerebral ischemia?

In MELAS syndrome due to the 3243A>G mutation as well as in POLG1-associated encephalopathy headache and seizures during the episodes are frequent. Missing of these symptoms argues against stroke-like episodes but for “normal” strokes in the patient. This has to be discussed. Was an EEG performed that frequently shows epileptic activity in POLG1 defects?

If we believe that there were stroke-like episodes due to mitochondrial disease the next question is how to classify them (MELAS or POLG1-associated encephalopathy). This question is addressed in the paper highlighting the complexity of the genotype-phenotype relationship in mitochondrial disorders. However, the authors should emphasize that MELAS was defined as a clinical syndrome in 1984 and POLG1 associated encephalopathy is a molecular genetically defined term thus it is difficult to compare them?

2. The authors have to highlight the novel findings in their case. Is it just a novel POLG1 mutation p.D1186H (with uncertain pathogenicity)?

Some other minor details should be addressed:

Background:

Our paper (Deschauer et al. 2007) has reported a young man with a single stroke-like-episode (not episodes as mentioned in the manuscript) fulfilling clinical criteria of MELAS.

Case presentation:

1. Hemiparesis should be graduated using MRC score.

2. The authors should specify neurophysiological examination. I guess they
performed needle EMG. What do they mean by “mouth muscle”? Why did the authors examine several facial muscles? No facies myopathica is mentioned. If the authors believe that this is important they should define EMG findings in detail as EMG of facial muscles shows small and short potentials in normal individuals. Which other muscles were examined in legs and arms?

3. What was the course of aphasia after the second episode.

4. Sensory neuronopathy and cerebellar ataxia are frequent finding in patients with POLG1 mutations. Thus the authors should state if there was sensory or cerebellar ataxia?

5. What was the time interval between onset of symptoms and MRI scans? This information is important for interpretation of diffusion weighted images.

5. It is unnecessary to mention the results of histological investigation and genetic testing in the patient’s history as they are presented in detail later.

6. At the end of the patient’s history the authors state that other mtDNA mutations were searched. What is meant by “other”? Are other mtDNA point mutations (as mentioned in the introduction) excluded?

7. It is not important to mention the restriction enzyme Hae III for RFLP as the method is not shown in detail. In contrast the authors should explain briefly (or give a reference for) the PCR assay showing multiple mtDNA deletions as this is demonstrated in figure 2B.

8. The authors should quantify the amount of ragged-red fibers and COX-negative fibers.

9. The authors should clearly state in the section "Genetic analysis" if the POLG1 mutations were detected in heterozygous state.

Discussion

1. In the case presentation the authors show a normal lactate level but in the discussion they have mentioned lactic acidosis.

2. The authors state that the p.T251I and p.P587L mutations are reported already but give no references. Is p.D1186H a novel mutation? Are the reported mutations known as recessive mutations? The authors should examine family members to find out if the mutations are present in cis or trans.

3. The author should discuss the results of diffusion MRI regarding normal stroke or mitochondrial disease. How do they explain that MRI was unchanged after the second episode despite global aphasia and right-sided hemiparesis.

Finally there are several typos or unusual terms such as brachial bicep muscle, sensorimotor bilateral hypoacusia, oculistic examination, POLG-encefalopathy, mitochondrial disease, mitochondrial POLG1, mitochondrial signs.....
**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.