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Letter to the Editor

The features of the m.10197G > A mtDNA mutation

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Dear Editor,

We would like to thank Dr. Finsterer for his comments on our recent paper entitled "Clinical and neuroimaging features of the m.10197G > A mtDNA mutation: new case reports and expansion of the phenotype variability" [1]. Our expert colleague went through our manuscript and raised a number of questions to which we are pleased to reply.

Dr. Finsterer asked about MR spectroscopy (MRS) in patient 1 who did not show high lactate levels in the CSF. Unfortunately, brain MRS was not performed in this case, and we cannot inform the readers regarding the presence of a lactate peak in the brain parenchyma.

A second question concerns the interpretation of brain MRI scans in patient 2. It is the opinion of our distinguished colleague that "…the morphological appearance is not convincing of stroke-like lesions" in this case. On the contrary, we believe that there are several neuroradiological features supporting the diagnosis of MELAS stroke-like lesions in this child. First, the cortical lesions were in different stages of evolution, mainly displaying vasogenic edema, but also small focal areas of cytotoxic edema ("shifting spread" pattern) [2]. By definition, vasogenic edema is characterized by increased apparent diffusion coefficient (ADC) values on diffusion-weighted images (DWI), whereas cytotoxic edema is characterized by restricted diffusion with low ADC values. Of note, cytotoxic edema in MELAS stroke-like lesions is likely secondary to the prolonged mitochondrial energy failure, eventually leading to ion pump failure and metabolic cell death [2]. Second, the lesions did not involve the cerebral vascular territories, and the arterial MR angiography was completely normal, ruling out non-embolic arterial ischemic strokes. Third, the absence of heart defects, significant thrombophilia and cervical artery dissection makes the diagnosis of embolic arterial strokes unlikely in this patient, especially in view of the genetic diagnosis of a mitochondrial disease. In similar cases with a confirmed mtDNA mutation, we believe that the use of advanced MRI techniques, including those measuring perfusion or oxygen extraction in the brain — as suggested by Dr. Finsterer —, has a poor cost-benefit ratio [3–4]. Also, it could be redundant in efforts to distinguish MELAS from arterial ischemic strokes [5–6], especially when MRI images are reviewed by an experienced, board certified pediatric neuroradiologist (as in our case). That said, we think that the neuroimaging features in patient 2 strongly suggest an evolution into an overlapping MELAS/Leigh syndrome [7].

A further question concerned the clinical-radiological correlation of the progressive symptoms presented by patient 3. We take this opportunity to specify that Fig. 1B in our manuscript also shows involvement of the anterior portion of the posterior limb of the internal capsule. This might explain, at least in part, the left hemiparesis observed in this patient. We believe that reference to a possible acute demyelinating encephalopathy (ADEM) in this case — Dr. Finsterer alluded to this possibility — is inappropriate. For the sake of clarity, we underline that ADEM is diagnosed on the basis of clinical and radiological criteria. The presence of encephalopathy is a mandatory criterion [8], not met by our patient 3. The absence of other acquired conditions in this patient strengthens our conviction that this child's neurological manifestations were related to his Leigh syndrome.

Another question raised by Dr. Finsterer highlights an apparent discrepancy between the text and data in Fig. 4 regarding the frequency of seizures in children harboring the m.10197G > A mutation. Although these data might appear contradictory, they are not. The relative frequency of seizures in cases with a confirmed m.10197G > A diagnosis is reported in the text,whereas Fig. 4 gives absolute values for seizures among all clinical features displayed by the patients. Presenting the data from these two different perspectives served to underline the great clinical variability among families and the relatively high frequency of dystonic postures in patients, as pointed out in our text.

A question was also asked about cardiac involvement in patient 2. As indicated in our text [1], a systolic cardiac murmur was detected in this patient only through careful cardiac evaluations. Routine blood tests and cardiac ultrasound ruled out heart muscle defects. It is worth mentioning that the authors are familiar with mtDNA-related disorders and performed a careful, "mitochondrially-oriented" examination. This allowed us to rule out, in our children, signs/symptoms of other organ involvement. Nonetheless, our study was mostly retrospective and we cannot exclude the possibility of future multiorgan involvement.

We were also invited to clarify the meaning of the term "mid-aortic syndrome" used in reference to patient 2. "Mid-aortic syndrome", also known as coarctation of the abdominal aorta, refers to segmental or diffuse narrowing of the distal descending or abdominal aorta [9], as shown in our Supplementary Fig. 2 [1]. It may be a congenital anomaly or acquired secondary to a number of conditions [9]. As mentioned in the text, we were tempted to hypothesize that the congenital anomalies presented in patient 2 could be the result of mitochondrial dysfunction

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during embryonal development. Although unproven, we think that these are intriguing findings worth future investigation.

Finally, our colleague asked about types of seizure and antiepileptic drugs (AEDs). It is obvious that part of our discussion was overlooked. In answer to this question, we reiterate that patient 2 showed episodes of absence, generalized tonic and tonic-clonic seizures, and bilateral epileptiform anomalies on fronto-temporal areas with a tendency to spread to both sides. He is currently taking standard AEDs (levitiracetam, lamotrigine, and clobazam) but he was not on a ketogenic diet.

We very much appreciated Dr. Finsterer's contribution and also the “extra space” we have been given in order to reply, as this has allowed us to improve the quality of our report, explain data considered unclear, and thus contribute to further expanding the spectrum of Leigh syndrome due to m.10197G > A mtDNA mutation.

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