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Correspondence

Response to: Letter to the Editor regarding: The expanding phenotype of MELAS caused by the m.3291T>C tRNA mutation E. Kelland, C.A. Rupar, Asuri N. Prasad, A. Downie and C. Prasad (1) by Josef Finsterer, MD, PhD [1], Sinda Zarrouk-Mahjoub, PhD [2]

Keywords:
MELAS
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We thank Dr. Josef Finsterer, MD, PhD and Sinda Zarrouk-Mahjoub, PhD for their interest in our publication and for the pertinent queries that have been raised.

We offer our responses to their questions (*in italics*).

We have the following comments and concerns.

Apparently, the m.3291T>C mutation does not manifest significantly in the heart [1]. Did the propositus undergo comprehensive cardiologic investigations, including echocardiography and long-term ECG-recordings? Hypertrophic and dilated cardiomyopathy as well as noncompaction, aortic root ectasia, and atrial fibrillation, frequent cardiological manifestations of mitochondrial disorders, [2] may go subclinical for years [3]. Ventricular runs may remain asymptomatic when occurring during the night. Were cardiac abnormalities reported in any of the affected/unaffected family members?

We agree with Dr. Josef Finsterer about the varied clinical cardiac manifestations in the mitochondrial disorders (2). The proposita has undergone extensive cardiac investigations and remains under follow up with cardiology. So far the only abnormality she has is Wolff-Parkinson-White syndrome (WPW) on the basis of EKG findings, but remains asymptomatic from a cardiac point of view. Echocardiogram has been unremarkable. The mother has a normal echocardiogram and EKG with no abnormalities. Other family members (brother and sister) are asymptomatic from a cardiac perspective and have not had formal cardiac investigations.

Stroke-like episodes (SLEs) have a variable clinical presentation [4]. How did they manifest clinically in the presented patient? Did they also manifest with seizures? In which cerebral region did equivalent stroke-like-lesions occur? Which type of treatment was provided for SLEs? Did the frequency of SLEs decline after initiation of the vitamin-cocktail? Which remnants of the stroke-like-lesions were seen on MRI? Topiramate is an inhibitor of the mitochondrial carboanhydrase-VB. Topiramate has beneficial [5] and unfavourable effects [6] to mitochondria. As an inhibitor of the mitochondrial transition pore it has an anti-obesity effect but can be also effective in migraine and epilepsy. Did the patient suffer from migraine, a frequent phenotypic manifestation of mtDNA mutations, and did migraine respond to Topiramate? Why did she require two antiepileptic drugs in a relatively low dosage? Was reduced weight (35.7 kg at age 15 years) a side effect of Topiramate?

When the patient initially presented it was as a status epilepticus, and the seizure semiology suggested a generalized seizure. The patient was transferred from a peripheral hospital intubated and on ventilation support. It was when she remained in an encephalopathic state after extubation that a MR imaging of the head disclosed cortical signal abnormality (T2, FLAIR) in the right frontal lobe. In particular, the medial and inferior aspects of the gyrus rectus, and orbital aspect of the right frontal lobe. The signal abnormality was confined to the cortex and did not involve the u fibres or the subcortical white matter. During the recovery phase of hospitalization, she had findings of ptosis, external ophthalmoplegia, and generalized weakness, easy fatigability but largely focal findings were not detected on neurological examination. By definition, stroke like episodes are characterized by cortical or subcortical white matter lesions which are hyperintense on T2 and FLAIR sequences which resolves on follow up imaging. The patient had many similar lesions which resolved with time. Some do progress to infarction which were seen in this patient 5 and a half years following the first MRI in the right lateral temporal and frontal cortices where there are irregular areas of cortical volume loss and subcortical white matter hyperintensity compatible with encephalomalacia seen in old infarcts.

Some 7 months later she presented with recurrence of breakthrough seizures, vomiting, and headache. She showed an increase in the size and distribution of lesions. She also showed on examination findings features consistent with a left pronator drift and left hemiparesis, an extensor plantar response however was seen on the right side, suggesting bilateral corticospinal tract involvement. A month later, she presented with another seizure cluster of focal dyscognitive seizures associated with oral automatisms, and drooling. She showed a partial response to IV benzodiazepines, after which she manifested with generalized tonic clinic seizures which were self-limited. On this occasion, cortical signal abnormalities documented in multifocal regions (temporal poles, inferior frontal and occipital lobes bilaterally) which appeared to have shown significant progression in comparison to the prior study. These regions also were documented to show MR Spectrographic evidence of lactate accumulation without any concomitant evidence of restricted diffusion on diffusion weighted sequences.

Vitamin cocktail was provided along with arginine. The frequency of stroke-like events was decreased after the introduction of arginine (3). In the initial 6 months of the presentation, she was placed on Lamotrigine 125 mg twice a day replacing the Dilantin that had been started in the acute phase. She had also been placed on the mitochondrial cocktail. When she experienced breakthrough seizures, the dose of Lamotrigene was increased to 175 mg twice a day in weekly increments. However, this failed to control her seizures, Carbamazepine was added for a brief period, which had to be discontinued due to increased fatigue and it was during this period at 7 months after presentation when she complained of headaches along with breakthrough seizures that Topiramate was added cautiously. As pointed we are aware that Topiramate could have both positive and negative effects in individuals with mitochondrial disorders, hence the dose was kept low. We were guided by the effectiveness of

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Topiramate in another patient with MELAS who had chronic headaches. We were also concerned about the side effects of Topiramate in terms of weight loss, and cognitive functions. Hence the decision to keep her on low doses and only increase the dose cautiously guided by symptom exacerbation. She was also started on chronic L-Arginine supplementation with the hope that her stroke-like episodes would stabilize. Within 3 months of starting this combination of Lamotrigine, Topiramate and L-Arginine supplementation, she has remained seizure free for nearly 6 years of follow-up (4). There have been no hospitalizations for stroke like episodes either.

It can be speculated whether we were merely fortunate or whether this combination truly worked for this patient in preventing major exacerbations. The evidence in this n of 1 case is that after commencing this combination, she has had complete seizure control and no stroke-like episodes for the period of follow up.

It is not possible to state unequivocally whether the poor weight gain of the patient was due to the Topiramate or the primary mitochondrial disorder. She has been gaining weight after she had a Gastrostomy tube placed for nutritional supplementation and her present weight at age 22 is 53.5 kg.

The patient presented with clinical manifestations of KSS [1]. Which were the clinical manifestations of KSS? Was there an AV-block-III? Did she require a pacemaker? Was CSF protein elevated?

The patient had features of ophthalmoplegia and ptosis (seen commonly in chronic progressive external ophthalmoplegia and Kearns Sayre syndrome). Both ophthalmoplegia and ptosis are not a common feature of MELAS. She also had Wolff-Parkinson-White syndrome (WPW) on the basis of EKG findings (1). She did not require a pacemaker and the CSF protein was not elevated. Thus there were some overlapping features of KSS (not classic) as has been mentioned in our paper (5).

Overall, this interesting case report requires a detailed description of the phenotype, a more comprehensive cardiologic investigation, and an explanation for the antiepileptic regimen.

We agree that it is important to report varied clinical phenotypes with m.3291 mutation.

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