Suspicious MELAS Requires Genetic and Biochemical Confirmation

Sir,

We read with interest the article by Khandwala *et al*. about a 16-year male with suspected mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome (MELAS).[1] We have the following comments and concerns:

The main disadvantage of the report is that the diagnosis was neither genetically confirmed nor confirmed by biochemical investigations of an affected tissue documenting decreased respiratory chain activity.

We do not agree with the statement that MELAS is the most frequent among the mtDNA-related mitochondrial disorders (MIDs).[1] The most common MIDs are the non-specific mitochondrial multiorgan disorder syndromes (MIMODSs), of which the phenotype does not fit to any of the specific MIDs tagged with an acronym.[2]

Since MELAS is, per definition, associated with lactic acidosis not only in the blood but also in the cerebrospinal fluid (CSF), we should be informed about CSF lactate values on the initial spinal tap. If lactate was not determined in the CSF, it should be mentioned if there was a lactate peak on MR-spectroscopy.

The second MRI was suggestive of basal ganglia calcification.[1] Did the patient undergo CT of the cerebrum to confirm the suspicion? Basal ganglia calcification is a typical feature of MIDs.[3] Was there any indication for a movement disorder? Since the patient had symmetric lesions on SWI in the globus pallidus, red nuclei, and substantia nigra, Leigh syndrome should be excluded. Why were the cerebellar lesions in the first magnetic resonance imaging (MRI) interpreted as ischemic, although there was a vasogenic edema?

MELAS is hereditary with a positive family history in about two-thirds of the cases.[4] Did any of the first degree family members, in particular the mother, present with phenotypic features of a MID?

The patient manifested with epilepsy. Which antiepileptic drugs (AEDs) did the patient receive for focal seizures after the initial diagnosis of ischemic stroke? Which type of seizures did he develop on the second admission? Was the AED regimen changed? Did he receive mitochondrion-toxic AEDs, such as valproic acid, carbamazepine, phenytoin, or phenobarbital, which may worsen or perpetuate seizures.[5]

Stroke-like episodes are usually treated with non-mitochondrion toxic AEDs and nitric oxide-precursors, such as L-arginine or L-citrulline. Were these compounds effective in the presented index case? Did stroke-like lesions regress on MRI?

Overall, this report could be more meaningful by providing supplementary information about the family history and the AED regimen applied. Additionally, the patient should undergo biochemical and genetic investigations to confirm the suspected MID.

REFERENCES

1. Khandwala K, Ahmed A, Sheikh T. MELAS: A complex and challenging diagnosis. *J Coll Physicians Surg Pak* 2018; **28**: S46-8.
2. Finsterer J, Bastovansky A. Multiorgan disorder syndrome (MODS) in an octagenarian suggests mitochondrial disorder. *Rev Med Chil* 2015; **143**:1210-4.
3. Finsterer J, Kopsa W. Basal ganglia calcification in mitochondrial disorders. *Metab Brain Dis* 2005; **20**:219-26.
4. Poulton J, Finsterer J, Yu-Wai-Man P. Genetic counselling for maternally inherited mitochondrial disorders. *Mol Diagn Ther* 2017; **21**:419-29.
5. Finsterer J. Toxicity of antiepileptic drugs to mitochondria. *Handb Exp Pharmacol* 2017; **240**:473-88.

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Author's Reply:

Thank you for your comments. We appreciate your concerns regarding the patient diagnosis.

We agree that the main disadvantage of the report is that it was neither genetically confirmed nor confirmed by biochemical investigations. This is because genetic confirmation usually does not readily available; and is generally very expensive to conduct in our setting. In addition, the patient was non-affording and did not follow-up with some other confirmatory tests, which were advised.

Cerebrospinal flaid (CSF) lactate values were not done in the initial spinal tap. The initial magnetic resonance imaging (MRI) showed cerebellar lesions, which were typically sub-acute ischemic looking. Dropout on ADC mapping does not always necessarily signify vasogenic

edema. The patient did not undergo a CT brain on the second instance; however since the initial CT scan did not show calcification, we did give a differential of iron deposition in the basal ganglia. Leigh syndrome was not included in the differential as patients usually present before the age of 2 years and invariably death results in childhood. In addition, there were no characteristically increased T2 signals in the globus pallidus, red nuclei or substantia nigra to raise the suspicion.

There was no history of movement disorder or significant positive family history. The patient initially received phenytoin on initial presentation; however, this anti-epileptic drug (AED) regimen was changed to levetiracetam and lacosamide, subsequently, when he presented with right-sided facial twitching and one episode of generalised tonic clonic seizure. L-Carnitine was also prescribed which did aid in curbing the symptoms to an extent.

As mentioned, the stroke-like lesions did regress on subsequent scans. However, the patient intermittently presented with new lesions throughout the subsequent years. We have only made a suggestion of the diagnosis, keeping in mind the overall conducted investigations and clinical picture. But obviously confirmation is pending.

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