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Letter to the Editor

Before Attributing Rapid Cognitive Decline in MELAS to Diabetes, Alternative Causalities Must be Ruled Out

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With interest we read the article by Tran *et al.* [1] who reported on a 36 year-old female with mitochondrial encephalopathy, lactic acidosis, and stroke-like episode (MELAS) syndrome due to the variant. m.3243A>G in *MT-TL1* that manifested phenotypically with short stature, visual impairment, hearing impairment, seizures, headache, myopathy, vomiting, a stroke-like episode (SLE), diabetes, and rapidly progressive cognitive decline [1]. The patient profited from insulin and a dipeptidyl-peptidase-4 inhibitor [1]. The study is excellent but has limitations that are cause of concerns and should be discussed.

We disagree with the notation that acute-onset diabetes in the index patient was responsible for cognitive decline [1]. MELAS patients can develop dementia in the absence of diabetes and since MELAS commonly manifests with seizures, cognitive decline can also result from extensive seizure activity, which can be also non-convulsive. Therefore, we should know whether cerebral MRI showed progressive lesions between age 34 years, when MELAS was diagnosed and onset of diabetes and rapid cognitive decline. Cognitive impairment can be also a feature of a SLE, which the patient developed during hospitalisation at age 36y [1].

We also disagree with the notion that diabetes in patients with a MID is generally associated with encephalopathy [1]. There are number of reports about MID patients with diabetes who did not develop cerebral involvement [2].

A limitation of the study is that the current medication was not comprehensively described. Of particular interest is the anti-seizure drug (ASD) drug therapy, since several of the ASDs are mitochondrion-toxic, including barbituric acid, valproate, phenytoin, carbamazepine, and zonisamide [3].

Another limitation of the study is that the index patient did not undergo electroencephalography (EEG) recordings. Because she presented with recurrent generalised seizures associated with impaired consciousness [1], it is crucial to know whether episodes of impaired consciousness were attributable to seizure activity only on EEG (non-convulsive status epilepticus).

A further limitation is that none of the first-degree relatives underwent clinical neurologic examination or genetic testing. Particularly family members manifesting with diabetes should undergo examination of the mtDNA to see if the m.3243A>G variant was also present in these patients with a milder phenotype than that of the index patient.

Another limitation is that the heteroplasmy rate of the m.3243A>G variant was not reported. Knowing heteroplasmy rates in clinically affected and unaffected tissues is important to assess the severity of the phenotype, the speed of progression, the outcome of these patients, and for genetic counselling.

We should also know why the patient did not receive NO-precursors, such as L-citrulline or L-arginine for the SLE at age 36y. Though not generally accepted as a treatment of SLEs, particularly L-arginine has been proven beneficial in several patients with an acute SLE [4].

Since rapid cognitive decline can be also associated with cerebral lactic acidosis, it is important that either magnetic resonance spectroscopy (MRS) or direct measurement of lactate in the CSF had been done.

Overall, the interesting study has limitations that put the results and their interpretation into perspective. Addressing these issues would strengthen the conclusions and could improve the status of the study. In MELAS seizures, lactic acidosis, and leukoencephalopathy should be ruled out as causes of rapid cognitive decline before attributing it to diabetes.

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Statement of Ethics: a) The study was approved by the institutional review board (responsible: Finsterer J.) at the 4th November 2022. b) Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

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Compliance with Ethics Guidelines: This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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