Letter to Editor:
Effect of Selective Serotonin-Noradrenaline Reuptake Inhibitors on Mitochondrial Function

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In a recent paper, Cozart et al. reported a case of a 46-year-old female with Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-Like Episodes (MELAS) syndrome. She developed major depression after a stroke and benefited from the Selective Serotonin and Noradrenaline Reuptake Inhibitor (SSNRI) duloxetine. Her family history was positive for early dementia (maternal grandmother) and early deaths in the female lineage [1]. The report has a number of shortcomings, which need to be discussed. We have the following comments and concerns.

MELAS is frequently associated with psychiatric abnormalities, including depression [2, 3]. The psychiatric manifestations of MELAS usually respond favorably to conventional antipsychotics or antidepressants [4, 5]. Recognizing psychiatric abnormalities in MELAS is crucial, because the psychiatric disease may be the initial manifestation at onset, psychiatric abnormalities may indicate non-convulsive epileptic conditions, and the psychiatric disease may be a manifestation of a Stroke-Like Episode (SLE); which is accessible to treatment different from antipsychotics or antidepressants.

MELAS is not only a clinical diagnosis, and needs to be confirmed by biochemical and genetic studies. In about 80% of the cases, MELAS is caused by the pathogenic variant m.3243A>G. However, a number of other mtDNA or nDNA mutations may also phenotypically manifest with MELAS. It would be of value to learn about the genetic background of the index patient, including the heteroplasmy rates in various affected/unaffected tissues in case of an mtDNA variant. Which were the muscle biopsy findings and which respiratory chain complexes demonstrated reduced activity? Which organs were affected in addition to the brain? We should also be informed if a genetic defect could be detected in the first-degree relatives of the index patient.

Strokes in patients with a Mitochondrial Disorder (MID) can be ischemic or an SLE [6]. These are two completely different entities in terms of etiology, pathogenesis, presentation, and treatment [6]. Which were the MRI findings in the index patient? Was it a true vascular lesion (DWI hyperintense, ADC hypointense) or a lesion not confined to a vascular territory (DWI hyperintense, ADC hyperintense)? Why were steroids prescribed with steroids after the stroke? Steroids may have beneficial as well as detrimental effects in MID patients [7]. The patient was suspected to have had a subclinical second stroke, earlier [1]. Which were the morphological find-

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ings on Magnetic Resonance Imaging (MRI) after the first stroke? Was the first stroke visible on imaging performed for the second stroke? Which were her cardiovascular risk factors at the time of the first/ second stroke?

The patient was reported to have experienced at least two seizures so far; but interestingly, her current medication did not include Antiepileptic Drugs (AEDs). Two seizures with a lesion on cerebral imaging represent a high risk of seizure recurrence; thus, an absolute indication for AEDs. The patient had insomnia and was taking duloxetine, which carries the risk of hyponatremia; therefore, there is an additional need to prescribe this patient with AEDs. Were AEDs discontinued because the patient did not tolerate them or because of low compliance? Which were the Electroencephalography (EEG) findings during/ after the first/ second "stroke"? Did MR Spectroscopy (MRS) reveal a lactate peak?

A similar case as the one reported by Cozart et al. has been previously reported by Chai et al. [5]. In the 46-year-old female reported by Chai et al. depression was developed after a SLE, which was most likely misinterpreted as ischemic stroke [5]. Additionally, this patient profited from an SSRI (fluoxetine) [4]. The overall beneficial effect of SSNRI/ SSRI could be explained by the stimulation of mitochondrial functions by these compounds [8].

With regard to the treatment of MELAS and MIDs in general, it is crucial to avoid compounds (e.g. topiramate) which cause weight loss, anorexia, or gastrointestinal dysmotility. This is because gastrointestinal abnormalities, including vomiting, anorexia, dysmotility, and weight loss can be a dominant feature of phenotype [9]. Overall, this interesting report could be more meaningful by providing supplementary data about the genetic findings, the EEG, cerebral imaging, MRS, and about the prospective investigations of organs subclinically affected in the index case. It is also crucial that first-degree relatives be clinically and genetically investigated for the presence/absence of a MID.

Ethical Considerations

Compliance with ethical guidelines

The study complies with standard ethical standards.

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Authors' contributions

Design, literature search, discussion, and first draft: Josef Finsterer; Literature search, discussion, and critical comments: Sinda Zarrouk-Mahjoub; Both authors contributed equally.

Conflict of interest

There are no conflicts of interest to be declared.

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