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Letter to the Editor

Elective surgery should not be performed during a stroke-like episode

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Abstract
MELAS is a genetic, syndromic, multisystem mitochondrial disorder with stroke-like episodes (SLEs) as a hallmark of the phenotype. SLEs must be clearly differentiated from ischemic stroke, as treatment and outcome vary significantly between the two. MELAS is phenotypically and genotypically heterogeneous, but is due to the variant m.3243A>G in *MT-TL1* in 80% of cases. No patient with MELAS due to a *SOX5* variant was reported. Due to the genetic and metabolic specifics of the syndrome, diagnostic and therapeutic management require the guidance of a multidsciplinary team familiar with the management of MIDs. Since surgery is associated with stress, it is conceivable that surgery or anaesthesia could exacerbate the MELAS phenotype. Patients with existing SLE should not undergo elective surgery.

Keywords: MELAS, Stroke-Like Episode, Stroke-Like Lesion, SOX5, Stroke, Headache

Introduction

We read with interest the article by Cassimatis *et al*. who reported on a 21-year-old male diagnosed with mitochondrial encephalopathy, lactic acidosis, and stroke-like episode (MELAS) syndrome due to a variant in *SOX5* [1]. MELAS in the index patient manifested as stroke-like episodes (SLEs,) mental retardation, epilepsy with verum and functional seizures, headache, myopathy with monoparesis, general wasting and hypotonia, weight loss, and lactic acidosis [1]. The robotic appendectomy in the index patient was complicated by multiple bilateral infarcts [1]. The study is impressive, but it has limitations that should be discussed.

We disagree with the diagnosis "infarction" [1]. The patient had preoperative classical SLE, which manifested itself structurally as stroke-like lesion (SLL) on MRI [1]. SLLs are pathognomonic for MELAS and show a typical pattern on multifunctional MRI [2]. SLLs present as dynamic cerebral lesions that initially expand, reach a maximal extent, and regress with no residual lesion or persist as a cyst, laminar cortical necrosis (LCN), white matter hyperintensity, atrophy, or toenail sign [3]. In the expansion phase, they appear as T2/FLAIR, DWI, and PWI hyperintensity as well as OEF hypointensity. MR-spectroscopy shows a lactate peak and FDG-PET hypometabolism [2]. SLLs can be caused by a variety of triggers, but the most common are seizures. In some cases, they respond to NO-precursors. How can the authors be sure that the preoperative stroke was at least two weeks old?

We also disagree with the statement that MELAS is "relatively rare" [1]. The classical MELAS mutation m.3243A>G, is responsible for the syndrome in 80% of cases, and occurs with an increased allele frequency in stroke and diabetic patients [4, 5]. MELAS is usually diagnosed using the Hirano or Japanese criteria. According to the Hirano criteria, MELAS is diagnosed when SLEs occur before age 40, and seizures or dementia, lactic acidosis or ragged-red fibers, normal early development, recurrent headache, or recurrent vomiting are present. According to the Japanese criteria, MELAS is diagnosed when a suitable phenotype and a causative mutation are present. Which criteria were used for the index patient?

Not only surgical complications but also anaesthesiological complications, such as hypotonia, muscle weakness, or malignant hyperthermia-like reactions can occur in MELAS patients. MELAS patients are generally more sensitive to drugs than others when metabolization of these drugs occurs through mitochondrial pathways. Therefore, anaesthesia should avoid mitochondrion-toxic sedatives, analgesics, muscle relaxants, and anaesthetics as much as possible.

The patient was reported to have multiple syncopes daily [1]. However, the cause of these syncopations could not be clarified. Were they due to seizures, cardiac involvement, carotid artery stenosis, or autonomic nervous system impairment? Because MELAS can also be complicated by stenosis or dissection of the carotid arteries [6], it is important to rule out this differential

cause by carotid ultrasound.

There is no work-up of cardiac involvement. MELAS is multiorganic and commonly affects the heart [7]. Since cardiac involvement manifests itself with arrhythmias, conduction defects, and cardiomyopathy, and thus has a strong impact on outcome, it is imperative to carefully monitor cardiac performance.

The anti-seizure drugs (ASDs) that the patient was regularly taking are absent. Since various ASDs are potentially mitochondrion-toxic (carbamazepine, valproic acid, barbiturates, phenytoin, zonisamide), it is important to know the ASDs, in order to assess whether or not the ASDs contributed to the surgical complications.

In summary, this fascinating report could benefit from discussing the objections raised above. We agree that MELAS patients require special considerations and preventive measures to maximise the safety of their surgical care. Since the index patient is the first patient with MELAS due to a *SOX5* mutation, there is a need to prove its pathogenicity by functional and biochemical investigations.

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