LETTER TO THE EDITOR

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ADVERSE REACTION TO ANESTHESIA IN A M.8993T>C CARRIER WITH LEIGH SYNDROME

Reação adversa à anestesia em um m.8993T>C transmissor com síndrome de Leigh

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With interest, we read the article by Lopes et al. about a 16-month-old female with Leigh syndrome (LS) due to the mitochondrial DNA (mtDNA) variant m.8993T>C in the *ATP6* gene with a heteroplasmy rate of >90%.[1] The patient initially presented axial hypotonia, which markedly increased after anesthesia for a cerebral magnetic resonance imaging (MRI). During follow-up, LS progressed to recurrent exhaustion, lactic acidosis, epilepsy, ataxia, and dystonia.[1] We have the following comments and concerns.

The key message of the report, that the patient experienced an increase of hypotonia after anesthesia, needs to be more broadly discussed. We should be informed if the patient received local, regional, or general anesthesia. If general anesthesia was applied, we should have been informed which drugs were used in which sequence, and which dosage. It is well known that some anesthetics may worsen the phenotype of a mitochondrial disorder.[2]

It is not comprehensible why the patient received phenytoin (PHT) without having seizures. The patient initially neither had convulsive nor non-convulsive seizures, and the electroencephalography (EEG) did not show epileptic activity. Apnoea and cyanosis one day after anesthesia do not necessarily reflect epileptic activity, but could be also attributed to metabolic, respiratory or cardiac dysfunction. Thus, we should have been informed about the results of the troponin, pro-brain natriuretic peptide (pro-BNP), D-dimer, blood gas analysis, the cardiologic exam, the electrocardiogram (ECG), and the pulmonary investigations during this episode. Furthermore, PHT has been reported to be potentially mitochondrion-toxic,[3] why it should not be applied as first-line treatment of seizures in mitochondrial disorder (MID) patients. The patient was later switched on phenobarbital and levetiracetam, with beneficial effects, but it was not mentioned if any side effects have occurred. This is crucial as phenobarbital can be mitochondrion-toxic as well,[3] and may worsen epilepsy. We should also be informed if the ketogenic diet was offered since it has been reported that it can be highly beneficial for mitochondrial epilepsy.[4]

A further shortcoming is that the report does not mention if the mother who carried the mutation with a heteroplasmy rate of 75% presented any phenotypic features of a MID. Despite a lower heteroplasmy rate than her daughter's, it is conceivable that she had developed clinical manifestations of the mutation as well. Thus, it is recommended that the mother should be prospectively investigated for clinical or subclinical manifestations of a MID.

Overall, this interesting case requires a broader discussion of the adverse reaction to anesthesia, a thorough discussion of the effects of the potentially mitochondrion-toxic antiepileptic regimen, and more widespread discussion of the clinical presentation of the index case shortly after anesthesia. The reaction to anesthesia is crucial as some MIDs manifest only mildly or remain subclinical, considering adverse reactions to anesthesia can be the initial manifestation of the disease.

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AUTHOR'S RESPONSE LETTER

LEIGH SYNDROME: A CASE REPORT WITH A MITOCHONDRIAL DNA MUTATION

Síndrome de leigh: a propósito de um caso clínico com mutação no DNA mitocondrial

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The child was initially followed in a small local hospital, where she was monitored due to a psychomotor developmental delay. In this local hospital, it is not possible to perform MRI, so it was done in a private center. Instructions to parents included a six-hour fasting before the exam. No pre-medication was given, and the MRI was performed with sevoflurane sedation (in 100% oxygen). The child was observed for some time until she woke up, and then she was fed and went home.

Until the performance of the MRI, the hypothesis of mitochondrial disease was not considered as a possible diagnosis, so no special measures were taken. In the hospital where I work, patients with mitochondrial diseases or any other inborn errors of metabolism have anesthetic consultation prior to any intervention. There is an anesthesia protocol for all patients with metabolic diseases.

When the child visited the pediatric care center with apnea and cyanosis, the pediatrician interpreted her case as a convulsive episode. The protocol was diazepam and then phenytoin. No cardiac evaluation, troponin, pro-BNP, D-dimer, or pulmonary investigation was made at that time. After the result of the MRI (Leigh syndrome), one week later, she was referred to our center for the metabolic evaluation. At this time, she was examined by a neuropediatrician and the antiepileptics drugs were changed. The patient had no reaction to phenobarbital. She is still being treated with levetiracetam and phenobarbital.

All patients with mitochondrial disease undergo a cardiac evaluation, which was performed in this patient. The electrocardiography and the echocardiography were normal.

The mother was examined by the adult metabolic team, and she has no symptoms so far.

The effects of using anesthesia in patients with mitochondrial disease have been well reviewed in the literature since almost all anesthetics impair the mitochondrial function[1-3]. The difficulty in this clinical case was that the differential diagnosis did not consider mitochondrial disease as a hypothesis.

All circumstances that can cause metabolic stress should be avoided due to the risk of decompensation in patients with mitochondrial disease. These circumstances include prolonged fasting, hypoglycemia, postoperative nausea and vomiting, hypothermia (with resulting shivering), prolonged tourniquets, acidosis, and hypovolemia.

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