To the editor:

A 10-year-old girl presented for cataract surgery under general anesthesia. The preanesthetic checkup was unremarkable. Preoperative investigations were normal including liver and renal function tests which were ordered as the child seemed small and malnourished. A standard anesthesia technique was used with sevoflurane induction and maintenance with 33% oxygen in nitrous oxide, sevoflurane, fentanyl and vecuronium. Standard intraoperative monitoring showed a steady state of all monitored parameters. The entire anesthetic was remarkably uneventful. However at the end of the 1 hour procedure, the child did not regain consciousness or show any recovery from muscle paralysis and was shifted to the Intensive Care Unit for elective ventilation. Arterial blood gas analysis revealed a severe and unexplained metabolic acidosis, which rapidly worsened and progressed to renal failure, circulatory collapse, hyperkalemia and eventually death within a few hours. The parents of the child refused consent for autopsy. After much contemplation the most likely diagnosis that comes to mind is an undiagnosed mitochondrial disorder.

The first disorder of mitochondrial function was described by Luft in 1959 and since then multiple cases have been reported. The term “mitochondrial disorder” (MD) was coined to describe any defect in the mitochondrial electron transport chain. In spite of an increasing recognition of MD, common presentations in children remain difficult to define and most authors agree that while adults present with recognizable mitochondrial syndromes, clinical presentations in children are nonspecific.

Certain “red flags” which indicate the possibility of MD in children are short stature, neurosensory hearing loss, progressive external ophthalmoplegia, axonal neuropathy, diabetes mellitus, hypertrophic cardiomyopathy, and renal tubular acidosis and MD should be considered in any child presenting with multisystem involvement or with single-system involvement without a clear explanation.1

MDs are one of the most common inborn errors of metabolism, with an estimated prevalence of approximately 1:5000,2 which is probably an underestimate due to variable symptomatology, under diagnosis and under reporting.

MDs can be divided into two main categories. In the first, respiratory complexes in the respiratory chain are affected as in MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke) and Kearns-Sayre syndromes. In the second category, lipid metabolism is affected due to a defect in fatty acid transfer across the mitochondrial membrane due to carnitine deficiency or a defect in β-oxidation of fatty acids making energy production from lipid metabolism insufficient.3 These disorders affect many part of the body, but the brain, muscle, liver, heart, and kidney which have a high energy demand are especially vulnerable and involved early. Neurological manifestations include headaches, hearing deficits, seizures and learning disabilities with mental retardation. Cardiac muscle damage may lead to conduction abnormalities and cardiomyopathy. Respiratory and gastrointestinal systems are involved later, as is endocrine involvement leading to diabetes and exocrine pancreatic insufficiency. Although these disorders may present with a varied symptomatology and at a different ages, the main symptoms appear to be a progressive muscle weakness and exercise intolerance.4

Diagnostic confirmation is not straightforward and these disorders still lack sufficiently sensitive and specific biomarkers and establishing a diagnosis remains challenging, costly, and, at times, invasive.5 Clinical features alone are rarely pathognomonic, laboratory and radiological investigations only provide important clues and while muscle biopsy is an essential part of diagnosis, it is also not highly sensitive and is often not available.

Patients with MD are at risk of metabolic decompensation during stress, intercurrent illness or reduced oral intake resulting in lactic acidosis leading to ‘metabolic encephalopathy’. A detailed preoperative anesthetic

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consultation and appropriate laboratory testing is necessary prior to any surgical procedure. Associated cardiac involvement mandates diligent intraoperative monitoring. In addition to standard ASA monitoring, arterial cannulation may be considered for continuous hemodynamic monitoring and frequent analysis of arterial blood gases (ABG), electrolytes, blood glucose and lactate. Precautions against aspiration with rapid sequence induction of anesthesia may be required depending on the degree of muscle weakness and these patients may have a myopathy and exaggerated sensitivity to muscle relaxants. Respiratory muscle involvement is associated with an increased risk of pulmonary complications. It would seem pertinent to avoid prolonged use of propofol for maintenance of anesthesia and to use neuromuscular relaxants judiciously. They may also potentially be hypersensitive to volatile anesthetics. Use of regional anesthesia may permit decreased use of opioids and other anesthetic agents. Local anesthetics are generally well-tolerated in these patients and there is no clear established link between malignant hyperthermia and MD. Normothermia should be maintained to prevent additional stress and increase in metabolic demands. Due to impairment in beta oxidation of fats, patients with MD are prone to develop ketosis. This is prevented by avoiding prolonged fasting and/or administration of a dextrose infusion during fasting. Surgery should be scheduled first thing in the morning. Underlying metabolic abnormalities, including diabetes mellitus or baseline lactic acidosis, may worsen with surgical stress, resulting in electrolyte imbalances. Ringer lactate solution leads to an increase in the lactate load and should be avoided. The release of inflammatory mediators along with the underlying oxidative phosphorylation defect may result in mitochondrial failure in various organs postoperatively leading to clinical deterioration unrelated to the anesthetic used. This metabolic decompensation can lead to severe lactic acidosis and subsequent ‘metabolic encephalopathy’ which may have been the case in this child.

While a consensus statement from the Mitochondrial Medicine Society reinforces that patients with MD are at an increased risk of anesthesia related complications and adequate preoperative preparation is crucial for good perioperative outcome, a review of routine management of MD patients undergoing anesthesia found that adverse events after general anesthesia are rare and in most cases unrelated to the anesthesia. The dilemma appears to lie in the identification of the disorder rather than its management. The symptoms of MD are often subtle and overlooked by the less attentive parent, particularly those who are uneducated and belong to a low socioeconomic status with limited access to healthcare facilities. Due to the ubiquitous nature of oxidative phosphorylation, a defect of the respiratory chain should be kept in mind in a variety of clinical presentations and at any age. Making minor changes in anesthetic management may be lifesaving and even a slight suspicion of the likelihood of a MD should prompt us to minimize fasting and encourage intake of carbohydrate rich clear fluids up to 1–2 hours before surgery and adopt other simple measures like avoidance of ringer lactate, cautious use of anesthetic agents and performing ABG analysis. The more adept that clinicians become at recognizing MDs, the more opportunity there will be for improving diagnosis, and ultimately treatment. A spread of the awareness of these diseases in the anesthesia community is required.

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CONFLICT OF INTEREST
None.

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