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CASE REPORTS/CASE SERIES

Anesthetic considerations in mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome: a case series

Considérations anesthésiques lors d'un syndrome d'encéphalomyopathie mitochondriale avec acidose lactique et épisodes ressemblant à des accidents vasculaires cérébraux: une série de cas

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Abstract

Purpose *Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome (MELAS) is a rare inherited mitochondrial disorder associated with severe multiorgan pathology and stress-induced episodes of metabolic decompensation and lactic acidosis. The purpose of this case series is to review the medical records of patients with MELAS who underwent anesthetic care at the Mayo Clinic to observe their perioperative responses to anesthesia and to assess outcomes.*

Principal findings *From September 1997 to October 2010, nine patients with MELAS were identified who underwent 20 general anesthetics, 12 prior to MELAS diagnosis. Debilitating neurologic symptoms involved eight patients, and three patients had substantial cardiac comorbidities. The patients tolerated commonly used anesthetics and muscle relaxants, including succinylcholine. Lactated Ringer's solution was used frequently. One patient was noted to have elevated postoperative serum lactate, but his serum lactate was chronically elevated. Metabolic acidosis was not observed in any patient. Hyponatremia and hyperkalemia, sometimes profound, were observed in seven patients, but these abnormalities also occurred at times remote from surgery. Two patients developed renal dysfunction following cardiac surgery and abdominal surgery for severe sepsis.*

Conclusion *The MELAS patients developed episodes of hyponatremia and hyperkalemia of variable severity unrelated to the timing of surgery, suggesting these patients are prone to major electrolyte disturbances. Given the propensity to develop acid-base disturbances and lactacidemia, it is prudent to review and normalize electrolyte abnormalities and to adjust the anesthetic plan accordingly. Fortunately, the limited data suggest that patients with MELAS tolerate commonly used anesthetic drugs well.*

Résumé

Objectif *L'encéphalomyopathie mitochondriale avec acidose lactique et épisodes ressemblant à des accidents vasculaires cérébraux (MELAS) est un trouble mitochondrial héréditaire rare associé à une pathologie grave touchant plusieurs organes et des épisodes de décompensation métabolique et d'acidose lactique provoqués par le stress. L'objectif de cette série de cas est d'examiner les dossiers médicaux de patients atteints de MELAS et ayant reçu des soins anesthésiques à la Clinique Mayo afin d'observer leurs réponses périopératoires à l'anesthésie et d'évaluer leurs devenirs.*

Constatations principales *Pour la période allant de septembre 1997 à octobre 2010, nous avons identifié neuf patients atteints de MELAS ayant subi 20 anesthésies générales, dont 12 avant que le diagnostic de MELAS n'ait été établi. Les symptômes neurologiques débilitants ont touché huit patients, et trois patients ont manifesté des*

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comorbités cardiaques importantes. Les patients ont toléré les anesthésiques couramment utilisés et les curares, y compris la succinylcholine. Une solution de lactate Ringer a été fréquemment utilisée. Chez un patient, un lactate sérique postopératoire élevé a été noté, mais son lactate sérique était chroniquement élevé. L'acidose métabolique n'a été observée chez aucun patient. Chez sept patients, on a observé de l'hyponatrémie et de l'hyperkalémie, parfois profondes, mais ces anomalies sont également survenues à des moments éloignés de la chirurgie. Deux patients ont manifesté une dysfonction rénale à la suite d'une chirurgie cardiaque et d'une chirurgie abdominale pour sepsis grave.

Conclusion *Les patients atteints de MELAS ont manifesté des épisodes d'hyponatrémie et d'hyperkalémie plus ou moins graves et non liés temporellement à la chirurgie, ce qui indique que ces patients sont enclins à subir des perturbations électrolytiques majeures. Étant donné leur propension à manifester des perturbations acido-basiques et une lactacidémie, il est prudent de vérifier et de normaliser les anomalies électrolytiques ainsi que d'adapter le plan anesthésique en conséquence. Heureusement, les données limitées dont nous disposons indiquent que les patients atteints de MELAS tolèrent bien les médicaments anesthésiques couramment utilisés.*

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome (MELAS)[1] is a rare maternally inherited mitochondrial respiratory chain disorder associated most commonly with the mitochondrial DNA *MTTL1* point mutation at nucleotide 3243, A > G.[2] This mutation (or disease) results in a metabolic deficit of oxidative phosphorylation, resulting in impaired integration of pyruvate into tricarboxylic acid (Krebs') cycle[3] and predisposing for the development of lactacidemia, especially under conditions of increased metabolic stress. Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome typically manifests between the ages of five and 20 yr with variable phenotypic presentation and frequently progresses to severe multiorgan pathology and early death.[4,5] The disorder is characterized primarily by severe neurologic manifestations, including stroke-like episodes (confirmed by magnetic resonance imaging (MRI) as non-ischemic cerebral events not confined to a specific vascular territory), seizures, cognitive impairment, acute mental status changes (encephalopathy, psychosis), and migraines.[6] Commonly, patients have cardiac manifestations (preexcitation Wolff-Parkinson-White [WPW] syndrome, cardiac conduction pathway blockade, cardiomyopathy), diabetes mellitus, sensorineural hearing loss, gastrointestinal dysfunction, malnutrition, and muscle wasting. These associated morbidities may increase the risk for perioperative complications.[7-11] Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome patients need anesthesia for diagnostic (muscle biopsy, electrophysiology studies) and therapeutic procedures (cochlear implant, cardiac surgery, pacemaker implantation). Since MELAS is rare (12.5 per 100,000),[12] it is not feasible to perform prospective studies to define anesthetic risk, but potential specific anesthetic concerns have been raised in response to anecdotal reports. For example, controversy exists regarding patient sensitivity to nondepolarizing muscle relaxants (NDMR).[7-10,13] In addition, the avoidance of lactated intravenous fluids has been advocated because of impaired lactate metabolism.[14,15] As with other mitochondrial disorders, there is the concern of increased susceptibility to malignant hyperthermia (MH). To gain a further understanding how best to manage these patients, we analyzed the management and outcomes of nine genetically confirmed MELAS patients who underwent 20 procedures with anesthesia at a single institution over a span of one decade.

Methods

After obtaining Institutional Review Board approval from Mayo Clinic Rochester, Minnesota, a computerized search of the Medical Records Database was conducted for the period September 1997 to October 2010 to identify patients with genetically confirmed MELAS syndrome. In order to ensure all cases were captured, the list of patients was cross-referenced with the MELAS database maintained by the department of Pediatrics and Medical Genetics. Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome diagnosis was established with a combination of clinical signs and symptoms and with confirmation with either muscle biopsy to confirm mitochondrial myopathy[16] and/or genetic testing of the mitochondrial genome (point mutation of guanine substitution for adenine nucleotide at 3243 [A3243G] of the mitochondrial DNA genome [m.3243 A > G]).[5,17] Only patients who underwent surgeries or procedures with anesthetic management at Mayo Clinic were included in the present review. We reviewed demographics (sex, age), genetics records (biochemical and molecular testing), clinical presentation, diagnostic clinical tests (electrocardiogram, echocardiogram, magnetic resonance imaging [MRI], computerized tomography [CT] scans of the head, and muscle biopsy results), surgical/procedural records, American Society of Anesthesiologists physical status, anesthetic course (type of anesthetic, airway management, duration of anesthesia, anesthetic agents and drugs), intraoperative hemodynamics, cardiac dysrhythmias, types

of fluids (lactated Ringer's solution [L/R], isotonic saline solutions [N/S], dextrose-containing solution, colloid solutions), volumes of fluid administered, and intraoperative body temperature. We also recorded and compared pertinent preoperative, intraoperative, and postoperative laboratory values (arterial blood pH, serum bicarbonate, lactate, glucose, and electrolytes) as potential markers of metabolic decompensation. However, when immediate preoperative serum lactate was not obtained, lactate concentrations obtained perioperatively were compared either with "baseline" serum lactate concentrations obtained as part of the medical evaluation for the mitochondrial disorder or with values obtained during the follow-up period (temporally unrelated to the time of surgery).

Finally, we recorded the postoperative course and disposition (admission regular wards, intensive care unit [ICU], or outpatient). Admission to the ICU was categorized as planned (post cardiac surgery or patients who were preoperatively critically ill or admitted for monitoring) or unplanned (unexpected perioperative instability that required postoperative intensive monitoring and treatment). All information was entered into a standardized data collection form, and all questionable entries were discussed and categorized by consensus with the senior authors. Demographics and perioperative characteristics were summarized using descriptive statistics.

A diagnosis of MELAS can be established with a combination of clinical signs and symptoms, but the presence of stroke-like episodes before the age of 40 is of paramount importance. Diagnosis is confirmed with genetic testing. In addition, pathognomonic muscle biopsy findings are used to confirm mitochondrial myopathy. In 1963, W.K. Engel, a neurologist from Mayo Clinic, introduced modification of Gomori trichrome stain, which made it possible to identify abnormal deposits of diseased mitochondria as irregular purplish patches that were named "ragged red fibres" (RRF). The "ragged blue fibres" (RBF), another marker of pathological mitochondrial proliferation, demonstrate a more specific equivalent of RRF which is detected using a succinate dehydrogenase stain.[16] Finally, pathologists use additional histochemical staining of the muscle fibres to demonstrate absence of respiratory chain enzyme–citochrome-*c* oxidase (COX).

Principal findings

We identified nine patients with genetically confirmed MELAS syndrome (i.e., with heteroplasmic m.3243 A > G mutation present in the mitochondrial $tRNA^{Leu\ (UUR)}$ gene), who underwent anesthetic management for 20 procedures. Twelve of those procedures were performed before diagnosis of MELAS was established.

Preoperative clinical characteristics

Table 1 shows the clinical characteristics of our MELAS patients. Eight had substantial debilitating neurological disorders, including stroke-like episodes ($n = 8$) (Fig. 1, brain MRI and CT scans from Pt# 3), seizures ($n = 8$), myopathy/muscle weakness ($n = 5$), and mental status alterations, including encephalopathy ($n = 5$). The only patient (Pt# 2) who had no neurologic impairment other than sensorineural hearing loss had significant gastrointestinal involvement resulting in megacolon, which prompted the genetic workup that identified the mitochondrial disorder. Three patients had substantial cardiac morbidities, including third degree atrioventricular block requiring a pacemaker, cardiomyopathy requiring heart transplantation, WPW syndrome requiring radiofrequency ablation, and aortic regurgitation requiring valve replacement. Three patients had insulin-dependent diabetes mellitus and one had glucose intolerance.

Histological MELAS characteristics

Muscle biopsy and histochemical analysis has an important role in confirmation of MELAS diagnosis and they were obtained in three patients. Figure 2a illustrates pathognomonic muscle biopsy findings in one of our patients (Pt# 3). Presence of muscle fibre atrophy (Type 1 and Type 2 fibres) and their pathological groupings (shown as different intensity of red staining in Fig. 2A), rather than being randomly distributed, suggests an ongoing fibre denervation and renervation pattern. In addition, pathologic accumulation of mitochondria in subsarcolemmal areas (depicted as "blue or red ragged fibres") (Fig. 2b) and the absence of citochrome-*c* oxidase in fibres (COX-negative fibres) (Fig. 2c) represent a "morphological signature" of mitochondrial myopathy.

Anesthetic course

All patients received at least one general anesthetic, and four had at least one additional procedure performed under monitored anesthesia care (Table 2). Indications for anesthesia included diagnostic procedures (muscle biopsy, $n = 3$; MRI under anesthesia, $n = 2$; cerebral angiogram, $n = 1$; esophagogastroduodenoscopy, $n = 3$; bronchoalveolar lavage, $n = 1$), minor operations (cochlear implant, $n = 1$; gastrostomy tube placement, $n = 1$), and major operations (cardiac, $n = 3$; abdominal, $n = 4$; and gynecological, $n = 1$). All contemporary anesthetic induction agents (propofol, etomidate or sodium thiopental) were used. Airway was managed with endotracheal tubes ($n = 14$), laryngeal mask airway device ($n = 1$) and spontaneous breathing with oxygen *via* mask or nasal

Table 1 MELAS syndrome manifestations in case series patients

Pt#	Sex Age (yr)† Height (cm)	Echocardiographic (ECHO) and Electrocardiographic (ECG) Findings	Diabetes Mellitus and Gastrointestinal Disorders	Neurologic and Cognitive Deficit and Radiology Findings (head)
1.	♀ 58 160	ECHO: Patent foramen ovale with bidirectional shunting ECG: 3rd degree A-V block (paced)	Diabetes mellitus	Strokes X 3; generalized seizures (levetiracetam); aphasia; mild dementia; ataxia; diplopia; migraines; SNHL CT scan: Infarcts of the L PCA & distal L MCA distributions. Cerebral & cerebellar volume loss
2.	♂ 65 165	ECHO: Regional wall motion abnormalities; large pleural effusion ECG: LBBB; short PR interval; PVC; PAC	Diabetes mellitus (autonomic neuropathy) Megacolon; intestinal pseudo-obstruction; malnutrition (BMI 16 $kg \cdot m^{-2}$); chronic diarrhea	SNHL (cochlear implant uneventful anesthesia elsewhere)
3.	♂ 14 168	ECHO: Pericardial effusion ECG: 1st degree AV block	Gastroparesis; dysphagia; weight loss (BMI 17 $kg \cdot m^{-2}$)	Stroke X 1; severe myopathy; tonic-clonic and myoclonic seizures (carbamazepine, valproic acid, phenobarbital, phenytoin); encephalopathy; tremor; migraines; SNHL MRI: Infarcts of L temporal, parietal, posterior frontal, & occipital lobes, L posterior thalamus, & R occipital & inferolateral frontal lobes
4.	♀ 52 157	ECHO: pericardial effusion; Left ventricular hypertrophy; biatrial enlargement ECG: left posterior fascicular block; inferolateral ischemia	Diabetes mellitus Malnutrition (BMI 16 $kg \cdot m^{-2}$)	Stroke X 4; myopathy; generalized tonic-clonic seizures (phenytoin, levetiracetam); ataxia; aphasia; encephalopathy; psychosis; SNHL MRI: Infarct of temporal lobe; diffuse cerebral atrophy of cerebellum
5.	♀ 26 153	ECHO: normal ECG: marked sinus arrhythmia; short PR interval; PAC	Weight loss (BMI 14 $kg \cdot m^{-2}$)	Stroke X 1; L hemiparesis; myopathy; cerebral palsy; partial complex seizures (levetiracetam); aphasia; dysarthria; encephalopathy; migraines; SNHL MRI: Infarct of L MCA distribution; volume loss & encephalomalacia R temporal lobe
6.	♀ 60 154	ECHO: normal ECG: short PR interval	Glucose intolerance; gastrointestinal myopathy; weight loss (BMI 18 $kg \cdot m^{-2}$)	Stroke X 1; generalized seizures (levetiracetam); aphasia; dysarthria; visual impairment; SNHL MRI: Infarct of L PCA distribution; volume loss, gliosis, and encephalomalacia of L occipital & posterior temporal lobes
7.	♀ 30 170	ECHO: pericardial effusion; hypertrophic cardiomyopathy with congestive heart failure (class III); pulmonary hypertension; biatrial enlargement ECG: short PR interval; 1st degree AV block; PVC, inferior & anterolateral ischemia	Malnutrition (muscle wasting) (BMI 18 $kg \cdot m^{-2}$)	Stroke X 1; L hemiparesis; myopathy; generalized seizures (levetiracetam); short-term memory loss; gait imbalance; migraines; SNHL MRI: Infarct of thalamus & R cerebrum

Table 1 continued

Pt#	Sex Age (yr)† Height (cm)	Echocardiographic (ECHO) and Electrocardiographic (ECG) Findings	Diabetes Mellitus and Gastrointestinal Disorders	Neurologic and Cognitive Deficit and Radiology Findings (head)
8.	♂ 21 160	ECHO: severe AVR (bicuspid valve); moderate MVR & TVR; Left Atrial enlargement; LV hypertrophy ECG: WPW (frequent SVT); Left ventricular hypertrophy with strain	Weight loss (BMI 16 $kg \cdot m^{-2}$); nausea; vomiting	Stroke X 1; aphasia; "subclinical" seizures as evidenced by EEG changes following stroke (levetiracetam); mental retardation; migraines; SNHL MRI: Infarct of L temporal lobe
9.	♂ 10 134	None£	Gastroparesis; dysphagia; nausea; vomiting; severe constipation	Stroke X 1; myopathy; generalized seizure (topiramate, diazepam); attention deficit hyperactivity disorder; SNHL

£ Patient with limited medical record information from outside institution. † Age at mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes syndrome (MELAS) diagnosis. L = left; R = right; LV = left ventricular; Pt = patient; ♂ = male; ♀ = female; BMI = body mass index; AVR = aortic valve regurgitation; MVR = mitral valve regurgitation; TVR = tricuspid valve regurgitation; PAC = premature atrial complexes; PVC = premature ventricular complexes; LBBB = left bundle bunch block; AV = atrioventricular; WPW = Wolff-Parkinson-White syndrome; SVT = supraventricular tachycardia; SNHL = sensorineural hearing loss; MCA = middle cerebral artery; PCA = posterior cerebral arteries; MRI = magnetic resonance imaging; CT scan = computerized tomography scan

cannula ($n = 5$). Nondepolarizing neuromuscular blocking drugs (NMBDs) were administered in 14 patients, and succinylcholine was administered in four patients, all prior to the diagnosis of MELAS. The depth of neuromuscular block was monitored using a train-of-four device, and neostigmine was administered in six patients as a reversal agent. There were no recorded instances of atypical/unusual responses to NMBDs, as expected doses of NMBDs were administered for the appropriate cases, and there was no evidence to suggest incomplete NMBD reversal or recurarization. General anesthesia was maintained with volatile anesthetics (desflurane, isoflurane, halothane) in 14 patients and with propofol infusion in three patients.

Intraoperative fluids

Lactated Ringer's solution was administered in 13 cases, and in five cases (four patients), L/R was administered after MELAS was diagnosed. One patient (Pt# 3) who received L/R 1L was found to have an elevated postoperative serum lactate of 6 $mmol \cdot L^{-1}$ (reference, 0.62-2.3 $mmol \cdot L^{-1}$) that decreased to 2.7 $mmol \cdot L^{-1}$ the next day. However, this patient's "baseline" lactate concentrations were chronically elevated between 3.1 and 5.1 $mmol \cdot L^{-1}$. Despite the use of L/R solution, sometimes in relatively large volumes (Pts# 1, 2, 7, 8), none of the patients developed acid-base decompensation (metabolic acidosis). One patient (Pt# 2) with intra-abdominal sepsis developed non-sustained ventricular tachycardia and hypotension and was managed intraoperatively with vasopressin and aggressive fluid resuscitation (L/R 5L and N/S 1L). Despite the volume of fluid administration, he did not develop metabolic acidosis (pH 7.36/HCO_3 18 $mEq \cdot L^{-1}$, anion gap 6 $mEq \cdot L^{-1}$ immediately after surgery; and pH 7.49/HCO_3 23 $mEq \cdot L^{-1}$, anion gap 7 $mEq \cdot L^{-1}$ five hours after surgery). Serum lactate was never obtained because his surgery was performed prior to the diagnosis of MELAS.

Electrolyte disturbances

Three patients developed postoperative hyponatremia and hyperkalemia (Table 3). In one patient (Pt# 4), hyponatremia (122 $mmol \cdot L^{-1}$) was observed on the fourth postoperative day and was attributed to free water overload through the feeding tube, as the intravenous fluid he was administered postoperatively was 0.9% normal saline. Another patient (Pt# 7) developed electrolyte imbalance following cardiac transplantation and postoperative renal failure but was also diagnosed with adrenal insufficiency. At some point during their care at the Mayo Clinic, four other patients developed hyponatremia associated with higher serum potassium which was unrelated to surgery (Table 3). One 14-yr-old patient (Pt# 9) had an unexplained

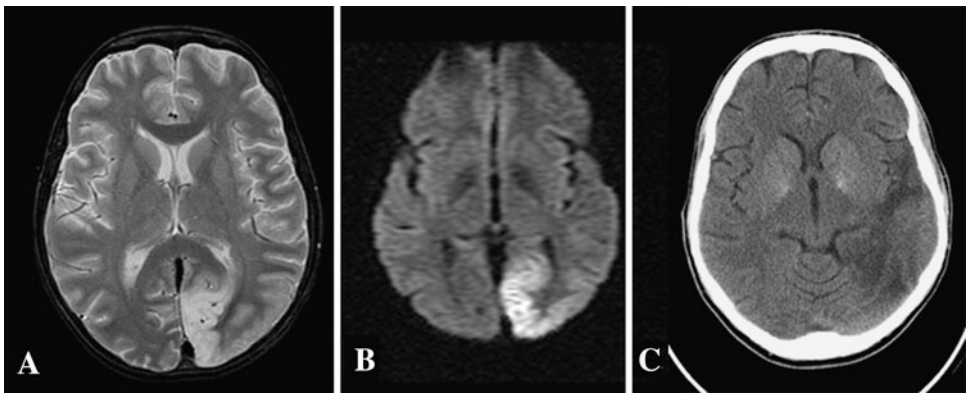


Fig. 1 MELAS imaging in a 23-yr-old male (Pt# 3). (A) Axial T2 weighted image demonstrates predominantly cortical T2 hyperintensity involving the medial left occipital lobe, consistent with an acute infarct in the posterior cerebral artery (PCA) territory. (B) Axial diffusion weighted image demonstrates restricted diffusion in the same territory, supporting the diagnosis of an acute infarct. (C) Axial computed tomography scan through the same region demonstrates low attenuation changes in the evolving PCA infarct and basal ganglia calcifications bilaterally, which, in a younger patient, can be a clue to the diagnosis of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome (MELAS)

episode of severe hyponatremia (118 $mmol \cdot L^{-1}$) and hyperkalemia (in the absence of metabolic acidosis as assessed from bicarbonate 25 $mEq \cdot L^{-1}$), and he had only slightly elevated lactates (3.9 $mmol \cdot L^{-1}$) associated with high urinary sodium excretion (177 $mEq \cdot L^{-1}$, reference 30-90 $mEq \cdot L^{-1}$) 13 months after surgery. This was corrected and the patient was discharged, but he died unexpectedly at home one month later.

Postoperative course

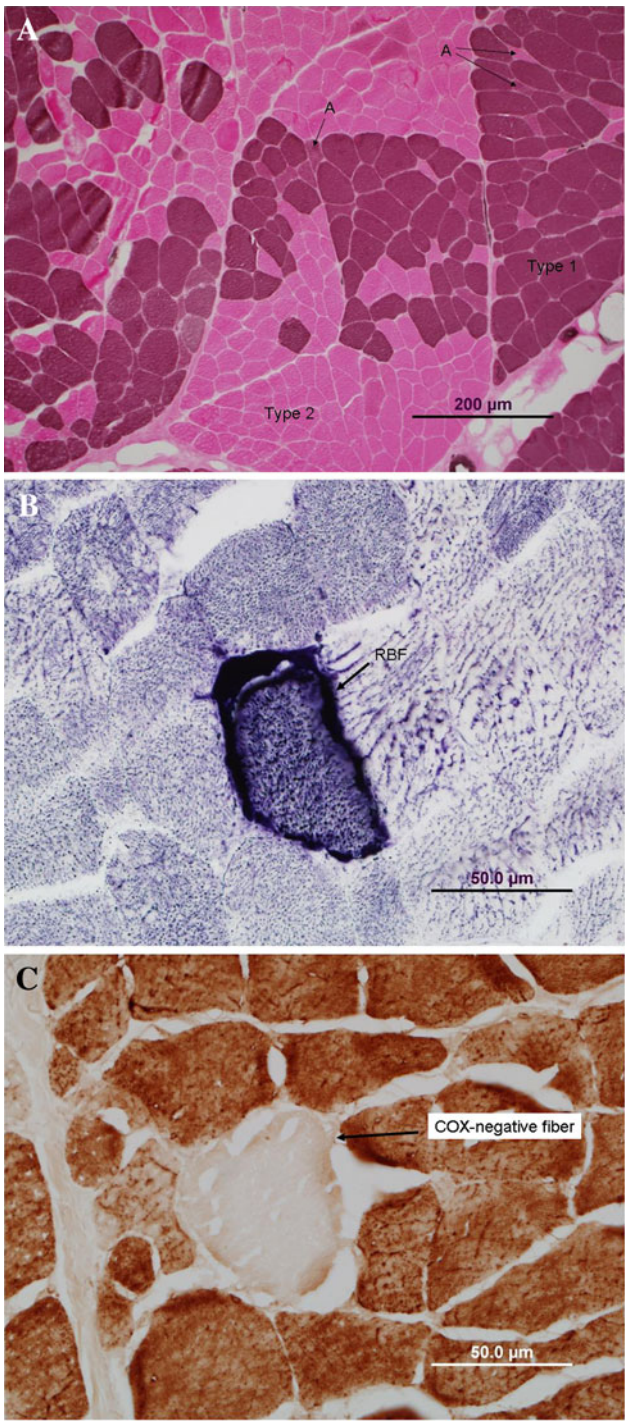
Compared with their preoperative baseline characteristics, which, in some cases, were substantially abnormal (Table 1), none of the patients' mental (cognitive) status declined postoperatively. No patient had preoperatively identified renal disease; however, two patients developed postoperative renal failure, the first after cardiac surgery and the second after emergent exploratory laparotomy for colonic volvulus at an outside institution. Both of these patients required dialysis. In all patients, intraoperative temperatures were managed with forced-air warmers, and body temperatures were maintained from 36°C to 37.8°C. As anticipated, seven patients were admitted to the ICU postoperatively for various reasons, including routine monitoring after complex cardiac surgery (Pt# 7, 8), a preoperative critically complex medical condition (Pt# 2), or titration of antiepileptic therapy (Pt# 3).

Discussion

The most important observation in this case series is noting that seven of nine patients with MELAS developed perioperative episodes of hyponatremia and hyperkalemia of variable severity unrelated to the timing of surgery. This finding suggests that patients with MELAS are prone to major electrolyte disturbances, and it is prudent for the anesthesiologist to review preoperative laboratory values carefully and to adjust the anesthetic plan accordingly. The other major finding of our case series is noting that surgery under anesthesia is generally well tolerated, and patients tend not to develop major acid-base abnormalities (metabolic acidosis) despite the frequent use of L/R solution. Furthermore, our patients did not exhibit an aberrant response to NMBDs. Although some patients had an altered mental status preoperatively, there were no cases of exacerbated neurocognitive decline in the postoperative period.

Perioperative acid-base balance

Since lactate metabolism in MELAS is impaired, it has been recommended to avoid hydration with lactate-containing fluids.[14,15] However, L/R was used in substantial amounts in several of our patients, mostly before MELAS diagnosis was established and, in some cases even after MELAS was confirmed. Although we found no evidence of metabolic acidosis in patients who received L/R, the retrospective nature of this case series raises the possibility that cases of metabolic acidosis were not recognized. Some patients had elevated postoperative serum lactate concentrations, but unfortunately, they did not have serum lactate values established prior to surgery. However, in these patients, the elevated postoperative lactate values were within their typical "baseline range" (Table 2). Lack of consistent documentation of pre- and postoperative lactate



◀ **Fig. 2** Muscle histochemistry of the vastus lateralis muscle in Pt# 3 (routine light microscopy and immunohistochemistry). (a) Atrophic fibres (arrow A) of both histochemical types (Type 1, dark red stained, and Type 2, light red stained) indicate fibre denervation. Marked both fibre Type 1 and 2 grouping (rather than random fashion) are pathological and implies reinnervation of denervated fibres. (b) Staining for succinate dehydrogenase shows presence of "ragged-blue fibre" (RBF) (arrow), which is consistent with mitochondrial myopathy. Dark blue areas at periphery of fibre depict increased accumulation of activity, i.e., pathological increase in mitochondrial number and volume in subsarcolemmal and interfibrillar fibre parts. (c) Histochemical stains for cytochrome-*c* oxidase (COX) activity. The central fibre in the field (arrow) shows muscle fibre devoid of COX activity (COX-negative fibres) characteristic for mitochondrial myopathy, such as mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome (MELAS)

concentrations precluded our formulating any definitive conclusions regarding the safety of administering L/R solutions in these patients. Given these theoretical concerns that L/R administration could trigger metabolic decompensation, it may be prudent to avoid its routine use in MELAS patients until further prospective studies confirm its safety in this patient population. It is also prudent to monitor closely the acid-base status and serum lactate levels in major surgical procedures in patients with recognized MELAS syndrome.

Hyponatremia and associated hyperkalemia

In seven patients, we found instances of hyponatremia and hyperkalemia that were temporally unrelated to surgery (Table 3). Sasano *et al.*[18] described a patient who developed severe hyponatremia, hypovolemic shock, and lactic acidosis on the third postoperative day. He attributed this occurrence to excessive sodium wasting following a gastrectomy.[18] Kubota *et al.*[19] described periodic hyponatremia in four of his seven MELAS patients, and in two patients, the finding could be attributed to excessive sodium excretion due to adrenal insufficiency. One of our patients (Pt# 7) was diagnosed postoperatively with adrenal insufficiency. Another patient was found to have a severe episode of hyponatremia, increased urinary sodium excretion, and hyperkalemia (Pt# 9), the cause of which could not be confirmed. Although adrenal insufficiency has never been described as a part of MELAS syndrome, several reports in patients with mitochondrial disorders described clinical pictures consistent with it. For example, Southgate *et al.*[20] reported recurrent renal salt wasting in a patient with a mitochondrial defect. Boles *et al.*[21] reported adrenal insufficiency in a patient with Kearns-Sayre syndrome, and Shimizu *et al.*[22] reported hyporeninemic hypoaldosteronism with hyperkalemia in a patient with mitochondrial cytopathy. It is not known whether these episodes of hyponatremia associated with hyperkalemia, such as encountered in several of our patients, could be corrected with corticosteroid administration, but the possibility of MELAS-associated adrenal insufficiency needs to be studied in the future. At the same time, the pathogenesis of hyponatremia in MELAS may also be attributed to malnutrition and/or excessive parenteral hydration (Pt# 4) or sodium loss following gastrectomy.[18] However, one would expect to encounter lower serum potassium in these

Table 2 Surgical and anesthetic characteristics and outcomes

Pt#	Age[††] ASA PS	Procedure (indication) Anesthesia Type (duration)	Airway Anesthetics agents	Operative Fluids type, L	Preoperative Labs[‡] ▼ Remote Baseline	Postoperative Labs[¥]	Disposition Outcome
1	58	Muscle biopsy[†] (suspected MELAS)	NC	N/S, 0.5	S-Lactate: 1.7	Electrolytes: NL	Surgical ward
	III	MAC (43 min)	P; F		Glucose: 171	Glucose: 190	
	58	Cerebral angiogram[†] (multiple strokes)	ETT	L/R, 1.5	S-Lactate: 1.1	Electrolytes: NL	Surgical ward
	III	GA (83 min)	P; Iso, N_2O; V (6 mg)		Electrolytes: NL	ABG: NL	
					ABG: NL Glucose: 190	Glucose: 140	
2	64	Colectomy[†] (megacolon)	ETT	L/R, 5.0	Electrolytes: NL	Electrolytes: NL	ICU
	III	GA (247 min)	P; M; F; H; Des; S (100 mg); V (6 mg); N	N/S, 1.0 Colloids, 0.8		ABG: NL Glucose: 248	
	64	Celiotomy[†] (intra-abdominal sepsis)	ETT	L/R, 4.0	Electrolytes: NL	Na_s: 130; K_s: NL	ICU
	III	GA (210 min)	E; M; F; H; Des; S (80 mg); C (14 mg); N	Colloids, 1.0	ABG: NL Glucose: NL	ABG: metabolic alkalosis (pH 7.51; HCO_3 27) Glucose: 215	
3[‖]	14	Muscle biopsy[†] (suspected MELAS)	Mask	N/S, 0.250	S-Lactate: 4.4	S-Lactate: 3.2	Surgical ward
	III	MAC (70 min)	P; M; F		Na_s: 131 K: NL	Na_s: 130	
					ABG: NL	K_s: NL	
					Glucose: NL	HCO_3: 27	
						Glucose: 175	
	17	EGD (dyspepsia)	Mask	[‡‡]D5L/R, 0.5	S-Lactate: 3.5	S-Lactate: 3.2	Surgical ward
	III	MAC (25 min)	P; M		Electrolytes: NL	Electrolytes: NL	
					ABG: NL	ABG: NL	
					Glucose: NL	Glucose: NL	
	17	MRI (new onset of weakness and seizures)	ETT (pre existing)	N/S, 0.5	S-Lactate: 5.1	S-Lactate: 2.2	ICU
	III	GA (60 min)	P		Electrolytes: NL	Electrolytes: NL	
					ABG: NL	ABG: NL	
					Glucose: NL	Glucose: NL	
	18	EGD (persistent vomiting)	NC	N/S, 1.0	S-Lactate: 4.9	Not obtained	Outpatient
	III	MAC (15 min)	P; M		Electrolytes: NL		
					Glucose: NL		
	23	Cholecystectomy (cholelithiasis)	ETT	[‡‡]L/R, 1.0	Electrolytes: NL	S-Lactate 6	ICU
	III	GA (175 min)	P; F; Des;	N/S, 2.0	Glucose: NL	Electrolytes: NL	
			V (9.5 mg); N		▼ S-Lactate 2.2 (9 mo before)	Glucose 144	

Table 2 continued

Pt#	Age[††] ASA PS	Procedure (indication) Anesthesia Type (duration)	Airway Anesthetics agents	Operative Fluids type, L	Preoperative Labs[‡] ▼ Remote Baseline	Postoperative Labs[¥]	Disposition Outcome
4	52	PEG tube placement (malnutrition)	ETT	[‡‡]L/R, 1.0	S-Lactate: 4.3	Electrolytes: NL	Surgical ward
	III	GA (120 min)	P; M; F;		Electrolytes: NL	Glucose: NL	
			Iso; V (5 mg); N		Glucose: NL	▼ S-Lactate: 2.2 (5th POD)	
					ABG: NL	▼ Na_s 122 on 6th POD	
5	26	MRI and lumbar puncture (stroke)	ETT	[‡‡]L/R, 0.5	Electrolytes: NL	S-Lactate: 3.8	Surgery ward
	III	GA (50 min)	Sev; Iso; N_2O		Glucose: NL	ABG: NL	
						▼ S-Lactate: 3.1 (30th POD)	
6[€]	61	Kidney mass ablation (tumour)	ETT	N/S, 1.0	Na_s 132; K_s 5	Electrolytes: NL	Surgery ward
	II	GA (180 min)	P; F; H; Iso;		▼ S-Lactate: 1.1 (2 yr before)	Glucose: NL	
			C (18 mg)				
7	22	Cardiac transplant[†] (cardiomyopathy)	ETT	L/R, 4.0	Electrolytes: NL	Na_s 133	ICU (adrenal insufficiency, and acute renal failure post-op)
	IV	GA (540 min)	P; K; M; F; Hal; N_2O;	Colloids, 1.7	Glucose: NL	K_s 7.0 (dialysis)	
			S (80 mg);			ABG: NL	
			PC (14 mg)			Glucose 147	
						▼ S-Lactate: 4.8 (9 mo later)	
	27	Cochlear implant[†] (SNHL)	ETT	L/R, 2.0	Glucose: NL	Not Obtained	Outpatient
	III	GA (180 min)	P; M; F; Des; S (80 mg)		▼ S-Lactate: 3.0 (2 yr before)		
	29	Oophorectomy[†] (ovarian cyst)	ETT	L/R, 3.0	S-Lactate: 2.6	Not Obtained	Outpatient
	IV	GA (66 min)	P; F; Hal; V (3 mg); N		Electrolytes: NL		
					Glucose: NL		
	29	Bronchoalveolar lavage[†] (lung infiltrate)	ETT	L/R, 0.5	Electrolytes: NL	Not Obtained	Outpatient
	III	GA (60 min)	P; M; F		Glucose: NL		
8	16	Cardiac RF[†] ablation (SVT)	ETT	D5% 0.45% N/S, 2.0	Electrolytes: NL	Not Obtained	ICU
	III	GA (235 min)	P; F; Iso; N_2O; V (5 mg); N			▼ S-Lactate: 1.9 (3 mo later)	
	21	Aortic valve replacement[†] (Severe AR)	ETT	L/R 2.0	S-Lactate: 2.4	Electrolytes: NL	ICU
	III	GA (239 min)	STP; M; F; Iso; PC (8 mg)	N/S, 1.9	Electrolytes: NL	Glucose: 150	
				Colloids, 0.33	Glucose: NL		
	21	Muscle biopsy[†] (suspected MELAS)	LMAD	N/S, 1.0	S-Lactate: 2.3	Not Obtained	Outpatient
	III	GA (70 min)	P; M; F;		Electrolytes: NL		Died 30 d later suddenly
			Des; N_2O				

Table 2 continued

Pt#	Age[†] ASA PS	Procedure (indication) (duration)	Anesthesia Type	AirwayAnesthetics agents	Operative Fluids type, L	Preoperative Labs[‡] ▼ Remote Baseline	Postoperative Labs[¥]	Disposition Outcome
9[€€]	13 III	EGD with biopsy (dysphagia) GA (20 min)		Mask P; Des	[‡‡]L/R, 0.75	Not Obtained ▼ S-Lactate: 5.4 (6 mo before)	Not Obtained	Outpatient Died 1 yr later

[‡‡] Patient received lactated Ringer's solution after mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes syndrome (MELAS) diagnosis was established. [†] Surgery performed before MELAS diagnosis; [††] Age at the time of surgery; [‡] Obtained within seven days before surgery; When immediate preoperative lab values not available, the given value (▼) is the one obtained closest to the time of surgery. [¥] Measured within 48 hr after the procedure; [€] Patient had previous uncomplicated emergency surgery elsewhere for volvulus. [€€] Previous surgeries outside Mayo: fundoplication at age nine; tonsillectomy at age three, hemiorrhaphy at age four; [‖]Lactate concentration ranged from 2.2 to 5.9 mmol·L^{-1} on follow-up visits

Pt# = patient number; mo = month; yr = year; d = day; min = minutes; POD = postoperative day; ASA PS = American Society of Anesthesiologists physical status; ETT = endotracheal tube; NC = nasal cannula; LMAD = laryngeal mask airway device; MAC = monitored anesthesia care; GA = general anesthesia; EGD = esophagogastroduodenoscopy; M = midazolam; P = propofol; K = ketamine; E = etomidate; STP = Sodium thiopental; Iso = isoflurane; Hal = halothane; Sev = sevoflurane; Des = desflurane; N_2O = nitrous oxide; S = succinylcholine; V = vecuronium; C = cisatracurium; PC = pancuronium; N = neostigmine; F = fentanyl; H = hydromorphone; NL = normal; NS = 0.9% normal saline; D5L/R = 5% dextrose with lactated Ringer's solution; D5% 0.45%N/S = 5% dextrose with 0.45% normal saline; L/R = lactated Ringer's solution; S-Lactate = serum lactate concentration (normal range 0.6-2.3 mmol·L^{-1}); Glucose (normal range 70-100 mg·dL^{-1}); Na_s = serum sodium (normal range 135-145 mmol·L^{-1}); K_s = serum potassium (normal range 3.6-4.8 mmol·L^{-1}); HCO_3 = serum bicarbonate (normal range 22-29 mmol·L^{-1}); pH (normal range 7.35-7.45); ABG = arterial blood gas; MRI = magnetic resonance imaging; PEG tube = percutaneous endoscopic gastrostomy tube. AR = acetylcholine receptors; RF = radio frequency

situations, rather than hyperkalemia. Finally, Fanconi syndrome (a disease of the proximal tubules of the kidneys) has been associated with mitochondrial cytopathy[3,16]; however, it is characterized by hyponatremia, hypokalemia, glycosuria, and acidosis, and these findings were not present in our patients. Regardless of the etiology, the observation that these electrolyte disturbances occur without temporal relationship to surgery is of concern, as such disturbances may occultly be present preoperatively. Review of patient electrolyte status preoperatively is prudent. In cases of clinically relevant hyponatremia and hyperkalemia, consultation with an endocrinologist may be warranted for investigation of possible adrenal insufficiency.

MELAS and diabetes mellitus

A clear link was established between maternally inherited diabetes mellitus and A3243G point mutation in the $tRNA^{Leu\ (UUR)}$ gene and MELAS syndrome. Among 39 MELAS patients, Kadowaki *et al.*[23] identified eight (20.5%) as diabetic patients, while in our series, three (33.3%) had insulin-dependent diabetes, and one had glucose intolerance. It has been recommended to hydrate MELAS patients with glucose-containing fluids to prevent catabolism.[14] We suggest that perioperative management should be guided according to serum glucose concentrations. Many of our patients experienced perioperative hyperglycemia and required insulin - no hypoglycemic events occurred.

Muscle relaxant considerations

Evidence regarding variable response of MELAS patients to muscle relaxants is conflicting and is generalized from observations described in case reports or related (non MELAS) mitochondrial disorders.[13] For example, a normal response to pancuronium and succinylcholine was observed in a patient with Kearns-Sayre syndrome.[13] In several MELAS cases, increased sensitivity to NMBDs was reported for vecuronium,[9] mivacurium,[10] rocuronium, and atracurium.[8] In contrast, one report described resistance to cisatracurium.[7] Finally, a patient with an undefined mitochondrial myopathy developed hyperkalemia in response to succinylcholine.[24] Variable response to muscle relaxants can be attributed to pharmacokinetic and pharmacodynamic factors unrelated to MELAS syndrome. For example, the resistance to NMBDs during chronic antiepileptic therapy (MELAS patients are almost universally receiving this therapy, Table 2) has been attributed to induction of hepatic drug metabolism,[25-27] increased protein binding,[28,29] and up-regulation of acetylcholine receptors.[27,30-32] In contrast, acute administration of an anticonvulsant drug can enhance the effects of NMBA.[27,33]

Table 3 Episodes of hyponatremia and/or hyperkalemia in MELAS patients during care at the Mayo Clinic

Pt#	Serum Sodium (reference, 135-145 mEq·L^{-1})	Serum Potassium (reference, 3.6-4.8 mEq·L^{-1})	Electrolyte Measurements in Relation to the Time of Surgery
2	131	5.2	5 days after surgery
3	130-133	4.2-4.6	Intermittent finding, not related to surgery
4	122	5.2	4 days after surgery
5	135	5.1	2 weeks before surgery
6	132	5.0	3 days before surgery
7	133	7.0	2 days after surgery (adrenal insufficiency & acute renal failure)
	132	5.9	1 mo after surgery
9	118	5.4	13 months after surgery (died suddenly 1 mo later at home; cause unknown)

Pt# = patient number, refers to patient numbers from Table 1

Therefore, the net response to muscle relaxants in MELAS patients may depend on a complex interplay between induced-metabolism effects (antiepileptics) and the sensitivity effects related to associated myopathy. Review of anesthetic records in our series did not indicate that anesthesiologists used excessive amounts of NMBDs (for the duration of surgery), which might indicate possible NMBD resistance (Table 2). Furthermore, the recovery from NMBD blockade appeared uneventful. However, for antiepileptic therapy, the majority of our patients were receiving either levetiracetam or topiramate (6/8), neither of which alters the pharmacological response to NMBDs.[34] Only one patient (Pt# 3) had a severe myopathy, and succinylcholine was not administered in this patient. However, since this is a retrospective case series, we cannot exclude the potential for an aberrant and undocumented response to NMBDs. We caution for extra care in the titration and monitoring of muscle relaxants in patients with MELAS syndrome.

Susceptibility to rhabdomyolysis and MH

Patients in our series had no abnormal temperature fluctuations, signs of hypermetabolism, or signs of rhabdomyolysis. There are reports of patients with MELAS who developed rhabdomyolysis. One case involved a 33-yr-old woman who became critically ill with metabolic decompensation (severe metabolic acidosis with lactacidemia) following an induction of anesthesia for a therapeutic abortion. During her illness, she developed rhabdomyolysis.[35] Other cases of rhabdomyolysis have occurred spontaneously[36] in the setting of the administration of simvastatin[37] and in patients with the A3243G mutation who did not have MELAS syndrome.[38,39] Exercise-induced rhabdomyolysis arising from the A3260G mitochondrial DNA mutation has been described in patients with MELAS.[40] There have been no cases of rhabdomyolysis documented in the perioperative period, and in our series none occurred despite the use of succinylcholine. Propofol was administered in 17 cases without incident, and no patient developed clinical signs suggestive of propofol infusion syndrome (i.e., no evidence of metabolic acidosis or rhabdomyolysis). However, propofol was not used for prolonged ICU sedation. Propofol infusion syndrome has never been described as a complication in patients with MELAS syndrome; however, caution is recommended with its use in patients with mitochondrial disorders.

Presently, there is no clear evidence to support that mitochondrial myopathy increases susceptibility to MH. One patient with a mitochondrial myopathy had a positive halothane contracture test and was labelled as "susceptible to MH" although he never experienced a MH episode.[41] Another patient with mitochondrial myopathy developed a "MH crisis" after induction with succinylcholine; however, definitive laboratory confirmation of MH was not provided.[42] Since MELAS and MH are rare conditions, a definitive conclusion regarding their association cannot be made from these rare case reports. Malignant hyperthermia triggering agents have been used routinely in patients with mitochondrial disorders at both the Mayo Clinic[43] and the Cleveland Clinic[44] and, in the majority of our cases, without evidence of MH or hypermetabolism.

Cardiac implications

Patients with MELAS have an increased risk for development of perioperative dysrhythmias. They have a higher prevalence of cardiac conduction defects, specifically atrioventricular conduction blocks and preexcitation WPW syndrome.[1,5,45-50] Several of our patients had electrocardiographic changes frequently associated with MELAS, including an asymptomatic short PR interval, WPW syndrome with frequent supraventricular tachycardia requiring

radiofrequency ablation, and a third-degree atrioventricular block that required a pacemaker implantation. One of our patients had severe cardiomyopathy and received a heart transplant, and the patient with WPW had severe aortic regurgitation requiring valve replacement at the age of 21. Interestingly, cardiomyopathy has been reported to complicate MELAS syndrome arising from an A3260G mitochondrial DNA mutation.[40] It is important to note that one patient (Pt# 2) developed intraoperatively nonsustained ventricular tachycardia and hypotension, which, at the time, was attributed to concomitant severe sepsis.

In conclusion, because of multi-organ pathology, MELAS patients may have an increased risk for development of perioperative cardiac, neurologic, metabolic, and endocrine complications. During anesthesia, MELAS patients in this series did not manifest aberrant responses to muscle relaxants, nor were there complications that could be attributed to anesthesia management *per se*. Importantly, we did not encounter major alterations of acid-base balance despite administration of L/R solution, sometimes in large volumes. However, we did observe frequent episodes of electrolyte imbalance (simultaneous presence of hyponatremia and hyperkalemia), which were mostly unrelated to the timing of surgery. While this electrolyte pattern may resemble the pattern typical for patients with adrenal insufficiency, this endocrine mechanism remains speculative in light of other frequent MELAS-associated gastrointestinal and/or renal disorders. However, since these electrolyte imbalances may be unexpected (incidental findings), serum sodium and potassium should be monitored closely throughout the perioperative period in MELAS patients.

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