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Anesthetic management for an infant with mitochondrial cytopathy

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Introduction

Mitochondrial cytopathy [1] is a rare congenital disorder characterized by progressive multiple-organ dysfunction due to impaired production and conversion of adenosine triphosphate (ATP) in mitochondria. The main target organs are the muscle and encephalon which characteristically require a large amount of energy. The heart, liver, and pancreas are sometimes involved.

Although the clinical features of this disease are well described in the literature of pediatrics and general medicines, there are few reports about the management of anesthesia in patients with mitochondrial cytopathy. We report a case of general anesthesia for a 5-month-old infant with convulsion, difficulty in breathing, and uncontrollable diabetes resulting from severe mitochondrial cytopathy who underwent tracheotomy, and we discuss the problems of the anesthetic management for mitochondrial cytopathy.

Case report

A 5-month-old male Japanese infant was admitted to our hospital for failure to thrive. He had been normal at birth and his family history was noncontributory. On admission, he had stopped breathing and required controlled mechanical ventilation. He exhibited convulsions, increased deep tendon reflexes, and solid edema in all limbs. Biochemical testing revealed diabetes [blood sugar 277 $mg \cdot dl^{-1}$, Hb_{A1c} 4.1% (normal range: 3.8%–5.3%), Hb_{A1} 8.1% (normal range: 5.3%–7.1%), insulin 1.5 $\mu U \cdot ml^{-1}$ (normal range: 5–12 $\mu U \cdot ml^{-1}$)], hyperlactemia 21.7 $mg \cdot dl^{-1}$ (normal range: 4–16 $mg \cdot dl^{-1}$) and hyperpyruvemia 1.9 $mg \cdot dl^{-1}$ (normal range: 0.3–0.9 $mg \cdot dl^{-1}$) and increased urinary excretion of 2-OH-*n*-butyrate, fumarate, and 2-ketoglutalate. The latter are intermediates of the tricarboxylic acid (TCA) cycle which are not normally observed in the urine. An electroencephalograph showed multiple focal spikes. Computed tomography (CT) revealed atrophy of the frontal lobe. Mitochondrial encephalomyopathy was diagnosed. He was administered the following medications: for convulsions, phenobarbital 40 $mg \cdot day^{-1}$, sodium valproate 140 $mg \cdot day^{-1}$, and carbamazepine 10 $mg \cdot day^{-1}$; for diuresis, furosemide 4 $mg \cdot day^{-1}$; and for hyperglycemia 0.08 $U \cdot kg^{-1} \cdot h^{-1}$ of insulin by continuous subcutaneous infusion. Although chest X-rays showed small granulomatous shadows in both lung fields due to prolonged administration of controlled mechanical ventilation, the blood gases were well controlled: pH 7.42, partial arterial pressure of CO_2 ($Paco_2$) 36 mmHg, and O_2 (Pao_2) 134 mmHg and base excess (BE) −0.1 at an inspired oxygen fraction (FIo_2) 0.35. At the age of 5 months he weighed 7.1 kg and was 72 cm tall. Tracheotomy was scheduled for prolonged controlled ventilation under general anesthesia.

No premedication was given. The infant was too small to monitor the level of neuromuscular blockade. Anesthesia was induced with diazepam 1 mg, fentanyl 30 μg, and vecuronium 1 mg was administered for immobilization. However, muscle relaxation was not sufficient and a total dose of 2.2 mg (0.3 $mg \cdot kg^{-1}$) vecuronium was necessary for complete paralysis. Anesthesia was maintained with fentanyl using air and oxygen. As fluid management, we administered 95 ml of Solita T1 (Shimizu pharmacy corporation, Japan) (Na 90, Cl 70, lactate 20 $mEq \cdot l^{-1}$ and glucose 26 $g \cdot l^{-1}$). He developed hyperkalemia (6.1 $mEq \cdot l^{-1}$) intraoperatively due to the suspension of insulin infusion and furosemide. The potassium level decreased

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to 5.2 mEq·l^{-1} following the induction of diuresis by furosemide 0.5 mg. The anesthetic time was 140 min, blood loss was 2 g, and urine volume was 38 ml. All cardiovascular, respiratory, and temperature measurements stayed within the normal ranges, and no metabolic acidosis occurred perioperatively.

Discussion

Mitochondrial myopathy is a group of disorders with a variable clinical picture and an underlying mitochondrial metabolic defect due to mutation of mitochondrial genes. Although mitochondrial myopathy had ever been classified as Kearns–Sayre syndrome (KSS), mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), and so on according to clinical symptoms, it has been classified into five categories according to deficiency of enzymes [2,3] (Table 1). Our patient was diagnosed with acute encephalomyopathic type in complex IV deficiency, which is characterized as remarkable brain atrophy, muscle weakness, and multisystem involvement. Such patients present several challenges to anesthesiologists.

D'Ambra et al. first referred to the anesthetic management of patients with mitochondrial cytopathy in 1979 [4]. Since then, several additional cases have been reported [5–13] (Table 2). Although these reports mention various types of mitochondrial cytopathies, metabolic disorder and myopathy are common anesthetic problem in all types of this disease.

Metabolic disorders such as hyperlactemia or hyperpyruvemia due to a greater oxygen demand than supply in peripheral tissue lead to metabolic acidosis [7,9,11]. To avoid metabolic acidosis, the anesthetic level, ventilation, heart rate and blood pressure (cardiac output), Sao_2, and hemoglobin level should be monitored and enough oxygen delivery should be maintained [8–11]. Go et al. reported intraoperative metabolic acidosis induced by hyperlactemia due to depression of lactate resolution in spite of good oxygen delivery [7]. Therefore, it might be better to avoid large amounts of lactated Ringer's infusion in cases with mitochondrial cytopathies, though no metabolic disorder was recognized in our case.

Myopathy is a second common anesthetic problem. Patients with mitochondrial cytopathy have an increased susceptibility to malignant hyperthermia (MH) [14]. One child with mitochondrial myopathy developed signs of MH after the induction of general anesthesia [5]. As the relationship between MH and this disorder has not been clarified, it is wise to select neuroleptanesthesia and nondepolarizing muscle relaxants to avoid MH [14].

In patients with mitochondrial myopathy, muscle relaxants should be used cautiously because of muscle weakness. Although D'Ambra et al. [4] reported that responses to depolarizing and nondepolarizing muscle relaxants were normal in cases of Kearns-Sayre syndrome, it is preferable to avoid them [8–10]. If these agents are required during surgery, a minimal dose of a nondepolarizing muscle relaxant should be administered under careful monitoring of neuromuscular blockade, especially in patients with severe muscle weakness, as seen in our case [6,7,10]. However, a large dose of vecuronium (0.3 mg·kg^{-1}) was ultimately required to induce muscle relaxation in the present case compared with the dose used for intubating a healthy man: 0.07–0.1 mg·kg^{-1} [15]. Since any drug that can influence the central nervous system can also influence the neuromuscular junctions, anticonvulsants given as preoperative medication might modify the neuromuscular blockade. Phenytoin produces resistance to neuromuscular blocking drugs by antagonizing acetylcholine at the prejunctional receptors [16]. Pancuronium and carbamazepine compete for the same site at the neuromuscular junction [17]. The numerous anticonvulsants administered to this patient might make him resistant to the competitive neuromuscular blockers. Since patients with mitochondrial cytopathies often receive anticonvulsants, the possibility of the development of resistance to neuromuscular blockade must be kept in mind.

Cardiomyopathy is another possible lethal complication of this disease [12,18]. Although no cardiac event occurred in the present case, the heart must be carefully monitored perioperatively, and temporary pacing might be necessary in the event of a sudden A-V block.

Table 1. Classification of mitochondrial cytopathy

Abnormality of mitochondrial transport of substances
Carnitine deficiency
Carnitine palmityl transferase (CPT) deficiency
Combined CPT and carnitine deficiency
Abnormality of mitochondrial utilization of substrates
Pyruvate dehydrogenase complex (PDHC) deficiency
Abnormality of TCA cycle
Fumarase deficiency
a-Ketoglutal acid dehydrogenase deficiency
Abnormality of electron transport
Complex I (NADH CoQ-reductase) deficiency
Complex II (succinate CoQ-reductase) deficiency
Complex III (CoQcytochrome *c* reductase) deficiency
Complex IV (cytochrome *c* oxidase) deficiency
Complex V (ATPase) deficiency
Combined Complex I–V deficiency
Abnormality of energy conservation and transduction
Luft's disease
Mitochondrial ATPase deficiency

TCA, tricarboxylic acid.

Table 2. Anesthetic management in ten cases of mitochondrial cytopathy

Author (year) [reference No.]	Age/Sex	Diagnosis	Major symptom	Operation	Anesthesia Muscle relaxant	Fluid with lactate	Perioperative complications
D'Ambra (1979) [4]	23 Y/F	KSS	Ptosis, limb weakness	Nephrostomy	GO-meperidine SCC, pancuronium	Not described	None
Ohtani (1985) [5]	2 Y/F	Unknown[a]	Lumbar lordosis, muscle weakness	Muscle biopsy	GOF SCC	Not described	Malignant hyperthermia
Nogata (1986) [6]	42 Y/F	KSS	Opthalmopegia, muscle atrophy	Mastectomy	NLA pancuronium	Not described	None
Go (1987) [7]	12 Y/M 15 Y 15 Y	MERRF	Mental retardation, myoclonus epilepsy	1) Appendectomy 2) Laparotomy 3) Laparotomy	GOF pancuronium GOE pancuronium GOE pancuronium	(+) (+) (+)	Hyperthermia (38.5°C) Metabolic acidosis Metabolic acidosis
Kameumi (1987) [8]	62 Y/M	KSS	Opthalmopegia, muscle atrophy	Tarsoplasty	GOF none	(+)	None
Shimizu (1988) [9]	6 Y/F	MELAS	Mental retardation, epilepsy	Muscle biopsy	GOF none	(+)	Metabolic acidosis
Burns (1989) [10]	6 weeks/F	Fumarase Deficiency	Jaundice Hypotonia	Liver biopsy	GOI none	(−)	Metabolic acidosis
Moritsune (1992) [11]	21 Y/F	CCOD	Lower diplegia, mental retardation	Phacoemulsification	GOE vecuronium	(−)	Metabolic acidosis
Klockgether-Radke (1993) [12]	1) 40 Y/F 2) 43 Y/M	KSS KSS	Retinitis pigmentosa Muscle weakness	Mastectomy Hernioplasty	NLA vecuronium NLA vecuronium	Not described Not described	Bradycardia Bradycardia
Breucking (1993) [13]	48 Y/F	Luft's disease	Fever, tachycardia, sweating	Repair of A-V fistula	NLA vecuronium	Not described	None
Maegawa (present study)	5 months/M	CCOD	Mental retardation, muscle weakness	Tracheotomy	NLA vecuronium	(+)	None

Y, year-old; M, male; F, female; KSS, Kearns-Sayre syndrome; MERRF, myoclonus epilepsy associated with ragged-red fibers; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes; CCOD, cytochrome *c* oxidase deficiency; NLA, neuroleptanesthesia; E, enflurane; F, halothane; I, isoflurane.

[a] Muscle biopsy disclosed ragged red myofibers and impaired oxidative phosphorylation in mitochondria.

Diabetes mellitus is commonly accompanied by mitochondrial cytopathy and is sometimes uncontrollable for insufficient insulin secretion as seen in our case [19]. Hypoglycemia induces lipolysis and hyperglycemia induces activation of phosphofructokinase leading to hyperlactemia due to increased glycolysis. Although blood sugar was maintained at a normal level in our case, hyperkalemia was observed, which might be a rebound reaction to the infusion of the insulin suspension. Control of blood sugar and electrolytes was essential for the perioperative management of this disease.

In conclusion, prevention of metabolic acidosis, control of blood sugar and electrolytes, monitoring for the possibility of MH, cardiac failure due to cardiomyopathy, and administration of adequate doses of muscle relaxants are the major considerations for anesthesia in patients with mitochondrial cytopathy.

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