Anesthetic management
of a patient with MELAS

Madam,
Mitochondrial diseases (MDs) have an incidence of 1:4000 live births. With advancing diagnostic and treatment facilities, increasing number of patients present for anesthesia for diagnostic procedures or palliative surgeries. MELAS is a subgroup of MDs characterized by mitochondrial encephalomyopathy, lactic acidosis, and stroke. These diseases have variable clinical presentation with multisystem involvement [Table 1]. Although clues to the disease may manifest in early years, most cases become clinically symptomatic after late childhood. Pediatric onset disease is more progressive with neurological, cardiac and liver dysfunction. These patients have increased sensitivity to most drugs used in anesthesia [Table 2]. However, to the best of our knowledge, there are no reports of any adverse events with ketamine and fentanyl in MD patients.

We report a 9-year-old girl, weighing 19 kg, with MELAS, and recurrent aspiration pneumonia due to bulbar involvement. She was on nasogastric tube (NGT) feeds and was planned for laparoscopic gastrostomy under general anesthesia. On examination, she was alert, conscious and dysarthric. Her respiratory rate was 30/min, oxygen saturation 93% on room air and 96% with oxygen supplementation. Bilateral coarse crepitations were present. Chest X-ray showed features suggestive of aspiration pneumonia.

In view of her pulmonary condition and increased vulnerability to anesthetic agents, an open procedure was settled on, after discussion with the surgeons, under a combination of sedation with fentanyl-ketamine and local field block. She was adequately fasted, while maintained on dextrose containing intravenous fluid to avoid increasing metabolic burden. The risk of potential aspiration was considered minimal as she was kept NPO adequately, in addition to the presence of NGT allowing for suctioning of gastric contents (if any). After establishing intravenous access and routine monitoring, ketamine 10 mg bolus (0.5 mg/kg) was given with which the child fell asleep. Subsequently, a field block was given with a mixture of 0.2% ropivacaine and 1% lignocaine. Fentanyl 5 mcg (0.25 mcg/kg) was given just before skin incision. With these minimal doses, the respiratory rate fell to 3/min. A pediatric open circuit was used to assess respiration and assist if necessary. The child did not have any response to surgical incision, neither did she require any further doses. The procedure was completed successfully at the end of which she was shifted to a high dependency unit for monitoring.

Though Markham et al. state that ketamine has been shown to inhibit oxidation in mitochondria in animal models, there is paucity in literature on its untoward effects in patients

### Table 1: Typical features of MELAS

| Areas of Involvement | Features |
|----------------------|----------|
| Clinical             | Neurologic: History of developmental delay, learning disabilities, attention deficit disorder, myopathy, exercise intolerance, hearing impairment, ataxia, seizures, stroke-like episodes (hallmark) |
|                      | Cardiac: Palpitations, dyspnea, cardiac conduction abnormalities hypertrophic/dilated cardiomyopathy |
|                      | Gastrointestinal: Pancreatitis, ischemic colitis, and intestinal obstruction |
|                      | Renal: Nephrotic syndrome |
|                      | Endocrine: Diabetes, hypo/hyperthyroidism |
| Biochemistry         | Elevated serum alanine and lactate levels in both blood and CSF, elevated serum creatine kinase |
| Radiology            | Cortical infarct lesions, calcifications in the basal ganglia, cerebral atrophy and calcifications in late stages |
| EEG                  | Multiple epileptiform activity with secondary generalization and poor sleep pattern, suggestive of epileptic encephalopathy |
| Histology            | Ragged red fibers (hallmark), mitochondrial proliferation and paracrystalline bodies on electron microscopy |

CSF = Cerebrospinal fluid, EEG = Electroencephalogram, MELAS = Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes
Letters to Editor

Table 2: Effects of anesthetics in MD

| Anesthetic agent         | Effects                                                                 | Comments                                      |
|--------------------------|-------------------------------------------------------------------------|-----------------------------------------------|
| Scoline                  | Possibility of myotonic crisis                                         | Contraindicated                               |
| Nondepolarizing muscle relaxants | Unpredictable effects with possibility of increased intensity and duration of paralysis | Should be used with caution                   |
| Anticholinesterases      | Possibility of myotonic crisis                                         | Contraindicated                               |
| Volatile anesthetics     | Potent inhibitors of complex I even on normal mitochondria in the levels used. Highly variable sensitivity implying lower MAC requirement, amplified vasodilatory effects and myocardial depression | Sevoflurane may be used especially when intravenous access not established preoperatively. Successful outcomes reported |
| Propofol                 | Inhibits complex I function, uncouples oxidative phosphorylation, and affects complex II, IV, and V to varying degrees as well as transport of long-chain fatty acids and β-oxidation | Contraindicated. However, single induction dose of propofol reported without any adverse outcome |
| Ketamine                 | Considered safe                                                         | No reported complication                      |
| Opioids                  | Mitochondrial depressant effects with remifentanil <fentanyl <morphine | Neuraxial administration not totally contraindicated due to the miniscule doses employed |
| Local anesthetics        | All inhibit acylcarnitine transferase and complex I. Bupivacaine reported to affect bio-energetics due to sarcomer disruption and alteration of mitochondrial structure in in vitro studies in a concentration dependent manner | Used cautiously in the least amount and concentration required. Agents preferred lidocaine >ropivacaine >bupivacaine and etidocaine. In muscle biopsy patients, LA preferably be given after the biopsy specimen isolation, due to possibility of interference with diagnostic value of tissue specimen |

MAC = Mitochondrial apoptosis-induced channel, MD = Mitochondrial disease

with MD. In our patient, we chose ketamine for its analgesic effects, bronchodilatory properties and ability to maintain airway reflexes as well as spontaneous respiration. There are no adverse reports with the use of fentanyl either, except at higher doses. However, we found an increased sensitivity to even a very minimal dose of both drugs, as manifested by a significant drop in respiratory rate. Close monitoring of the patient helped avert an untoward event. However, we wish to highlight that even these seemingly safe agents should be titrated to patient needs very cautiously, rather than a standard weight-based dosing.

Two large cases series reported suggest the possibility of safe anesthesia with appropriate preoperative assessment and monitoring. Nonetheless, it is also important to be aware of reports of delayed worsening of respiratory function with or without neurologic degeneration in mildly affected patients whose anesthetic course had been notably uneventful. Choosing between local, regional, or general anesthesia, depends on the patient (tolerability of an awake procedure, degree of neuropathy/myopathy, spinal cord involvement) as well as nature of surgery (degree of muscle relaxation required, postoperative analgesia). Even in the absence of negative literature, it should be considered that the requirement of any agent may be lower than in normal individuals, and titration of drugs to effect is more appropriate than a weight-based nomogram. It will be prudent to remember that a successful use of one agent in a patient does not mean that the agent is safe to use in all, but may simply be due to a biased reporting.

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