

Anaesthesia recommendations for patients suffering from

Mitochondrial Cytopathy, Mitochondrial Myopathy, Mitochondrial Encephalomyopathy

Disease name: Mitochondrial Cytopathy, Mitochondrial Myopathy, Mitochondrial Encephalomyopathy

ICD 10: G731.81

Synonyms: Mitochondrial diseases with typical combinations of clinical symptoms: Kearns-Sayre syndrom, progressive external ophthalmoplegia, Pearson syndrome, myoclonic epilepsy with ragged red fibers (MERFF), mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), neuropathy with ataxia and retinitis pigmentosa, maternally inherited Leigh syndrome, Leber's hereditary optic neuropathy, Leigh disease, POLG1 associated disorders, mtDNA depletion syndromes.

Although the mitochondria host several metabolic pathways including the tricarboxylic acid cycle, urea cycle, β -fatty acid oxidation, their primary function involves generation of adenosine triphosphate via aerobic respiration. Mitochondrial disorders are genetically and phenotypically a heterogeneous group with an estimated incidence of one in 4000. Genetically, the 13 protein subunits of the respiratory chain complexes I, III, IV and V encoded by mitochondrial DNA, the 22 tRNAs and the two rRNAs (mitochondrial encoded mitochondriopathy) or one of the approximately 1000 nuclear encoded proteins, which are important to mitochondrial structure and function.

Medicine in progress



Perhaps new knowledge

Every patient is unique

Perhaps the diagnostic is wrong



Find more information on the disease, its centres of reference and patient organisations on Orphanet: www.orpha.net

Disease summary

Mitochondrial encoded mitochondriopathies are inherited maternally, while nuclear encoded types are inherited with classical Mendelian inheritance (X-linked recessive, autosomal recessive or autosomal dominant). The most severe inherited mitochondrial disorders, many of them lethal, become clinically apparent during infancy. Later appearance in early adulthood has been described. In mitochondrial DNA encoded disorders, the normal and mutant mitochondrial DNA coexist. "Heteroplasmy" refers to the random differences in the ratio of mutant to normal mitochondrial DNA present in the target tissue during embryogenesis, which explains partially the marked variability in clinical manifestations.

Usually mitochondriopathies are multi-systemic diseases, although single organ manifestations or specific symptoms may prevail. Organs with high energy turnover like the central nervous system, muscle, heart, liver and kidney are typically affected. Impaired renal bioenergetics produce tubular acidosis, and skeletal muscle abnormalities, which present largely as dystonia. Dysphagia, pseudo-obstruction and constipation suggest gastrointestinal involvement. Vision and hearing may be reduced. Endocrine organ involvement resulting in diabetes mellitus, hypoparathyroidism, hypothyroidism and gonadal failure has also been described. Seizures and ataxia are associated with myoclonic epilepsy with ragged-red fibers (MERRF) and encephalopathy is a symptom of Leigh syndrome. Necrotizing lesions within the brain, particularly in the midbrain and the brainstem are typical pathological signs of Leigh syndrome. Clinically this syndrome, which typically begins within the first year of life, is characterized by dysphagia, epileptic seizures, muscle hypotonia, dystonia, ataxia, ophthalmoparesis, cardiomyopathy and finally respiratory failure. Dementia and stroke-like symptoms are major features of the mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS). Furthermore, the peripheral nervous system is affected, causing axonal sensory neuropathy. Cardiac involvement includes hypertrophic cardiomyopathy (seen in MELAS and Leigh syndrome) or heart block, dilated cardiomyopathy and pre-excitation syndrome.

Initial symptoms of adult-onset forms are typically progressive postural muscle weakness/exercise intolerance, sensory-neural hearing loss, ptosis, ophthalmoparesis, failing colour or night vision, and worsening ataxia. Hepatic insufficiency and renal involvement are common components of Toni-Debre-Fanconi syndrome (primarily in children).

Typical surgery

Pacemaker implantation, cataract extraction, insertion of a cochlear implant, muscle and skin biopsies, orthopaedic surgery, abdominal surgery.

Type of anaesthesia

Anaesthetics management of patients with mitochondrial disorders is challenging. Although anecdotally patients have been exposed to many different anaesthetic regimens without adverse consequences, it remains unclear which kind of anaesthesia is preferable. Hence, the choice of anaesthesia depends on the type of procedure, co-morbidities and other factors.

Based on available data there is no association with malignant hyperthermia, which is based on an altered cellular calcium metabolism. Nevertheless, anaesthetic medications might trigger metabolic changes that resemble MH-like episodes. However, such episodes are rare and in most cases unrelated to anaesthesia.

Spinal anaesthesia using bupivacaine and tetracaine has been used safely without residual neuromuscular abnormalities. Epidural analgesia may prevent life-threatening lactic acidosis during labour. However, due to a potential decrease in mitochondrial ATP synthesis and reduction of enzyme activities of the respiratory chain, local anaesthetics should be used cautiously. Finally, regional anaesthesia is not contraindicated. Here it is of major importance to discuss specific risks and advantages with the patient and the involved medical professionals.

General anaesthesia using intravenous, volatile anaesthetics as well as non-depolarizing muscle relaxants were reported to be safe. Nevertheless, most anaesthetic drugs have depressant effects on mitochondrial function. Long-term anaesthesia (>48 hours) and doses exceeding 4mg/kg/h [66 µg/kg/min] with propofol heightens the risk of mitochondrial dysfunction and monitoring of lactate levels is highly recommended. In susceptible individuals shorter duration of anaesthesia may cause dysfunction. Benzodiazepines were reported to be safe in single case reports. Many patients take benzodiazepines to treat and prevent epileptic seizures for decades without any issue. However, due to their potential negative impact on liver metabolism benzodiazepines should be dosed sparsely. Increased sensitivity to sedatives, hypnotics and opioids has been described. For minor surgery, ketamine is a good alternative.

No reports using (analgo-)sedation are available. In patients with advanced stages of disease (cardiopulmonary involvement, muscle weakness, ketosis), (analgo-)sedation should only be performed after careful evaluation of the individual risk, especially for respiratory failure and aspiration.

Necessary additional diagnostic procedures (preoperative)

Laboratory investigations of glucose and lactate levels, electrolytes, liver enzymes and creatine kinase are specifically performed perioperatively in mitochondriopathy. Biotinidase levels are decreased during infection and may require biotin substitution.

Assessment of the degree of musculoskeletal and neurological impairment including respiratory and swallowing functions should be made.

Measurement of forearm muscle oxygenation responses during and following arterial occlusion provides an easily performed screening test that detects impaired oxygen use. During and following arterial occlusion, which can be performed by a tourniquet, deoxy [Hb+Mb] and oxy [Hb+Mb] are registered. Patients with mitochondrial myopathy display altered oxygenation responses during and following arterial occlusion which might help to evaluate the patients individual impairment.

Lung function evaluation (spirometry, MIPs, MEPs) and blood gas analysis help to evaluate pulmonary function.

A 12-lead electrocardiograph should be performed to exclude pre-excitation syndromes and conduction defects (especially Wolff Parkinson White).

Liver function and hepatic mitochondrial redox potentials can be measured by arterial and venous ketone body ratios, calculated as the ratio of acetoacetate to 3-hydroxybutyrate. Metabolic dysfunction due to liver involvement may result in altered glucose, lactate and protein metabolism (such as diabetes).

Pre-operative baseline determination may help to assess the severity of increased values postoperatively.

Particular preparation for airway management

No data are currently available reporting airway difficulties in patients with mitochondrial disorder. Antacid prophylaxis is recommended.

Particular preparation for transfusion or administration of blood products

The vast majority of patients do not have bleeding issues. However, liver involvement might alter INR. Also thrombocytopenia and thrombocytopathia were described in rare cases in patients with mitochondrial disorders.

Although relatively contraindicated, several mitochondriopathic patients take valproic acid which might interfere with blood coagulation increasing bleeding time.

Particular preparation for anticoagulation

There is no evidence to support the need for routine anticoagulation. Immobilisation due to muscular weakness may require prophylaxis for thrombosis.

Particular precautions for positioning, transport or mobilisation

Patients with mitochondrial disorders often suffer from general muscle weakness that restricts cardiopulmonary capacity. Due to impaired energy supply, peripheral nerves are at risk of positional damage.

Probable interaction between anaesthetic agents and patient's long term medication

No causal treatment of mitochondrial disorders is currently available.

Corticosteroids may increase muscle weakness (steroid myopathy) - perhaps related to steroid-induced ROS generation and apoptosis.

Valproate acid should be avoided as it blocks OXPHOS and histone-deacetylase; phenytoin inhibits mitochondrial ATPase. Although relatively contraindicated several patients take valproic acid to prevent epileptic seizures. However in POLG1 patients valproic acid is absolutely contraindicated.

Medications which induce bradycardia such as amiodarone and beta-blockers must be used with extreme caution. Moreover, carvedilol was reported to inhibit (respiratory chain) complex I and amiodarone and tetracyclines to inhibit β -oxidation.

Respiratory chain complex 1 is also inhibited by biguanides, thiazolidinediones, fibrates, statins, haloperidol, chlorpromazine, quetiapine, risperidone and chloramphenicol.

Anaesthesiologic procedure

Due to prolonged gastric emptying time and reduced bulbar reflexes, a modified rapid sequence induction without succinylcholine is recommended. Administration of H₂-antagonists or proton pump inhibitors prior to anesthesia should be considered in no emergency cases.

Because of increased sensitivity hypnotics and opioids should be dosed sparsely. Propofol was used safely in a large number of patients. However, prolonged application (>48h) of propofol should be avoided. Volatile anaesthetics have been used. Sevoflurane was reported to be safe in a patient with myoclonic epilepsy and ragged red fibers. In a patient with Leigh syndrome and preexisting respiratory abnormalities, anaesthesia induction with propofol and maintenance with desflurane resulted in unsuccessful weaning and death. A combination of the preexisting oxidative phosphorylation defect and the postoperative raised inflammatory mediators which are inhibitors of the mitochondrial electron transport chain was suggested to play a major role in the fatal outcome of this case.

Depolarizing muscle relaxants are strictly contraindicated because of the risk of hyperkalemic cardiac arrest. Atracurium and vecuronium at low doses with close train of four monitoring are favourable. Some case reports suggest affected muscle as hypersensitive to mivacurium.

All mitochondrial myopathies require stringent peri-operative glucose adjustment to prevent hypo- and hyperglycaemia, the latter leading to lactic acidosis. Electrolyte balance should be ensured.

Excessive pre-operative fasting, metabolic stress and pain should be minimized.

Acute lactic acidaemia can be reduced by intravenous administration of dichloroacetate which stimulates the pyruvate dehydrogenase to convert lactate to pyruvate. However, due to its side effect to cause peripheral neuropathy it is not recommend to treat chronic lactic acidaemia.

Particular or additional monitoring

Tight control of body temperature is highly recommended. Autonomic regulation including temperature is often impaired in mitochondrial disease. Postoperative shivering increases energy requirements. All fluids should be warmed to body temperature.

Monitoring of neuromuscular blockade is highly recommended if any muscle relaxant is used. Evaluation of baseline values before muscle relaxant application is important.

Consideration should be given to attaching an external pacer/defibrillator to patients due a heightened risk of cardiac conduction abnormalities. External defibrillator/pacemaker should be immediately available.

Tight monitoring of lactate values is highly recommended. Evaluation of creatine kinase levels should be conducted frequently.

Depending on the stage of disease and the type of surgery, advanced monitoring such as arterial cannulation, stroke volume variation and esophageal doppler monitoring or a central venous line is recommended. In cases of cardiomyopathy the consultation of a cardiologist is recommended. Monitoring like TEE or PA catheters should be considered in these patients.

Possible complications

Patients with mitochondrial disorders have a high risk of respiratory failure and aspiration due to muscle weakness.

Succinylcholine should be avoided mainly due to a risk of hyperkalemia.

Duration of action is prolonged with non-depolarizing muscle relaxants.

Patients with mitochondrial disorders are highly sensitive to hypnotics, opioids and sedative drugs. In spontaneously breathing patients, cautious use of opioids is especially recommended since further impairment of regulation of breathing may lead to a respiratory acidosis and increase underlying metabolic acidosis.

Patients should be monitored postoperatively in an intensive care unit. Discharge may be delayed.

Postoperative care

The degree of postoperative monitoring depends on the surgical procedure and the preoperative condition.

Postoperative admission to intensive care unit should be preplanned. 24 hour monitoring is recommended.

Prolonged immobilization should be avoided.

If postoperative ventilation is necessary aggressive weaning should be instituted and non-invasive ventilation preferred. Vigilant monitoring of respiratory function is essential.

Arterial blood gas analysis should be closely monitored and adjusted accordingly.

Low hepatic mitochondrial activity, phagocytosis by Kupffer cells and the reticulo-endothelial system activity decline, postoperative infection is likely.

Information about emergency-like situations / Differential diagnostics

caused by the illness to give a tool to distinguish between a side effect of the anaesthetic procedure and a manifestation of the disease

A critical feature in all circumstances is sufficient oxygenation since hypoxia might lead to worsening of pre-existing metabolic acidosis.

Ambulatory anaesthesia

Ambulatory anaesthesia should be avoided if necessary extended postoperative surveillance is not possible.

Obstetrical anaesthesia

Regional anaesthesia might reduce oxygen consumption during labour by 25%. Epidural anaesthesia was reported to decrease serum lactate concentration during cesarean section. However, elective cesarean section may be indicated for patients experiencing dyspnea with minor exertion and decompensated lactic acidosis.

Literature and internet links

1. Shipton EA, Prosser DO. Mitochondrial myopathies and anaesthesia. *Eur J Anaesthesiol* 2004; 21:173-178
2. Klingler W, Lehmann-Horn F, Jurkat-Rott K. Complications of anaesthesia in neuromuscular disorder. *Neuromuscular Disorders* 2005; 15: 195-206
3. Niezgoda J, Morgan PG. Anesthetic considerations in patients with mitochondrial defects. *Pediatric Anaesthesia* 2013; 23:785-793
4. Finsterer J, Segall L. Drugs interfering with mitochondrial disorder. *Drug and Chemical Toxicology* 2010; 33(2):138-151
5. Muravchick S. Clinical implications of mitochondrial disease. *Advanced Drug Delivery Reviews* 2008; 60:1553-1560
6. Sasano N, Fujita Y, So M, Sobue K, et al. Anesthetic management of a patient with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) during laparotomy. *J Anesth* 2007; 21:72-75
7. Maurtua M, Torres A, Ibarra V, et al. Anesthetic management of an obstetric patient with MELAS syndrome: case report and literature review. *International Journal of Obstetric Anesthesia* 2009; 17:370-373
8. Muravchick S, Levy RJ. Clinical implications of mitochondrial dysfunction. *Anesthesiology* 2006; 105:819-37
9. Foolitt EJ, Sinha MD, Raiman JAJ, et al. Mitochondrial disorders and general anaesthesia: a case series and review. *British Journal of Anaesthesia* 2008
10. Driessen JJ. Neuromuscular and mitochondrial disorders: what is relevant to the anaesthesiologist? *Curr Opin Anaesth* 2008; 21:350-355
11. Gurrieri C, Kivela JE, Bojanic K, et al. Anesthetic considerations in mitochondrial encephalomyopathy, lactic acidosis and stroke like episodes syndrome: a case series. *Can J Anesth* 2011; 58:751-763
12. Nielsen TH, Bindslev TT, Pedersen SM, et al. Cerebral energy metabolism during induced mitochondrial dysfunction. *Acta Anaesthesiol Scand* 2013; 57:229-235
13. Kotzailias N, Finsterer J, Zellner M, Marsik C, Dukic T, Jilma B. Platelet function in mitochondrialopathy with stroke and stroke like episodes. *Thromb Haemost* 2004; 91:544-52
14. Abdallah C. Considerations in perioperative assessment of valproic acid coagulopathy. *J Anaesthesiol Clin Pharmacol* 2014; 10:7-9
15. Ibanez C, Fernandez-Gonzalez H. Emergency anesthesia in a woman with mitochondrial neurogastrointestinal encephalopathy. *Rev Esp Anesthesiol Reanim* 2011; 58(9):585-7
16. Boone J, Celie B, Dumortier J, et al. Forearm muscle oxygenation responses during and following arterial occlusion in patients with mitochondrial myopathy. *Respir Physiol Neurobiol* 2014; 190:70-5
17. Grattan-Smith PJ, Shield LK, Collins KJ. Acute respiratory failure precipitated by general anesthesia in Leigh's syndrome. *J Child Neurol* 1990; 5:137-41
18. Casta A, Quackenbush EJ, Houck C, et al. Perioperative white matter degeneration and death in a patient with a defect in mitochondrial oxidative phosphorylation. *Anesthesiology* 1997; 87:420-5

Last date of modification: March 2015

These guidelines have been prepared by:

Author

Kerstin Hoppe, Anaesthesiologist, University of Frankfurt, Germany
hoppekerstinmed@t-online.de

Co-Authors

Rainer Plunien, Anaesthesiologist, University of Ulm, Germany

F. Lehmann-Horn, Division of Neurophysiology, University of Ulm, Germany

Karin Jurkat-Rott, Division of Neurophysiology, University of Ulm, Germany

Michael Gösele, Department of Neuroanaesthesiology, University Hospital Ulm-Günzburg, Germany

Werner Klingler, Department of Neuroanaesthesiology, University Hospital Ulm-Günzburg, Germany

Peer Revision 1

Elizabeth Frost, Anaesthesiologist, Mount Sinai Medical Center, New York, USA
elzfrost@aol.com

Peer Revision 2

Mark Tarnopolsky, Division of Neurology, Department Pediatrics and Medicine, McMaster University Medical Center, Ontario, Canada
tarnopol@mcmaster.ca
