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Larsen syndrome

Methylmalonic acidemia (or aciduria)

orphanaesthesia

a project of the German Society
of Anaesthesiology and Intensive Care Medicine

SUPPLEMENT NR. 7 | 2022

OrphanAnesthesia –

ein krankheitsübergreifendes Projekt des Wissenschaftlichen Arbeitskreises Kinderanästhesie der Deutschen Gesellschaft für Anästhesiologie und Intensivmedizin e.V.

Ziel des Projektes ist die Veröffentlichung von Handlungsempfehlungen zur anästhesiologischen Betreuung von Patienten mit seltenen Erkrankungen. Damit will Orphan Anesthesia einen wichtigen Beitrag zur Erhöhung der Patientensicherheit leisten.

Patienten mit seltenen Erkrankungen benötigen für verschiedene diagnostische oder therapeutische Prozeduren eine anästhesiologische Betreuung, die mit einem erhöhten Risiko für anästhesieassoziierte Komplikationen einhergehen. Weil diese Erkrankungen selten auftreten, können Anästhesisten damit keine Erfahrungen gesammelt haben, so dass für die Planung der Narkose die Einholung weiterer Information unerlässlich ist. Durch vorhandene spezifische Informationen kann die Inzidenz von mit der Narkose assoziierten Komplikationen gesenkt werden. Zur Verfügung stehendes Wissen schafft Sicherheit im Prozess der Patientenversorgung.

Die Handlungsempfehlungen von OrphanAnesthesia sind standardisiert und durchlaufen nach ihrer Erstellung einen Peer-Review-Prozess, an dem ein Anästhesist sowie ein weiterer Krankheitsexperte (z.B. Pädiater oder Neurologe) beteiligt sind. Das Projekt ist international ausgerichtet, so dass die Handlungsempfehlungen grundsätzlich in englischer Sprache veröffentlicht werden.

Ab Heft 5/2014 werden im monatlichen Rhythmus je zwei Handlungsempfehlungen als Supplement der A&I unter www.ai-online.info veröffentlicht. Als Bestandteil der A&I sind die Handlungsempfehlungen damit auch zitierfähig. Sonderdrucke können gegen Entgelt bestellt werden.

Bisher in A&I publizierte Handlungsempfehlungen finden Sie unter:

www.ai-online.info/Orphsuppl
www.orphananesthesia.eu

OrphanAnesthesia –

a project of the Scientific Working Group of Paediatric Anaesthesia of the German Society of Anaesthesiology and Intensive Care Medicine

The target of OrphanAnesthesia is the publication of anaesthesia recommendations for patients suffering from rare diseases in order to improve patients' safety. When it comes to the management of patients with rare diseases, there are only sparse evidence-based facts and even far less knowledge in the anaesthetic outcome. OrphanAnesthesia would like to merge this knowledge based on scientific publications and proven experience of specialists making it available for physicians worldwide free of charge.

All OrphanAnesthesia recommendations are standardized and need to pass a peer review process. They are being reviewed by at least one anaesthesiologist and another disease expert (e.g. paediatrician or neurologist) involved in the treatment of this group of patients.

The project OrphanAnesthesia is internationally oriented. Thus all recommendations will be published in English.

Starting with issue 5/2014, we'll publish the OrphanAnesthesia recommenations as a monthly supplement of A&I (Anästhesiologie & Intensivmedizin). Thus they can be accessed and downloaded via www.ai-online.info. As being part of the journal, the recommendations will be quotable. Reprints can be ordered for payment.

Find a survey of the recommendations published until now on:

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orphananesthesia

Anaesthesia recommendations for

Methylmalonic acidemia (or aciduria)

Disease name: Methylmalonic acidemia (or aciduria)

ICD 10: E71.1

Synonyms: Methylmalonic aciduria, MMA, isolated methylmalonic acidemia

Disease summary: Methylmalonic acidemia (MMA) is a group of rare (approx. 1:50,000) autosomal recessive disorders of amino acid metabolism, involving defects in the conversion of methylmalonyl-CoA to succinyl-CoA (which would normally enter the Krebs cycle). The defect is genetically heterogeneous, and can be due to the lack of the enzyme methylmalonyl-CoA mutase (mut^0), a partial reduction in its activity (mut^-), or defects in cobalamin metabolism (vit B_{12} is a cofactor required in the conversion of methylmalonyl-CoA to succinyl-CoA). These defects result in the accumulation of methylmalonic acid.

Clinical presentation varies and depends on the genetic diagnosis. The most severe form is mut^0, which usually presents in the neonatal period, while other forms may present later in infancy and childhood when triggers of increased protein catabolism (infection, dehydration, trauma, surgery, stress) cause metabolic decompensation. The presentation may be non-specific, such as vomiting, lethargy and tachypnoea. Neurological manifestations include encephalopathy, seizures, hypotonia and stroke. Gastrointestinal complaints include recurrent vomiting, failure to thrive, and pancreatitis. If the acute crisis is untreated it may progress to coma and death.

Biochemical hallmarks of an acute metabolic decompensation are metabolic acidosis, an increased anion gap (caused by lactate, ketones and organic acids), elevated lactate and ketones ± hyperammonaemia.

Long-term complications include failure to thrive, chronic kidney disease or renal failure, pancreatitis, pancytopaenia, osteopaenia and intellectual disability. Cardiac involvement is rare, but includes dilated cardiomyopathy and prolonged QTc interval. Several patients have been reported with metabolic stroke and optic atrophy.

Long-term management is aimed at preventing metabolic decompensation. Patients are placed on a protein-restricted diet, given carnitine supplements (to promote the increased excretion of toxic metabolites) and hydroxycobalamin if cobalamin-responsive. Administration of metronidazole is aimed at reducing the burden of acid-producing bacteria in the gut. Ammonia scavenging drugs including carglumic acid, a synthetic analogue of N-acetyl glutamate, can be used to manage hyperammonaemia.

Kidney, liver, or a combined kidney-liver transplantation is increasingly being performed in patients with MMA. While transplanting either or both organs does not “cure” the disease, the aim is to supply a certain amount of the missing enzyme. Methylmalonyl–CoA mutase is mainly expressed in the liver, but renal transplantation will partially replace some mutase

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activity. Transplanting kidneys in MMA patients with renal failure both restores the impaired renal function and improves the metabolic enzyme defect, and thus reduces the number of episodes of metabolic decompensation and hospitalisation, and allows liberalisation of the diet. It does not prevent neurological complications. Liver transplantation is considered as a treatment option particularly in patients with frequent decompensations. Combined liver-kidney transplantation is a potential treatment option but it is associated with more post-operative complications than single organ transplantation.

Medicine is in progress

Perhaps new knowledge

Every patient is unique

Perhaps the diagnosis is wrong

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

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Typical surgery

- Insertion of long-term intravenous access lines or ports (for treatment, fluids, blood sampling or TPN).
- Gastrostomy or GJ tube insertion
- Imaging studies, including CT and MRI.
- Skin biopsy (usually done under local anaesthesia).
- Examination under anaesthesia (e.g., eyes) or brainstem auditory evoked responses (for hearing loss).
- Placement of haemodialysis catheters.
- Transplantation (kidney, liver or both).

Type of anaesthesia

General or loco-regional anaesthetic techniques may be used where appropriate.

Necessary additional pre-operative testing (beside standard care)

Blood tests include:

- Blood gas, lactate and ammonia (metabolic acidosis/hyperammonaemia is a sign of decompensated disease, and should prompt a review and discussion about the timing of elective surgery)
- Glucose and ketones reviewing anabolic state
- Full blood count - looking for chronic anaemia, neutropaenia, thrombocytopaenia
- Urea and electrolytes – chronic renal failure occurs in up to 50 % of cases and is most reliably assessed by the glomerular filtration rate. Hyperkalaemia has been associated with ventricular tachycardia and cardiac arrest after induction of anaesthesia in a child with MMA
- Amylase and lipase (particularly in patients with a history of previous acute or acute-on-chronic pancreatitis).

Cardiac evaluation: While cardiac involvement is considered to be rare, prolonged QTc and cardiomyopathy have been described. A baseline ECG and echocardiogram would be recommended (children may be asymptomatic if they perform very limited exercise).

Careful assessment and consultation with the patient's specialist is advised to determine metabolic stability and timing of surgery. The patient's metabolic status should be optimised prior to elective surgery.

Particular preparation for airway management

There are no specific airway complications described with MMA per se.

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Particular preparation for transfusion or administration of blood products

Patients with MMA may have a chronic anaemia or be pancytopaenic as a result of acute or chronic bone marrow suppression. This may or may not require transfusion, depending on the surgery being performed. There are no specific requirements described for transfusion of blood products.

Particular preparation for anticoagulation

No particular concerns around anticoagulation are described. The disease is not typically associated with thrombosis or the need for anticoagulation.

Particular precautions for positioning, transportation and mobilisation

Patients may be osteopaenic and at risk of fractures. They are also at risk of poor wound healing. Careful positioning is required.

Interactions of chronic disease and anaesthesia medications

Patients may be on anticonvulsants that may alter the metabolism of some anaesthetic drugs. Patients with movement disorders may be on L-dopa, clonazepam, or baclofen.

Anaesthetic procedure

Pre-operatively, the aim is to avoid prolonged fasting as it may cause protein catabolism and a metabolic crisis. Patients should be fasted as per standard guidelines, whereas prolonged fasting and dehydration should be avoided. The individual day-to-day fasting tolerance of the patient can be used as a baseline. Encourage the intake of clear, glucose polymer-containing fluids until two hours pre-operatively, or provide intravenous 10 % glucose in 0.45 % or 0.9 % saline, as follows:

- 8–10 mg/kg/min for neonates and infants
- 6–7 mg/kg/min for children
- 5–6 mg/kg/min for adolescents
- 4–5 mg/kg/min for adults.

It is recommended that this infusion shall be continued throughout the surgical procedure and post-operatively until feeds are re-established. TPN should be continued if the patient is TPN-dependent.

All chronic medication should be continued in the peri-operative period.

If the child is unwell or in the setting of metabolic decompensation (metabolic acidosis, elevated lactate and hyperammonaemia revealed on pre-operative blood tests), elective surgery should not be performed. In the setting of emergency surgery, pre-operative and peri-operative haemodialysis should be considered.

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Intraoperatively:

- Induction can be inhalational or intravenous.
- Some children may be overweight, making intravenous access difficult.
- There is no contraindication to the use of the volatile agents.
- While it is unlikely to be a problem if used for the induction of anaesthesia, avoid nitrous oxide for maintenance, especially in patients with cobalamin metabolism defects, as it inhibits vitamin B_{12}-dependent enzymes.
- While propofol was traditionally thought to be contraindicated for patients with MMA, it has recently been shown to be safe for both the induction and maintenance of anaesthesia or sedation in the setting of metabolically stable patients. For major surgery (such as transplantation) or in unwell children, it would seem prudent to avoid propofol for the maintenance of anaesthesia due to its mitochondrial effects.
- Dehydration and hypotension can trigger a metabolic crisis. Patients should be well hydrated with dextrose in saline as above. Despite a theoretical concern over the use of lactate-containing fluids, a recent study has not shown an association between the use of Ringer's lactate and metabolic decompensation.
- The use of catecholamines may cause catabolism leading to metabolic decompensation. Catecholamine use should be avoided where possible and all parameters closely monitored if catecholamines are required.
- Sufficient depth of anaesthesia and analgesia must be maintained to avoid surgical stress.
- Consider using drugs to decrease ammonia with continuous infusion intraoperatively.
- Monitor blood gases, lactate, electrolytes, glucose and ammonia during longer procedures.
- Manage hyperglycaemic patients with an insulin infusion. Be aware that they may be very sensitive to insulin as their pancreases function normally, and hypoglycaemia is a risk. Consider starting insulin at a low dose, e.g., 0.02 IU/kg/hr and titrate to effect.
- Avoid blood in the gastrointestinal tract that could act as a protein load and trigger decompensation. Consider placing a throat pack or gastric tube where appropriate, e.g., dental work, tonsillectomy.
- Avoid the use of steroids due to their catabolic effects and risk of triggering acute decompensation (there is no evidence as to whether a single dose used to prevent post-operative nausea and vomiting is safe or not, so it would seem prudent to avoid).
- Avoid nephrotoxic drugs due to their potential to precipitate or aggravate renal disease.
- Patients may be neutropaenic increasing the risk of sepsis and line sepsis. Observe local infection control practices and antibiotic guidelines.
- Prolonged QTc interval is a rare complication. Caution should be exercised with using drugs that prolong the QT interval.
- Anti-emetics: it is recommended that metoclopramide is avoided. Use ondansetron.
- Paracetamol, opiates and loco-regional anaesthetic techniques can be used for analgesia. Avoid non-steroidal anti-inflammatory drugs.
- The use of muscle relaxants is not contraindicated. Monitoring of their effects and of their reversal would seem prudent in hypotonic children.

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Particular or additional monitoring

Regular measurement of glucose, arterial blood gases, lactate, ammonia and potassium is recommended.

Possible complications

Dehydration, hypotension, hypoxia, the stress of surgery and anaesthesia, and the presence of intercurrent illness and infection can all trigger a metabolic crisis, leading to metabolic acidosis, hyperlactataemia and/or hyperammonaemia. Hyperkalaemia secondary to metabolic acidosis has been described as causing intraoperative ventricular tachycardia and cardiac arrest.

Post-operative care

Patients should be closely monitored after anaesthesia for signs of clinical deterioration and should be managed in high-dependency settings where appropriate.

Intravenous fluids should be continued until the child tolerates enteral feeding. Feeding can be commenced as is appropriate for the surgical procedure. Patients should not be without protein >48 hours; if enteral intake is not possible early post-operatively, TPN should be considered. The child should only be discharged after full recovery, once tolerating its usual diet and medication, and with normal metabolic results. The patient's metabolic team should guide dietary management and discharge.

Disease-related acute problems and effect on anaesthesia and recovery

Differential diagnoses for the acute metabolic crisis in MMA include sepsis, respiratory distress and diabetic ketoacidosis. MMA can also present with seizures or a reduced level of consciousness. Any delay in recovery from anaesthesia should prompt checking blood gases, glucose, electrolytes and ammonia.

Management of the acute crisis includes rehydration, providing glucose as a metabolic substrate (as above) while avoiding hyperglycaemia, and correcting any electrolyte abnormalities and acid-base disturbances. Consider dialysis for persistent acidosis or hyperammonaemia.

Ambulatory anaesthesia

Patients with MMA would not typically be considered for day-case anaesthesia. They should not be discharged home until they are fully recovered and have normal metabolic results. Discussion should be held with the metabolic team before considering ambulatory anaesthesia.

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Obstetrical anaesthesia

The safe use of epidural anaesthesia for labour has been described. No anaesthetic complications are described during anaesthesia for caesarean sections.

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