orphanaesthesia

Anaesthesia recommendations for

Glutaric acidaemia type 1

Disease name: Glutaric acidaemia type 1

ICD 10: E72.3

Synonyms: Disorders of lysine and hydroxylysine metabolism

Disease summary: Glutaric acidaemia type 1 (GA1) is a rare hereditary metabolic disorder with an autosomal recessive mode of inheritance. GA1 has an estimated overall prevalence of 1 in 100,000 newborns and is caused by a deficiency of glutaryl-CoA dehydrogenase, a mitochondrial enzyme involved in the metabolism of lysine, hydroxylysine and tryptophan. Untreated, approximately 90% of the patients will develop a neurological disease during a finite period of brain development (age 3-36 months) following an acute encephalopathic crisis often precipitated by gastroenteritis, intercurrent febrile illness, immunisation or surgical intervention. GA1 can also develop insidiously without clinically apparent crisis in 10 to 20% of the patients.

Presenting symptoms include macrocephaly at birth or shortly thereafter, psychomotor delay, dystonia and, later, spastic quadriparesis. Patients seem to have relatively normal cognition, respond to commands, but have trouble talking or performing tasks because of poor muscle coordination and severe spasticity. Also, mild cases causing only slight neurological complaints and/or fatigue have been described.

Brain imaging performed shortly after birth usually shows frontoparietal atrophy with widening of Sylvian fissures and arachnoid cysts. The brain is more vulnerable to head trauma which can lead to acute subdural or retinal haemorrhage.

The cerebral damage seen in GA1 is caused by the direct effect of glutaric acid or a related metabolite. Glutaric acid, 3-hydroxyglutaric acid, and glutaconic acid accumulate in the brain and lead to neuronal damage, lymphocyte infiltration, elevated concentrations of inflammatory cytokines and nitric oxide, glial proliferation, atrophy of striatal neurons and neurologic dysfunction.

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

Typical surgery

Neurosurgery (cerebral spinal fluid shunting procedures for hydrocephalus and subdural fluid collections); muscle biopsy, general surgery; neuroradiological imaging procedures.

Type of anaesthesia

No definite recommendation for either general or regional anaesthesia can be given.

Patient compliance and collaboration for regional anaesthesia may be difficult due to dystonia. No reports of spinal, epidural and caudal anaesthesia exist.

For general anaesthesia, there are no definite reports on the superiority of one anaesthetic drug over another.

No contraindication for sedation or analgesia. Consider risk of aspiration.

Necessary additional pre-operative testing (beside standard care)

If surgical intervention is planned, the responsible metabolic centre/specialist should be informed beforehand. This would enable all staff involved to discuss specific risks and to have a protocol for peri-operative metabolic management and monitoring.

No need for additional specific pre-operative tests. Routine pre-operative tests are usually normal.

Some patients have chronically reduced bicarbonate levels despite being perfectly compensated. During acute attacks one can expect hypoglycaemia, ketonuria and metabolic acidosis with a mild to moderate decrease of bicarbonate levels.

Particular preparation for airway management

Patients with severe dystonia may be at a greater risk for aspiration of gastric contents during general anaesthesia. Appropriate measures to avoid aspiration including the use of proton-pump inhibitors/H2 blockers and rapid sequence induction of anaesthesia should be considered.

At the end of the surgical procedure, tracheal extubation must be carried out when the patient is awake and when protective reflexes are present.

Particular preparation for transfusion or administration of blood products

Not reported.

Particular preparation for anticoagulation

Not reported.

Particular precautions for positioning, transportation and mobilisation

Not reported.

Interactions of chronic disease and anaesthesia medications

Not reported.

Patients are usually treated with a low-protein (lysine and tryptophan restriction) diet, riboflavin and carnitine supplementation. Carnitine dosage should be doubled during the peri-operative period.

Anaesthetic procedure

Regarding volatile anaesthetics, sevoflurane seems to be safe. Recent literature rules out episodes of malignant hyperthermia and other intraoperative events attributable to the general anaesthesia with sevoflurane in paediatric patients with mitochondrial disease.

Reports that propofol can provide lipid overload and inhibit oxidative phosphorylation, carnitine palmitoyltransferase transport of long-chain fatty acids, and β-oxidation of fatty acid in mitochondria raises concerns about a potential occurrence of propofol infusion syndrome and severe metabolic acidosis. Long procedures with total intravenous anaesthesia with propofol are probably not advisable. There are reports of thiopentone use for a safe induction without complications.

Expect prolonged responses to non-depolarising muscle relaxants and hyperkalaemic responses to succinylcholine. Antagonisation of neuromuscular blockade with pyridostigmine or neostigmine seems to be possible. Sugammadex to antagonise any residual neuro-muscular blockade might be a good option.

Limit the pre-operative fasting period to prevent hypoglycaemia, dehydration and mild metabolic acidosis caused by an overnight fast. Start a maintenance intravenous infusion containing glucose (6mg/kg/min) during the fasting period.

Avoid using Ringer's lactate while surgery is in progress since it contains lactic acid. Use dextrose dissolved in normal saline instead.

Patients with GA-1 are vulnerable to postoperative emesis. Antiemetic prophylaxis is advisable.

Particular or additional monitoring

Monitoring of the neuromuscular blockade will be strictly recommended if a neuromuscular blocking agent is used.

Monitor body temperature to avoid hypothermia, shivering and an increased oxygen demand.

Consider serial intraoperative arterial blood-gas analysis for closely monitoring pH status, electrolytes, lactate and glucoses.

Possible complications

An encephalopathic crisis and acute metabolic decompensation might occur during surgery and in the postsurgical period, especially in patients aged 0 to 6 years. With increasing age, in particular after the age of 6 years, the risk of acute neurological insult appears to be much reduced.

Conditions accelerating catabolism, such as repeated vomiting and diarrhoea (with or without fever), and the manifestation of severe neurological symptoms (i.e., hypotonia, irritability, rigour, dystonia, reduced consciousness) should be considered as alarming symptoms.

Emergency treatment should start before the onset of alarming neurological symptoms:

(1) Prevention or reversal of a catabolic state by administration of a high-energy intake (plus insulin to control for hyperglycaemia, if required);

(2) Reduction of glutaric acid or reduced production of related metabolites by transient reduction or total deprivation of natural protein for 24 to 48 hours;

(3) Amplification of physiological detoxification mechanisms and prevention of secondary carnitine depletion by L-carnitine supplementation;

(4) Maintenance of normal fluid, electrolytes and pH status via enteral or IV fluids.

Non-adherence to previously described emergency treatment recommendations has been associated with a high probability of developing striatal injury.

Post-operative care

If possible, the post-surgical metabolic management should be performed in a metabolic centre.

Consider emergency treatment as described above.

Disease-related acute problems and effect on anaesthesia and recovery

Repeated vomiting and diarrhoea (with or without fever), and the manifestation of severe neurological symptoms (i.e., hypotonia, irritability, rigour, dystonia, reduced consciousness)

should be considered as alarming symptoms in the post-operative period and might indicate an acute metabolic decompensation.

Ambulatory anaesthesia

Two cases reported (patients aged 12 and 16 years) for ambulatory neuroradiological imaging, for routine follow up.

Sedation was performed with a propofol bolus (1mg/kg) and maintained using propofol bolus (0.5mg/kg) in case of necessity, lasting approximately 10 minutes. Spontaneous breathing was maintained in this period without any complications reported.

Ambulatory anaesthesia should probably be considered only for older patients (over 6 years of age) and only in cases of low-risk procedures and surgery.

Obstetrical anaesthesia

During the last three decades, therapeutic concepts have been established which permitted to optimise and reduce the frequency of acute encephalopathic crises and thus morbidity and mortality in early diagnosed patients with GA1.

Therefore, GA1 is now considered to be a treatable condition. However, to the best of our knowledge, until present date, there are no reports about pregnancy and/or obstetrical anaesthesia in GA1 patients.

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