orphanaesthesia

Anaesthesia recommendations for patients suffering from

Maple syrup urine disease

Disease name: Maple syrup urine disease

ICD 10: E71.0

Synonyms: MSUD, branched-chain ketoaciduria, branched-chain-alpha-ketoacid dehydrogenase deficiency, BCKD deficiency, BCKDH deficiency, ketoacid decarboxylase deficiency

Maple syrup urine disease (MSUD) is an autosomal recessive condition with an incidence of approximately 1 in 150 000 live births with a higher incidence amongst children from consanguineous relationships [1]. It is caused by an enzymatic deficiency with reduction in oxidative decarboxylation of branched-chain amino acids (BCAA) (leucine, isoleucine and valine) resulting in elevated levels and toxic metabolites that cause neurotoxicity [2].

The clinical features of MSUD are variable, but the "classic" form is characterised by psychomotor retardation, cerebral degeneration, hypoglycaemia and seizures [3,4]. Adolescents with the condition may have attention deficit hyperactivity disorder, anxiety and developmental delay. The disease takes its name from the characteristic maple syrup odour of the urine from a metabolite of isoleucine [5]. Failure to thrive and feeding difficulties are also common.

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

Presentation of the classic form occurs in the neonatal period, often with a metabolic ketoacidosis, due to accumulation of leucine and 2-oxo isocaproate in the blood and tissues above critical concentrations during the first week of life [6]. If this is not identified and treated in a short time, the patient can die within a few days or weeks. Milder forms of the disease may present later in childhood.

The treatment of MSUD is two-stage, consisting of therapy to prevent acute decompensation and long-term nutrition therapy. Peritoneal dialysis has successfully reduced BCAA levels in neonates with MSUD [6]. The specific low protein diet limiting BCAA is a lifelong requirement, but compliance is not always optimal and these children must be monitored carefully in order to prevent developmental delay and neurological decompensation. Adequate nutrition can be assured with the use of MSUD-specific medical foods (metabolic formulas) combined with low protein foods.

There are five clinical variants [2]:

Classic MSUD

The most common and severest form typically presents in the the newborn period. There is little or no detectable branched chain α-keto acid dehydrongenase complex activity (<2%) [7]. Patients are prone to decompensation and neurological damage occurs if the condition is not treated.

Intermediate MSUD

Patients may become symptomatic at any age. There are variable features of neurological impairment and developmental delay. Decompensation can occur with catabolic illness, stress, inadequate caloric intake, or high protein consumption.

Intermittent MSUD

This is the second commonest variant where affected individuals appear completely normal and may have normal levels of the BCAA except during periods of extreme catabolic stress [7]. Symptoms usually present between 5 months and 2 years of age. Affected individuals are at risk of decompensation often presenting with ketoacidosis and other typical features of neurotoxicity.

Thiamine-responsive MSUD

Some individuals with mild forms of MSUD have greater metabolic control when using supplemental thiamine. To date there have not been individuals identified who can be successfully managed with thiamine alone without also limiting BCAA.

E3-deficient MSUD

This is a very rare form with only ten cases reported. Neonates are usually affected, with a lactic acidosis in addition to the typical presenting features. There is also an accumulation of both pyruvate and α-ketoglutarate in addition to the BCAA and their derivatives.

Decompensation

May be triggered by stressful situations such as injury or exercise, intercurrent illness, fasting, surgery, or caused by increased catabolism of endogenous protein.

The clinical manifestations are non-specific but include epigastric pain, vomiting, anorexia, muscle fatigue, and rarely pancreatitis. Neurological features may be similar to those of Wernicke encephalopathy including hyperactivity, lethargy, seizures, dystonia, hallucinations, and ataxia. If the condition is not treated severe ketoacidosis with rapid neurological deterioration and hypoglycaemia can occur, proceeding to death secondary to cerebral oedema and herniation.

Typical surgery

Patients may present for all types of surgery but day-case surgery should be avoided so that patients can be closely monitored post-operatively and catabolism avoided.

Some patients with MSUD may be offered liver transplantation as part of the management of the disease.

Type of anaesthesia

The conduct of anaesthesia will depend upon the severity of symptoms. Both general and regional anaesthetic techniques are safe to use. Anaesthetic agents with anticonvulsant properties such as propofol and thiopentone have been used with no adverse effects and some authors have also safely used ketamine.8,9 Volatile anaesthetic agents and nitrous oxide are safe to use as are all muscle relaxants.5,6,8 Short-acting agents, such as desflurane and remifentanil, may be preferred in order to facilitate recovery and minimise depressant effects on the respiratory system.6

Effective pain management is essential and therefore regional anaesthetic techniques should be considered as part of a multi-model approach to pain control. Local anaesthetic drugs are safe to use. Tramadol is also safe to use in patients with MSUD.8

Necessary additional diagnostic procedures (preoperative)

General principles.

An assessment of the patients' clinical and biochemical status must be made pre-operatively. A baseline venous or arterial blood gas should be performed to ascertain the patient's metabolic state. If a severe acidosis is present, surgery should be delayed where possible until this can be corrected [6].

Careful fluid management is required pre-operatively aiming for normovolaemia. Prolonged fasting will cause dehydration and acidosis, whilst over hydration risks cerebral oedema [6,10]. Glucose containing fluids (e.g. 10% dextrose at 8 – 10 mg.kg-1.min-1) should be commenced at the start of the fasting period to avoid catabolism and resultant metabolic decompensation. Some authors have also advocated using an infusion of 20% intralipid pre-operatively, with specialist advice, in order to provide calories without causing over hydration and haemodilution [9].

Patients presenting with metabolic decompensation must be optimised prior to surgery [6].

Elective and emergency surgery.

For elective surgery, patients should be scheduled first on the operating list and ideally managed in a specialist centre with expertise in the management of MSUD. A multidisciplinary team approach is required during the perioperative period with intensive care facilities available in case of decompensation. The metabolic team should be involved in optimising the patient pre-operatively and provide advice during the peri-operative period [10].

Elective surgery should be postponed if there is evidence of intercurrent illness that may increase the risk of decompensation.

Patients presenting for emergency surgery should ideally be transferred to specialist centres. If this is not possible, specialist metabolic advice should be sought. Good communication between the various members of the multidisciplinary team is essential.

Particular preparation for airway management

Standard management.

Particular preparation for transfusion or administration of blood products

Standard management.

Particular preparation for anticoagulation

Standard management.

Particular precautions for positioning, transport or mobilisation

Standard management.

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

There have been no reported incidents of anaesthetic drug interactions and the patient's special dietary therapy.

Anaesthesiologic procedure

The patients' special diet and oral supplementation must be maintained peri-operatively. A dextrose infusion should be continued to prevent hypoglycaemia and catabolism while the patient is fasting and throughout the procedure. This can be stopped when the patient resumes their normal diet. Early resumption of enteral intake is recommended and as such anaesthetic techniques that facilitate recovery should be considered (e.g. post-operative nausea and vomiting prophylaxis; minimise opioid use by using regional techniques).

Invasive monitoring with an arterial line or central venous access is recommended for prolonged surgery where patients are at risk of metabolic acidosis to enable regular sampling for glucose levels and blood gas measurements.

Adequate tissue perfusion and avoidance of hypothermia is important to prevent metabolic acidosis. Temperature monitoring and intraoperative warming with fluid warmers and forced-air warming devices are recommended. If metabolic acidosis does develop, ensure the patient is adequately hydrated and consider administering an infusion of sodium bicarbonate.

Patients undergoing procedures that may cause blood to accumulate in the stomach e.g. oral or gastrointestinal surgery, should have a nasogastric tube inserted as blood in the gastrointestinal tract represents a large protein load and may trigger an acute decompensation [5,10].

Particular or additional monitoring

As described above, monitor blood glucose and venous or arterial blood gas measurements at regular perioperative intervals.

Possible complications

Metabolic decompensation.

Cerebral oedema.

Hypoglycaemia.

Postoperative care

Close monitoring of the patient's blood glucose, urinary ketones and plasma amino acid level is required until they resume their normal dietary intake.

Patients at high risk for metabolic or clinical deterioration must be cared for in a high dependency unit postoperatively. Regular monitoring of their acid-base status is needed to recognise decompensation early.

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

Management of metabolic decompensation.

It is important to reverse catabolism by providing adequate calories through the use of glucose (and possibly insulin), intralipids and appropriate amino acid solutions. Intravenous fluid resuscitation promotes a diuresis to lower plasma leucine concentrations. Detoxification may also be achieved by removal of BCAA with peritoneal dialysis or haemodialysis [6].

Cerebral oedema secondary to hyponatraemia may develop and this should be treated with hypertonic saline, mannitol or furosemide [2].

The use of hypertonic glucose solutions may, however, cause an additional stress factor with increases in oxygen consumption, carbon dioxide production and release of noradrenaline. These patients may therefore benefit from fat emulsions that provide calorific intake without causing over hydration and haemodilution [6].

Ambulatory anaesthesia

In general, day case surgery is not recommended, as the patient requires close monitoring post-operatively.

However, some specialist units with expertise in managing these patients may perform day case procedures such as MRI scans under general anaesthesia or allow children with milder forms of MSUD to have day-case surgery.

Obstetrical anaesthesia

Successful management means more women are reaching child-bearing age and there are a few case reports of successful pregnancies in patients with MSUD [11,14].

General principles of maintaining a high-calorie, low BCAA diet are recommended during labour or the perioperative period, and in some case parental nutrition has been used [11].

Tchan et al discuss their management of two women with MSUD during their pregnancies [12]. They outline a detailed management plan for the peri-partum period for one of the patients that included six hourly blood glucose measurements, daily amino acid measurements, high energy supplements, infusion of dextrose containing fluids and intralipid 20% when not tolerating oral intake. Patients are at risk of decompensation post-partum due to the protein load from the involuting uterus. The management of labour pains was not referred to in these cases.

A good working labour epidural will ensure optimal analgesia during delivery and potentially reduce the risk of acute decompensation occurring secondary to the stress response. Labour pains may also be successfully controlled with patient controlled intravenous opioid analgesia where regional anaesthesia is contraindicated.

Literature and internet links

1. Wilcken B. Maple syrup urine disease, www.orphan.net April 2014, accessed November 25th 2014
2. Bodamer O. Overview of maple syrup urine disease, www.uptodate.com September 2014, http://www.uptodate.com/contents/overview-of-maple-syrup-urine-disease, accessed September 30th 2014
3. Schwartz J, Kolendrianos E. Maple Syrup Urine Disease. A Review with a report of an additional case. Develop. Med. Child Neurol. 1969;11:460-70
4. Levin M, Scheimann A, Lewis R, Beaudet A. Cerebral edema in maple syrup urine disease. J Pediatr 1993;122(1):167-8
5. Delaney A, Gal T. Hazards of anaesthesia and operation in maple-syrup-urine disease. Anesthesiology 1976;44(1):83-6
6. Kahraman S, Ercan M, Akkuş Ö, et al. Anaesthetic management in maple syrup urine disease. Anaesthesia 1996;5 :575-8
7. Axler O, Holmquist P. Intermittent maple syrup urine disease: two case reports. Pediatrics 2014;133(2):e458-60
8. Fuentes-Garcia D, Falcon-Arana L. Perioperative management of a patient with maple syrup urine disease. Br. J. Anaesth 2009;102(1):144-5
9. McCarron E, McCormack O, Howard C, et al. Management of maple syrup urine disease in the peri-operative period. Ir Med J 2013;106(9):277-8
10. Stuart G, Ahmad N. Perioperative care of children with inherited metabolic disorders. Continuing education in anaesthesia, Critical Care and Pain 2011:11(2):62-8
11. Wessel A, Mogensen K, Rohr F, et al. Management of a woman with maple syrup urine disease during pregnancy, delivery and lactation. J Parenter Enteral Nutr March 11th 2014, dot:10.1177/0148607114526451
12. Tchan M, Westbrook M, Wilcox G, et al. The management of pregnancy in maple syrup urine disease: experience with two patients. JMID Reports 2013:10:113-7
13. Van Calcar S, Harding C, Davidson S, et al. Case reports of successful pregnancy in women with maple syrup urine disease and propionic academia. Am J Med Genet 1992;44:64
14. Grünewald S, Hinrichs F, Wendel U. Pregnancy in a woman with maple syrup urine disease. J Inherit Metab Dis 1998;21:89.

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