Peri-Operative Management Of Maple Syrup Urine Disease: The Surgical Perspective

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Abstract

Maple syrup urine disease (MSUD) is a rare autosomal recessive inherited metabolic disorder. The main toxic amino acid leucine and its metabolites build up in the blood, precipitated by fasting, surgery and sepsis. This can result in confusion, seizure activity and potential cerebral oedema. We hope to raise awareness and understanding of the condition and its management for surgical teams who may encounter patients with MSUD.

Medical therapy aims to rapidly reduce toxic metabolites by restricting dietary intake of plasma-branched amino acids and supplementing with amino acids mixtures free of leucine, isoleucoine and valine. Strict dietary management, restricting catabolism and promoting anabolism, and monitoring nutritional status are fundamental to long term growth, development and health maintenance.

When considering surgery in a patient with MSUD, either electively or as an emergency, close monitoring is required. Advice from a metabolic expert is preferable. Fasting should be minimized where possible, the operation should be performed promptly and effectively and any sepsis should be treated. Daily monitoring of branched-chain amino acid levels and monitoring or nutritional and fluid intake are essential. Emergency feeding regimens, either orally, via nasogastric or total parenteral nutrition is required. Dialysis can filter toxic metabolites from the blood.

When patients with maple surgery urine disease require surgery a multi-disciplinary team approach is required. Under the advice of a metabolic team, the surgical team needs to work closely with the anaesthetic and dietetic teams. With correct monitoring and nutritional support patients can make a full recovery following emergency or elective surgery.

INTRODUCTION

Maple syrup urine disease (MSUD) is a rare autosomal recessive inherited metabolic disorder [1]. Menkes first recognized the condition in 1954 [2]. The incidence is 1:185,000 newborns worldwide [3]. In the UK there are small areas of higher incidence in immigrant populations and those with higher rates of consanguineous marriage [4]. It is caused by branched–chain alpha-keto-acid-dehydrogenase complex deficiency leading to accumulation of the branched-chain amino acids: leucine, isoleucine and valine [5]. The main toxic amino acid leucine and its metabolites build up in the blood, cerebrospinal fluid (CSF) and urine [5].

The condition can be detected soon after birth with elevated levels of branched chain amino acids by 12 hours, the smell of maple syrup detectable in the cerumen by 24 hours and in the urine by 72 hours [5]. Irritability and poor feeding can develop into lethargy, intermittent apnoea, stereotyped movements before coma and respiratory failure ensue [2]. Episodes of metabolic intoxication can be fatal [6]. Delays of initial condition recognition of 10-14 days can lead to mortality (up to 50%), and high rates of neurological problems [7].

Newborn screening uses mass spectrometry to detect the total leucine-isoleucine concentration in relation to other amino acids [8]. The 3 genes in which mutations are associated with MSUD are BCKDHA, BCKDHB and DBT [9].

There are 4 subtypes of the condition: classical, intermediate, intermittent and thiamine responsive [8]. Dietary branched-chain amino acids are normally used in

protein synthesis. They can be used as alternate energy source during excess consumption or during endogenous muscle protein catabolism [5]. Branched-chain alpha-keto-acid-dehydrogenase activity is less than 2% of normal in the classical (severe) form [4]. Activity in the other forms ranges from 3-30% with a more delayed presentation of symptoms [10].

During times of catabolic activity, for example illness, fasting, vomiting, sepsis or diarrhoea, muscle proteins release amino acids and leucine in particular [2]. This can result in confusion, ataxia, seizure activity and potential cerebral oedema. Urgent medical attention is required [11].

At our surgical department we have come across 2 cases of MSUD requiring surgical management in recent months: one elective and one emergency. Each case required careful multidisciplinary planning and management. Senior anaesthethic involvement as well as expert metabolic advice are essential and were sought in our 2 cases throughout their admissions. As an adult general surgery department we had not accounted such cases previously. We hope to raise awareness and understanding of the conditions and their management for surgical teams.

MANAGEMENT

The aims of medical therapy include rapid reduction of toxic metabolites by restricting dietary intake of plasma branched amino acids and supplementing with amino acids mixtures free of leucine, isoleucoine and valine [12]. This involves strict dietary management. Restricting catabolism and promoting anabolism, monitoring nutritional status and supplementing with thiamine (if responsive) are also fundamental to long term growth, development and health maintenance [5].

Patients are counseled and given sick day rules so they can manage and monitor their condition when unwell [8]. Patients carry emergency management plans to guide medical professionals when acutely unwell and presenting to primary or secondary care.

During acute illness intravenous fluids may be required as well as high energy intake, intravenous glucose and insulin, as well as lipid infusions [10, 13]. Peritoneal dialysis, haemodialysis or haemofiltration may be required to reduce metabolite levels [14-16].

Overall treatment strategy is divided into 5 main areas according to recent guidelines released in the US: acute nutrition management, controlling plasma levels of branched chain amino acids, use of thiamine, considerations during pregnancy and the option of liver transplantation in certain cases [5].

Acute nutrition management involves monitoring closely the patient's clinical and biochemical state [11], prevent catabolism and accumulation or endogenous branched chain amino acids, provide exogenous BCAA free protein, energy, fluids [14-17]. Supplements of valine or isoleucine may promote anabolism [16].

CONSIDERATIONS FOR THE SURGICAL TEAM

Unavoidable periods of catabolism present several challenges to the medical team [1]. If surgery is to be performed electively then a detailed treatment plan can be devised by the surgical, anaesthetic, metabolic and dietetic teams. In emergency surgery clear communication between teams and decisive management are required. Underlying principles are managing the acute nutritional state and preventing accumulation of branched amino acids in the blood [5].

PRE-OPERATIVE MANAGEMENT

A thorough medical assessment is a necessity. Precipitating factors should be identified, for example sepsis. Nausea and vomiting should be promptly treated with antiemetics [8]. Blood tests should be performed including a serum amylase. Patients are vulnerable to pancreatitis especially when leucine levels are falling to normal [8, 18]. Other modalities of investigation, such as CT or ultrasound scan, can be used to aid the diagnosis.

If unwell with sepsis an emergency feeding regimen can be started [10, 13]. If unable to tolerate oral intake then intravenous fluids should be commenced in the form of intravenous dextrose and saline [8]. If this situation in prolonged then nasogastric feeding with low protein and high calorie feeds may be required [10,13]. Hypercalorific feeding plans can cause hyperglycaemia in which case an insulin infusion may be necessary.

Fasting or sepsis can cause accumulation of branched chain amino acids. If levels rise above 1000 then there is a risk or neurological injury. Normal levels are usually less than 200, and treatment should aim to keep levels below 400 if possible [5]. Haemodialysis can be used preemptively if BCAA levels are not available, or if documented levels are uncontrolled above recommended levels, or if the patient is experiencing increasing symptoms. This can continue until

leucine levels return to normal (less than 200).

PERI-OPERATIVE MANAGMENT

The surgery itself needs to be done promptly and effectively. Senior members of the surgical team should perform the surgery, a Consultant when possible. Meticulous surgical approach to the primary pathology, control of sepsis, intraoperative antibiotics may all help post-operative recovery. From a surgical perspective there are no additional measures or care required, patients should receive the best possible surgical treatment, as with other patients.

Senior Anaesthetic involvement is advisable and intra-operative monitoring including arterial or venous blood gases, blood sugars and urine output is imperative. A worsening acidosis will influence decisions about postoperative care including the requirement for intensive care management and possible haemodialysis/filtration [14-16].

POST-OPERATIVE MANAGEMENT

Patients may require high dependency unit or intensive care monitoring. This allows close management of their nutritional intake, monitoring of amino acid blood levels and haemodialysis/filtration to control potentially toxic levels of leucine and its metabolites [14-16].

Once extubated and fully alert a patient's nutritional requirements should be met with a combination or oral and nasogastric (NG) feeding, as deemed appropriate [10, 13]. If NG tube was placed for a surgical reason feeding can be commenced once NG aspirates were low. Feeding rates can be gradually increased and supplemented with small amounts or oral diet, to meet the patients nutritional requirements. If there is poor absorption then TPN can be used to provide adequate nutrition [10, 13]. More major surgical intervention may need more extensive nutritional support in the form of prolonged NG feeding or TPN [10,13].

Branch-chained amino acid levels should be monitored daily and discussed with the Metabolic specialist on a regular basis [8]. Haemodialysis/filtration, if commenced, can continue until leucine levels normalise to below 200 [14-16].

Depending on the severity of surgical insult, patients can be nursed on a normal surgical ward if high dependency or intensive care input is not required. Close monitoring is required as the patient recovers. Oral intake, blood leucine levels, electrolytes and blood sugars need checking [8]. A good urine output should be maintained. If leucine levels increase then expert advice is required [8]. Treatment can include increasing calorie intake, giving isoleucine and valine and if further increases occur, haemofiltration [14-16]. Leucine levels rise in response to sepsis [8]. Considering this a septic screen should be performed if unexplained rises occur.

SUMMARY

Maple syrup urine disease is a rare autosomal recessive inherited metabolic disorder. Some geographical areas have higher prevalence of such conditions [4]. When managing patients with such conditions a clear treatment plan is required. Consultation with a Metabolic disease specialist is beneficial. Sick day treatment regimens should be commenced without delay. If possible fasting should be avoided. Nutrition needs to be provided orally, by nasogastric feeding or by total parenteral nutrition. Levels of leucine should be monitored regularly. If levels are poorly controlled, or indeed unavailable, then haemodialysis/filtration can be commenced as a protective measure.

Early diagnosis and treatment can lead to normal somatic and intellectual development [8]. There is a requirement for meticulous management during periods of catabolism. Development of intensive care services, such as availability of dialysis and haemofiltration, have improved outcomes [4].

When patients with maple syrup urine disease require surgery a multi-disciplinary team approach is required. Under the advice of a metabolic team, the surgical team needs to work closely with the anaesthetic and dietetic teams. Under the correct monitoring and nutritional support patients can make a full recovery following emergency or elective surgery.

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