

The Management Of a Case With Maple Syrup Urine Disease With Haemofiltration and Nutritional Support in the Perioperative Period

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Abstract

We present a case of a female adult patient with Maple Syrup Urine Disease (MSUD) who had recurrent episodes of raised Branched Chain Amino Acids levels (BCAA). Frequent increases in leucine >1000 µmol/L were associated with vomiting, reduced oral intake and general illness. Her recurrent episodes of vomiting might have been also caused by an oesophageal polyp. Due to poor food intake an eating disorder was suspected. As a result she was at increased risk of refeeding syndrome and acute metabolic decompensation. On the admission to the hospital with acute appendicitis, the management of her nutrition to increase the anabolism and prevent the accumulation of BCAA was challenging; she was not able to tolerate oral food but only a fraction of the total volume of prescribed supplements administered via nasogastric tube. Continuous venovenous haemofiltration over 3 days facilitated a reduction in BCAA levels and prevention of complications of acute decompensation. Her weight remained stable but low after the surgery.

Received: July 17, 2015; **Accepted:** August 10, 2015; **Published:** August 17, 2015

Synopsis: The management of a case with MSUD with haemofiltration and nutritional support in the perioperative period.

Introduction

Maple Syrup Urine Disease (MSUD) is a disorder affecting the breakdown of branched chain amino acids (BCAA) (leucine, isoleucine and valine) [1]. In MSUD leucine and its derivative α - ketoisocaproate are the main neurotoxic compounds that accumulate in cells and body fluids during proteolytic stress and cause metabolic decompensation [1-3]. Such crises are associated with a high risk of cerebral oedema and potentially death. The mechanism is not fully understood but it has been shown that rapid brain leucine accumulation displaces other essential amino acids. This subsequently leads to neurotransmitter depletion and disruption of normal brain growth and development [4]. Poor renal clearance of BCAA and neurotoxic α - ketoisocaproate can additionally contribute to the increase of leucine concentrations [2,5]. Renal replacement therapy (using continuous venovenous haemofiltration or intermittent haemodialysis) is indicated in severe metabolic crisis, in particular when BCAA-free nutritional

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Citation: Stepien KM, Wilcox G, Green D, et al. The Management Of a Case With Maple Syrup Urine Disease With Haemofiltration and Nutritional Support in the Perioperative Period. J Rare Dis Diagn Ther. 2015, 1:2.

formulas are insufficient or unavailable [3,6]. Of equal importance is the aggressive nutritional support needed to reverse catabolism and promote anabolism [7,8]. The aim of this is to increase the energy intake by up to 150%. Fluids should be replaced carefully (up to 150 ml/kg) with electrolyte monitoring to prevent possible cerebral oedema

[3,7]. Nutritional intervention is important to ensure an anabolic state, whenever renal replacement therapy is necessary to lower plasma BCAA and remove toxic metabolites. In such cases blood gases, haematocrit, total protein, sodium, calcium, phosphate, urea and creatinine must be monitored. Ideally, BCAA levels should be measured in blood before and after the dialysis or haemofiltration. It is recommended that isoleucine and valine are added to the feed, even if their blood levels are already in the 200-400 $\mu\text{mol/L}$ range, in order to help to lower elevated plasma leucine into the treatment range [7].

Should sickness and vomiting hinder any oral intake, enteral feeding or total parenteral nutrition are initiated to provide sufficient energy to prevent catabolism. There is some evidence that supplemental thiamine might increase dietary BCAA tolerance or decrease plasma BCAA on a constant dietary intake in individuals with some branched-chain α - ketoacid dehydrogenase activity [7]. Thiamine is often supplemented in patients with a high risk of refeeding syndrome to prevent severe neurological and cardiac problems.

We report the successful outcome of an adult patient with poorly controlled MSUD and suspected eating disorder, who underwent a laparoscopic appendectomy. We describe the detailed nutritional support she was provided with, as well as the effectiveness of haemofiltration in the perioperative period to prevent acute decompensation and encephalopathy. The patient had also developed a tolerance to frequent episodes of rises in BCAA levels prior to and after the acute presentation.

Case

We present a case of 19-year old female whose MSUD was diagnosed in infancy. She was admitted to the medical ward of her local District General Hospital with vomiting at the end of May 2014, when her leucine level was reported as 1349 $\mu\text{mol/L}$ and subsequently 1039 $\mu\text{mol/L}$, isoleucine was within normal reference ranges. She was also known to our dietetic and counselling services in the Metabolic Department. Due to a history of limited food intake and after a psychological assessment an eating disorder was suspected (her BMI was 16 kg/m^2). Lack of regular periods has remained a concern too, but gonadotrophin levels did not suggest hypogonadotropic hypogonadism (LH 12.3 U/L, FSH 6.1 U/L). She had mild learning difficulties and her underlying disordered eating was a significant risk factor for acute decompensation. On multiple occasions her monthly leucine levels varied between 600-1300 $\mu\text{mol/L}$. Importantly, her routinely checked BCAA levels on Dry Blood Spot were often high despite her not being unwell (leucine up to 1245 $\mu\text{mol/L}$, valine up to 507 $\mu\text{mol/L}$, isoleucine up to 657 $\mu\text{mol/L}$), which was a result of her not taking nutritional supplements.

Two weeks later she was readmitted to the same hospital with abdominal pain and signs of sepsis (C-reactive protein (CRP) 220 mg/L). Due to illness, she reported she had lost a stone (6 kgs) in her body weight shortly before her admission to hospital (weight 39 kgs). To inhibit protein catabolism and promote anabolism on the first day of the in-hospital stay, she was provided with her usual high calorie intake (30 mls Calogen[®] tds, 60g Polycal[®], 400ml Polycal Liquid, powder in 780ml Lucosade[®]) combined with her usual MSUD BCAA-free amino-acid formula (4 Lophlex LQ 20[®]). Her Basic Metabolic Rate was 1082 kcal but the aim was to increase her energy

intake to 2000 kcal. She was at increased risk of refeeding syndrome. She was not able to tolerate full amounts of emergency regimen but was supplemented with essential aminoacids: isoleucine and valine to prevent their deficiencies and to suppress her leucine levels, via a nasogastric tube. Her blood tests showed magnesium 0.66 mmol/L , phosphate 0.42 mmol/L (on Phosphate Sandoz tablets), and potassium 3.8 mmol/L (on 20 mmol potassium in 1 litre saline) highlighting her risk of refeeding syndrome. Lactate was 2.9 mmol/L (0.5-2.2 mmol/L).

Subsequently, a CT scan confirmed a ruptured appendix and she was managed with fluids (10 % glucose 10 % at 100 ml/hour).

Day 1 - Surgery

In the perioperative period, intravenous glucose and saline were initiated to maintain glucose levels at 6-8 mmol/L . At this stage she was not able to take anything via enteral route including isoleucine and valine, and no intravenous prescription was available. To lower BCAA levels natural protein was stopped. Unfortunately this proved insufficient and it was decided to start continuous venovenous haemofiltration in the intensive care unit at midnight on day 4 after admission. Importantly, haemofiltration helped to lower her leucine level to well below 1000 $\mu\text{mol/L}$ (leucine 197 $\mu\text{mol/L}$ (32-153), isoleucine 172 $\mu\text{mol/L}$ (35-105), valine 172 $\mu\text{mol/L}$ (68-300)).

Day 2 - Post surgery

The next step was to establish nasogastric (NG) feeding plans with protein-intake restriction. These were started the day after the operation and continued for three days until day 5 post surgery. The total number of calories was 500 kcal (13 kcal/kg) and consisted of protein and carbohydrates (800 mg isoleucine, 800 mg valine). On day 3 post surgery, the amount of calories was increased to 1414 kcal (38 kcal/kg) (800mg isoleucine, 800mg valine, 48g MSUD AID III[®], 160g EnergyVit[®]) and on day 4 to 1819 kcal (46 kcal/kg) (800 mg isoleucine, 800mg valine, 72g MSUD AID III[®], 220g EnergyVit[®]). On both days (3 and 4) Polycal[®] was replaced with EnergyVit[®], as the formula provides more calories per g than Polycal[®], and contains fat, vitamins, minerals and trace elements. The feeding was tolerated at 50 mls/hr, and on day 3 the rate was increased to 75 ml/hr. During three days of NG feed, the patient was still receiving haemofiltration (in total 68 hours) to remove the excess of BCAA's, in particularly leucine.

Day 5 - Post surgery

When the patient was started on an oral diet (5 days after the procedure), subsequent BCAA levels showed the effects of the oral diet with supplementary calories (leucine 691 $\mu\text{mol/L}$, isoleucine 615 $\mu\text{mol/L}$, valine 500 $\mu\text{mol/L}$) but remained stable. Subsequently the patient was discharged on day 9 post surgery. Her body weight on discharge day was 38.7 kgs.

3 months later the patient presented with three more episodes of cyclic vomiting that required recurrent admission to the hospital and further investigations. Subsequent endoscopy revealed an oesophageal polyp as a likely organic cause for these symptoms. Over many months she was unable to tolerate food but she

tolerated the emergency regimen (as described above). She has continued attending the psychology and dietetic appointments due to poor food intake. During recurrent rises in BCAA levels she was not encephalopathic or severely acidotic. Long-term, should recurrent episodes of acute decompensation persist, a liver transplant may be considered. In the meantime, the patient attended regular counselling sessions to help her overcome the disordered eating presumed to lead to rises in her BCAA levels and cyclic vomiting.

Discussion

In this report, we describe the challenging issues of the nutritional support and the effectiveness of continuous venovenous haemofiltration in an adult patient with MSUD who had recurrent acute biochemical disturbances following the rapid accumulation of BCAA.

Apart from her poorly controlled metabolic condition, she suffered from a suspected eating disorder and the oesophageal polyp. Low body weight/BMI was an extra stress factor that increased her risk of acute decompensation during surgery. Interestingly, she has been found to have high BCAA levels on multiple occasions (**Figure 1**) in particular leucine levels above 1000 $\mu\text{mol/L}$. The patient seemed to have developed a tolerance to high levels of this amino acid, as she never presented with ataxia, confusion or seizures. High leucine levels and oesophageal polyp were undoubtedly a cause of her recurrent vomiting episodes that still persisted after the appendectomy. Patients with increased BCAA levels often present with encephalopathy and require dialysis or haemofiltration to prevent brain damage. In this case haemofiltration was a preventative treatment of acute decompensation during the procedure.

Management options

The management of acute-phase response includes promoting anabolism by giving caloric support using glucose and 20% intralipid, control of infection, and commencement of low-protein intake with special formula supplementation [9]. The aim of peritoneal dialysis/haemofiltration is to remove accumulated branched-chain amino acids. In a study by Lee et al [9] this method of treatment was applied effectively in 62% of patients who have presented with acute decompensation of MSUD [9].

The choice of dialysis modality is influenced by institutional expertise and resources [6]. Both intermittent haemodialysis and continuous venovenous haemofiltration provide a higher leucine clearance compared to peritoneal dialysis (diffusive transport only) [10,11]. One of the concerns with intermittent haemodialysis is the rebound phenomenon that can occur once dialysis is stopped. Shortly afterwards a sudden rise in leucine levels may be observed, especially if the patient remains catabolic [12]. Continuous venovenous haemofiltration can theoretically prevent such a rebound because of its longer duration [12]. It is worth noting that BCAA normally rise in the post-operative state and it is partially driven by insulin resistance [13]. Therefore once haemofiltration, which has normalizing the BCAA, is ceased, some of the observed rebound in leucine levels may be a resumption of the 'usual' pattern of the post-operative BCAA elevation, exaggerated in absolute terms because of the MSUD. Importantly exogenous insulin may be used in such cases to promote anabolism especially when a patient decompensates metabolically [13].

Acute nutritional support

Nutrition plays an essential role in homeostasis in MSUD. During acute metabolic decompensation the main aims of nutritional

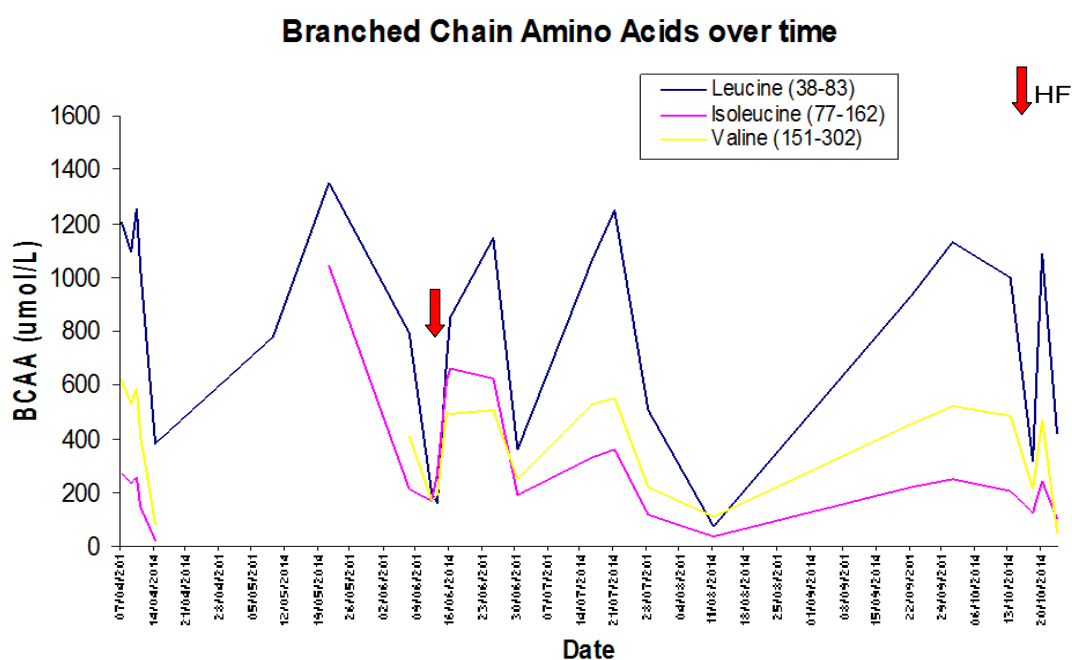


Figure 1 Branch Chain Amino Acids over an 8-month period. The red arrows indicates sudden falls in BCAA levels after haemofiltration.

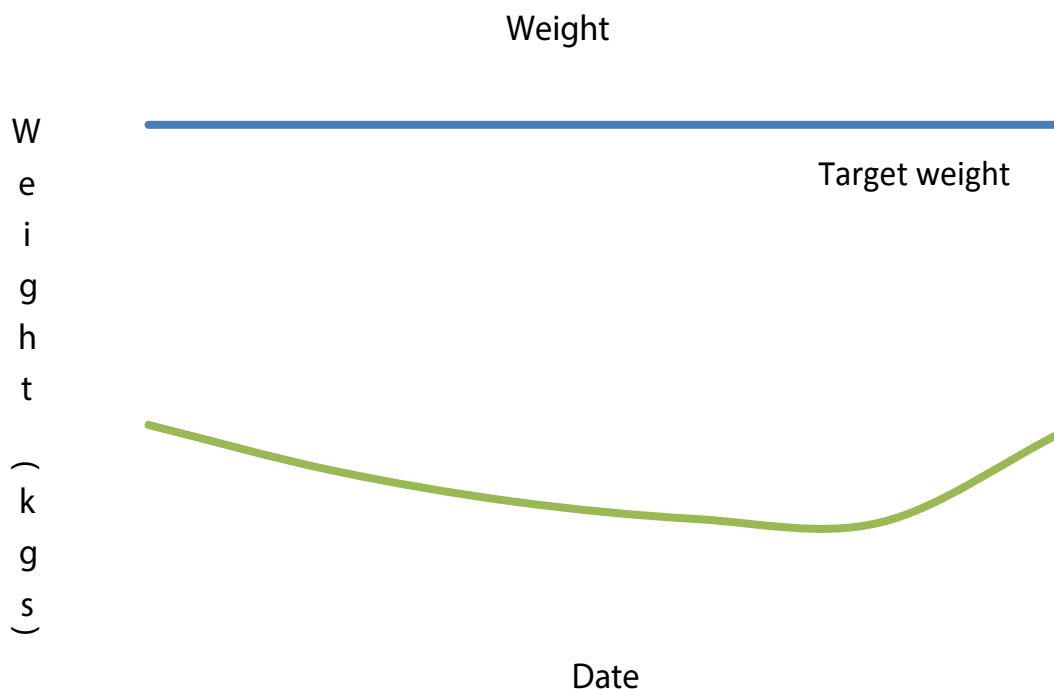


Figure 2 Weight (kg) fluctuations over 8 months; body weight has remained below the target body weight of 50kg.

therapy are to prevent catabolism and the accumulation of endogenous BCAA and other derivatives [7, 8, 14, 15], and to provide adequate BCAA-free exogenous protein, energy, fluid, and isoleucine and valine to promote anabolism [7]. Experimental studies have shown that ketoleucine is bound to albumin [2]. Hence, albumin infusion at the initiation of treatment might be useful to decrease BCAA and their derivatives transfer to the brain [2].

Inflammatory process as reflected by raised CRP, indicates protein catabolism and, to a lesser extent, hepatic protein synthesis [16]. Haemofiltration, as one of the continuous venovenous extracorporeal removal therapies, combined with nutritional intervention followed by nutrition alone, leads to a reduction in plasma leucine levels. This is a consequence of the increased protein anabolism and the removal of leucine by an extracorporeal technique [8, 14, 16]. Haemofiltration does, however, induce inflammation and protein catabolism [16]. After its discontinuation the patient might have excessive protein catabolism, resulting in raised plasma leucine. It is therefore necessary to enhance protein anabolism by continuous supplementation of amino acids, even if the haemodialysis or any other extracorporeal technique is used [16].

Haemofiltration and/or dialysis, along with enteral nutrition, is a recognised aggressive treatment option in seriously ill patients with MSUD [7, 8, 14, 15]. In our case total parenteral nutrition was considered but never instigated, as the patient was able to

tolerate enteral nutrition (nasogastric feeding) in the perioperative period. More importantly, there were no intravenous formulas of isoleucine and valine that could be added to the feeding. As the patient was at high risk of refeeding syndrome her thiamine (Pabrinex®), phosphate and potassium were supplemented to correct blood levels. Her energy intake was increased to 150% of her requirements but her body weight remained below the target body weight, though stable on discharge from hospital (**Figure 2**). One potential explanation is the increased catabolism in the perioperative period and after surgery.

In conclusion, we report the successful outcome of an adult patient with poorly controlled MSUD and suspected eating disorder who underwent a laparoscopic appendectomy. The use of haemofiltration in this case was a prophylactic treatment for upcoming catabolic processes during the surgery. The challenging issues included the long-standing poor food intake and chronic vomiting due to both the organic changes in the stomach and high leucine levels. Additionally, due to her risk of refeeding syndrome, the management of her MSUD during the surgical intervention required continuous high-calorie and amino acids supplementation via nasogastric tube as the oral intake was not possible. The case report illustrates an important association of eating disorders with MSUD and the role of psychological and counselling services in the management of metabolic diseases.

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