Case Report

Growth hormone as a rescue treatment in maple syrup urine disease with lessons from pediatric burn literature, case report and brief literature review

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ABSTRACT

Maple Syrup Urine Disease (MSUD) is a rare inherited disorder of branched chain amino acid metabolism characterized by cerebral edema and death in uncorrected metabolic crisis. It is conventionally treated with intensive nutritional therapy to prevent and correct metabolic crisis. This paper reports the use of growth hormone as a pharmacologic rescue agent in the case of an 11-year-old male with MSUD and metabolic crisis refractory to standard interventions. The initiation of short courses of growth hormone correlated with corrected mental status, resolution of metabolic acidosis, and improvement in plasma leucine levels on two occasions during an admission to the pediatric intensive care unit. This is the first known case report of the use of growth hormone in MSUD since contemporary dietary management became available. The discussion includes a literature review of the use of growth hormone in inherited diseases of amino acid metabolism and a brief discussion of protein anabolic pharmacotherapeutic agents shown to improve net protein balance in pediatric burn patients. We propose that growth hormone and other protein anabolic agents may be valuable adjuvants to standard therapy in children with inherited metabolic disease.

1. Introduction

Maple Syrup Urine Disease is an inherited metabolic disorder of amino acid metabolism in caused by deficiency in branched chain ketoacid dehydrogenase enzyme leading to the accumulation of branched chain amino acids (BCAA) such as leucine, isoleucine, and valine. Untreated, the buildup of these acids leads to progressive metabolic ketoacidosis, encephalopathy, and cerebral edema. The condition is typically detected on metabolic newborn screen and is treated by limiting dietary intake of natural protein containing branched chain amino acids while providing adequate essential non branched chain amino acids via special medical food [1]. Metabolic crisis can be triggered by catabolic states releasing branched chain amino acids from skeletal muscles or by decreased natural protein tolerance due to physiologic stress. In individuals with MSUD, acute illness can lead to a metabolic crisis, cerebral edema, and irreversible neurologic injury. Although MSUD has been known for decades, it is a rare disease and only recently have guidelines for its management been published [2,3]. This report discusses a case in which a child's metabolic crisis was not controlled by the strategies included in these guidelines. We report the use of growth hormone as an adjuvant therapy, which is referenced by older literature for MSUD [4] and some recent case series in other

inherited metabolic disorders [5–8] and is supported by recent research in pediatric burn patients [9].

The *Nutritional Management Guidelines for Maple Syrup Urine Disease* published in 2014 and guidelines published by Genetic Metabolic Dietitians International in 2013 provide recommendations for care of patients in metabolic crisis based around aggressive nutritional management to promote anabolism including supplying up to 150% of usual energy intake, BCAA free protein for 1–2 days, supplementation of valine and isoleucine, and electrolytes. In addition to these nutritional management strategies, seriously ill patients may need insulin infusion, dialysis, hemofiltration, parenteral nutrition and/or tube feeding while the source of the decompensation is addressed [2,3]. Protein anabolic pharmacotherapy has potential to complement nutritional management and ideally reduce the need for dialysis and other invasive interventions during periods of metabolic stress. Because inherited metabolic disease is rare, the literature on protein anabolic pharmacotherapy in this population is limited [4,10]. However, the protein catabolic state of severely burned children has been well documented, and several high-quality studies have been performed on protein anabolic pharmacotherapy in that population [9]. This paper proposes that this body of literature represents a valuable fund of knowledge which could be applied to the care of children with inherited metabolic disease.

2. Case summary

KP is a 11-year-old Hispanic male with MSUD detected on newborn metabolic screen and confirmed by blood amino acids with characteristic elevations including allosioleucine and the absence of elevation of glycine and alpha-ketoglutarate. DNA testing was offered and not pursued after family decided that they would not attempt any future pregnancy. Biopsy for enzyme assay was not requested since amino acid levels clearly indicated classical MSUD. Because he had an early episode of sepsis and congenital nystagmus, we screened for congenital disorders of glycosylation by analysis of transferrin with normal results. Nystagmus gradually resolved after surgery for exotropia. Growth was normal, there were no dysmorphic features and development was typical for a child with MSUD with history of episodes of MSUD crisis; therefore, other diagnostic genetic or endocine testing was undertaken. He had two significant episodes of severe metabolic decompensation before age 7. One episode was complicated by significant cerebral edema which required intensive care unit stay and use of mannitol. He had not received dialysis in the past. He has baseline learning and behavioral issues that are suspected to be related to MSUD and attention deficit hyperactivity disorder (ADHD). Prior to admission, his nutritional prescription was as follows: 45 kcal/kg total calories, 2.2 g/kg total protein, 0.18–0.2 g/kg/day natural protein, 275–500 mg/kg leucine, 240–450 mg/kg isoleucine, 325-500 mg/kg valine. He demonstrated good dietary compliance with the assistance of his mother and had stable blood amino acids for several months prior to admission with goal intake of 7 g of natural protein daily. He had normal growth velocity along the 10th percentile (Table 1).

He presented in septic shock and metabolic crisis with cerebral edema in May 2019 which required intubation, hemodialysis, and insulin continuous infusion in the Pediatric Intensive Care Unit (PICU). He was found to have pancreatitis and pneumonia with cavitary Group A *Streptococcus* infection of the lung. He was provided with trophic feeds of BCAA free formula for bowel rest in the setting of pancreatitis and abdominal distention while on vasopressor support. Dextrose and

intravenous lipid provided caloric supplementation and BCAA free total parental nutrition was provided. During the initial 6 days, natural protein was held because of persistently elevated levels of leucine. This prolonged restriction later lead to concern for negative amino acid balance, especially in the setting of recent hemodialysis. His recovery was complicated by pulmonary thrombosis and renal infarction due to hypercoagulable state during the metabolic crisis. Renal function was normal. He received three doses of dexamethasone peri-extubation without signs of worsened metabolic status post steroid treatment despite the risk of steroids to worsen metabolic status in MSUD due to net catabolic effect. After his neurologic and metabolic states stabilized, he was transferred to the pediatric progressive care unit to complete his course of antibiotics, resumption of his home feeds, and weaning off intravenous (IV) fluids. Because the patient's leucine levels remained high, his natural protein was restricted to 3.5–4 g/day with periodic attempts to increase back to 7 g. During this period his weight decreased by 1.1 kg. Weight was expected to be an inaccurate measure of nutritional status given major fluid shifts but decrease may be a reflection of negative nitrogen balance due to muscle wasting because of inactivity and possibly prolonged catabolism due to over restriction of leucine on admission.

While on the progressive care unit, he developed increased work of breathing, biphasic stridor, and tracheal tugging concerning for subglottic or tracheal stenosis. He was transferred back to the PICU for close monitoring in preparation for laryngoscopy and possible intervention under anesthesia. In preparation for the physiologic stress of the procedure, his IV fluids were increased to twice maintenance with D10W+ 0.9%NS. He went to the operating room (OR) on June 5th and was found to have 70% stenosis of the sub-subglottic region and underwent tracheostomy. A nasogastric tube was placed in the OR for continued administration of BCAA free formula. Because he was at high risk for decannulation due to his impulsive ADHD, his otolaryngologist required that he have sedation and muscle relaxation for a full 7 days until his first trach change. During that period, natural protein of 4 g/day was provided via PediaSure®, valine and isoleucine supplements were continued, intralipids were resumed daily for extra calories, and glucose infusion rate of no less than 6 mg/kg/min was maintained with D10W+ 0.9%NS. His amino acids, including all essential amino acids, were followed closely once or twice daily to monitor for catabolic shifts in the setting of post-operative physiologic stress and prolonged immobility.

Despite aggressive nutritional management, his amino acids trended up and continuous insulin infusion and increased dextrose to 8 mg/kg/min were started on June 8th to stimulate anabolism while he remained immobilized. He was hemodynamically stable, required only continuous airway pressure for respiratory support, and was without sign of end organ dysfunction on laboratory monitoring. In the evening on June 11th his AA levels were found to be markedly elevated with leucine 1050 nmol/mL and he developed a metabolic acidosis to 7.23 with an anion gap of 15 indicating a catabolic state (Fig. 1). He had altered mental status with decreased ability to follow commands. Dialysis was considered but would have been counterproductive overall given his negative protein balance over the course of admission. After consultation with other metabolic genetics colleagues and review of the available case reports and short case series reporting the use of growth hormone in children with inherited metabolic disease [4–8], a 3-day course of growth hormone was started and his natural protein was increased to 7 g to facilitate protein anabolism. No changes to respiratory support or infusions were made. Within 24 h he had normalizations of his anion gap and metabolic acidosis, his ability to follow commands improved, but his AA levels remained stably elevated. His first trach change was completed the next day on June 12th and sedation and paralysis were weaned. During airway interventions his branched chain amino acid free formula was held for most of the day and natural protein was again decreased to 3.5 g daily given his high AA levels (leucine still >1100 nmol/mL). As his activity level increased on June 13th, his serum branched chain amino acids began slowly down trending but leucine

Table 1
KP's anthropometrics prior to admission.

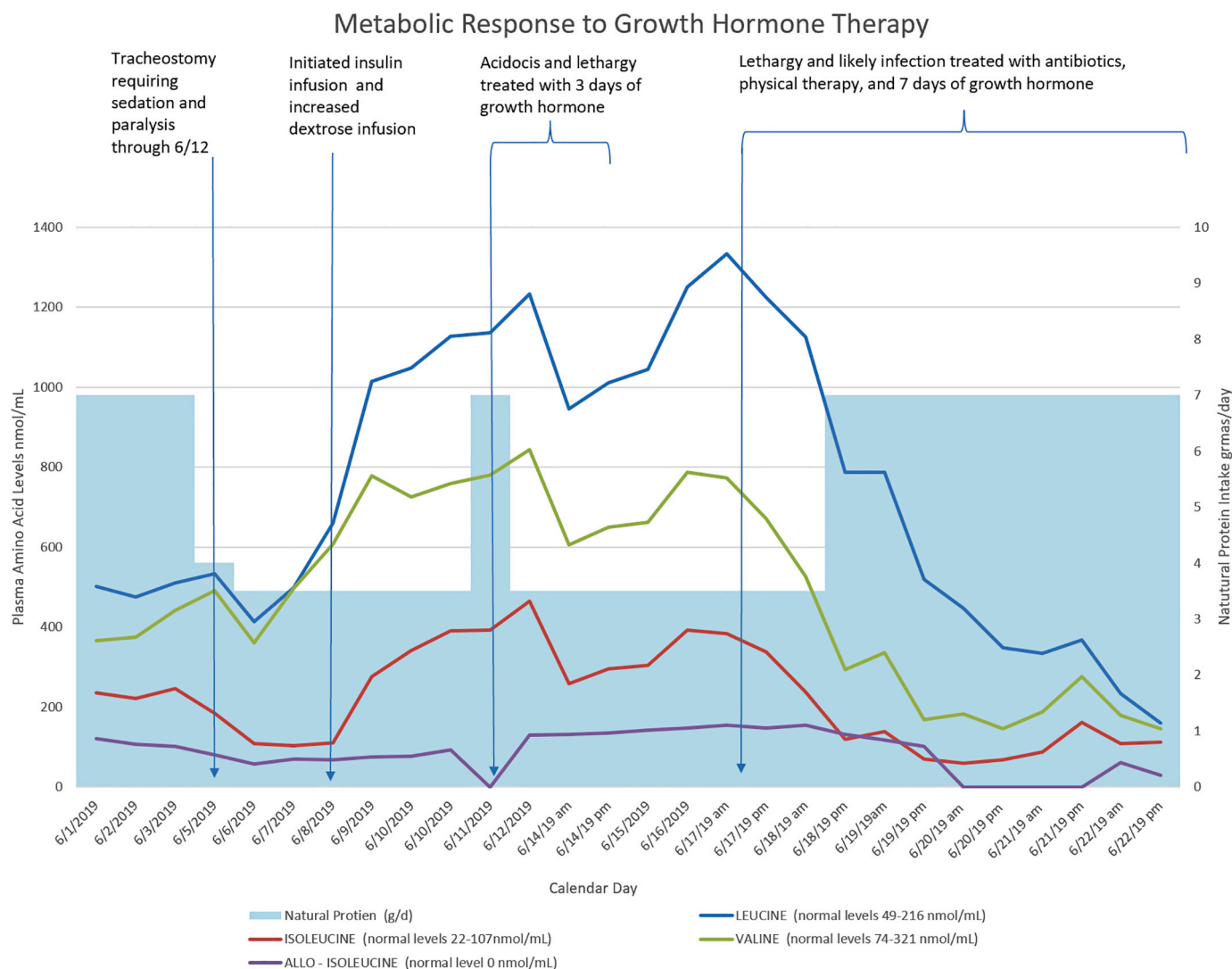| Anthropometrics prior to admission		Percentile	Z- score
Weight	38.2 kg	40th	−0.25
Height	136 cm	4th	−1.75
BMI	20.7	84th	0.98

Fig. 1. Graphical representation of metabolic crisis and response to interventions. Branched chain amino acid levels trended up and remained markedly elevated despite standard interventions including natural protein restriction, caloric supplementation with dextrose, and continuous insulin infusion to stimulate anabolism. Clinical signs of metabolic crisis and altered mental status were treated with short courses of growth hormone which correlated with improved mental status and improved branch chain amino acid levels.

remained close to 1000 despite continuous insulin infusion and optimization of nutritional management.

His BCAA levels began rising again on June 16th and he became lethargic on June 17th with a leucine level of 1322 nmol/mL. There was concern for possible infection as he had up-trending serum white blood cells and platelets, with red and white blood cells in his urine. Urine culture grew 25,000 *Enterobacter cloacae,* and he was treated with IV antibiotics. Serum ESR and CRP were elevated but overall down trending from his recent surgery. His renal ultrasound was normal and serum creatinine remained normal. Again, dialysis was discussed for treatment of metabolic crisis with altered mental status, but his mother did not consent. Continued literature search regarding protein anabolic pharmacotherapy options lead the authors to a body of literature reporting the use of growth hormone to treat the protein catabolic state of severely burned children with positive protein balance kinetics measured by radioisotope tracers [9]. A second course of growth hormone was started, this time for 7 days in conjunction with physical therapy as tolerated. BCAA levels stabilized then down trended sharply on June 19th to leucine 519 nmol/mL, isoleucine 70 nmol/mL, and valine 169 nmol/mL. His natural protein was increased to 7 g/day and his BCAA levels did not rise. He passed a modified barium swallow study and was transitioned

back to his home MSUD formula orally with nasogastric (NG) supplementation. He was allowed to take solids foods with mom keeping a protein count with a goal of 7 g per day so that natural protein provision was transitioned from formula to solid food. Enteral formula was supplemented as needed to achieve protein goal for the day. Insulin and dextrose were weaned off. By the completion of his second course of growth hormone on June 24th, his AA levels had normalized and he was tolerating his home nutrition and supplement regimen. He had regained his admission weight and continued to gain weight along the 50-60th percentile. He required prolonged admission for tracheostomy training and physical rehabilitation.

After resolution of his metabolic crisis, he displayed increased natural protein tolerance and was discharged on 12 g/day of natural protein. His natural protein prescription was gradually decreased to 8 g/day over a twelve-month period with close monitoring of his serum amino acid levels and growth curves. This period of increased natural protein tolerance is attributed to correction of his hospital acquired muscle wasting as well as the onset of puberty. He is scheduled for a laryngoscopy for evaluation of laryngotracheal reconstruction. Parental informed consent was obtained for the publication of this case report.

3. Results and discussion

3.1. Discussion of nutritional management

Current pediatric critical care guidelines recommend estimating the Resting Energy Expenditure (REE) as using the Schofield equation without stress factors, in the absence of indirect calorimetry [11]. For KP, his REE is estimated at 1340 kcal/day, or 44 kcal/kg. Estimated protein needs during critical illness are at least 1.5 g/kg [12]. We initiated nutritional support immediately upon admission. He was transitioned from parental to enteral, then to oral nutrition while maintaining calorie provision from 150 to 200% of REE. The calories provided well exceeded typical provision for critical illness, and later, his ambulatory state. Non BCAAs were also provided in excess of the recommended need for pediatric critical illness. This intensive approach was taken for KP with the intent to reverse catabolism and promote anabolism, which would result in the reduction of plasma leucine. However, his leucine levels remained persistently elevated despite seamless provision of aggressive nutrition support. Table 2 compares the protein and energy provided to standard of care ranges in ambulatory and acute illness [11–12].

3.2. Discussion of response to growth hormone

This case demonstrates that growth hormone can be used as a rescue intervention when standard of care nutritional therapy and use of insulin are unable to reverse metabolic crisis. Use of growth hormone to treat metabolic crisis in maple syrup urine disease has been mentioned in medical literature as early as 1968 [4]. However, this is the first recent case report documenting the protein anabolic response to growth hormone in inherited metabolic disease. The administration of growth hormone during the first course was effective at correcting clinical signs of metabolic encephalopathy, resolving his acidosis, and stabilizing his plasma leucine levels. In contrast, the rapid decline in his plasma amino acid levels with the second course, even in the setting of increase natural protein intake, was attributed to the protein anabolic effects of growth hormone augmented by the physiologic stimulus of physical activity Figure 1.

3.3. Discussion of pharmacology and safety

There are no known studies on the most appropriate dose of growth hormone in metabolic crisis. In this case, we used the standard dose approved for the available manufacturer for prepubertal children, which is 0.3 mg/kg/week divided by 7 for a daily dose of 0.04 mg/kg/day [13]. This dose represented a large volume and eight subcutaneous injections daily because the concentration/product available for use on our hospital's formulary. The product on formulary Genotropin MiniQuick® (somatropin) 0.2 mg injections. Several of the injections were able to be given while patient was still under sedation. By the time patient was off sedation, he only had a couple of days left of the somatropin, so the hospital was unable to purchase another somatropin product. The large number of injections may limit the feasibility of the use of this project in some clinical scenarios, but other products can be used to avoid this limitation.

There are no studies of the safety profile of growth hormone for short term use. The clinical practice guidelines for the use of growth hormone for growth hormone deficiency and idiopathic short stature discusses rare side effects of chronic administration. These rare side effects include: decreased insulin sensitivity, changes in cortisol metabolism which could theoretically unmask an undiagnosed adrenal insufficiency, theoretical increase risk of neoplasm in susceptible children, and problems associated with rapid linear growth including slipped capital femoral epiphysis (SCFE), increased scoliosis, and intracranial hypertension. The incidence of these adverse effects is reportedly <3% in children undergoing long term therapy and do not require specific surveillance [14]. Of these potential adverse reactions, decreased insulin sensitivity and altered cortisol metabolism would pose the greatest risk to a child in metabolic crisis. These effects have not been specifically studied or reported with acute administration of growth hormone.

The use of growth hormone in critically ill children has very limited evidence. Dysregulation of GH and insulin like growth factor 1 axis has been demonstrated in critically ill adults and children [15,16]. After the development of recombinant GH in the 1985, several studies in critically ill adults showed positive safety profiles and improvement in nitrogen balance [17]. However in 1999 a pair of prospective, double blind, randomized control trials of high dose growth hormone in adults with critical illness including surgery, trauma, and sepsis showed increased morbidity and mortality in the treatment group despite improved nitrogen balance [18]. The source of this increased mortality is unclear with some groups speculating that there may have been inadequate nutritional support, specifically glycine supplementation [17]. After this study, further exploration of GH in critical care settings has been limited. The Growth Hormone Research Society published a critical evaluation of the safety of recombinant GH administration in the Journal of Clinical Endocrinology and Metabolism in 2001. It states "Any GH treatment other than replacement in those who have GH deficiency should be considered as pharmacological. In specific conditions where pharmacological treatment with GH is being considered, standard safety data should be collected and protocols for new drug development followed. The detrimental outcome of high-dose GH treatment in intensive care patients cannot be extrapolated to other conditions, which may potentially benefit from GH treatment [19]."

3.4. Focused literature review

A literature search of pharmacologic effects of growth hormone on protein anabolism lead the author to a useful literature review by Diaz et al. discussing the catabolic state of burn victims and the effects of various pharmacologic agents on protein kinetics in severely burned children. We found this review to be relevant to our patient because it demonstrates the net protein anabolic effect of growth hormone. They report that growth hormone administered at 0.2 mg/kg once daily for 19 days increased the net protein balance of treated children by 67% compared to controls. Our patient responded well to standard dosing approved for treating growth hormone deficiency, however it is worth noting that the dose reported in the burn literature is five times greater than the dose used in our patient. Diaz et al. also summarized results of

Table 2

Comparison of recommended and provided nutrition in ambulatory and acute illness settings. KP was consistently provided with energy and protein in excess of recommended guidelines to promote anabolism.

	Ambulatory goal in MSUD	Ambulatory goals for KP prior to admission	Recommendations for child in critical care	Recommendations for acutely ill ambulatory child	Provision during acute and critical illness for KP
Natural Protein (g/day)	5–8 g/day	7 g/day	Not applicable	Not applicable	0–7 g/day
Total Protein (g/kg)	1.2–1.8 g/kg	1–1.5 g/kg	>1.5 g/kg	Not available	2–3.5 g/kg
Energy (Kcal/kg)	40–90 kcal/kg	45–55 kcal/kg	34 kcal/kg	44 kcal/kg	52–68 kcal/kg
Percent Resting Energy Expenditure	Not applicable	Not applicable	100% REE	130% REE	150% REE

studies of metformin, insulin, and testosterone in burned adults as well as oxandrolone, insulin, propranolol, and ketoconazole in burned children. Insulin, which has been a staple of treatment of metabolic crisis in children with MSUD for decades, was reported to increase both muscle protein breakdown and synthesis with a net increase in protein balance by 120% after treatment with 0.432 units/kg/h for 7 days in burned children. Ketoconazole showed no significant effect. Propranolol showed increase in net protein balance by 183% in burned children after treatment with 6.3 mg/kg/day divided in four doses per day for 2 weeks. Oxandrolone is a synthetic testosterone analogue with minimal virilizing effects which was shown to increase net protein balance by 107% after treatment with 0.1 mg/kg twice daily for 5 days [9].

Specific searches of the literature for studies of these drugs in MSUD revealed that metformin has a single study published [20]. This study demonstrated decrease in branched chain amino acid derived ketoacidosis and improvement in mitochondrial metabolic function in cultured patient fibroblasts and reports that the effects were preserved in a MSUD mouse model. There are no published clinical trials or case reports of metformin or any of the other reviewed pharmacotherapies in patients with MSUD.

Literature search for evidence supporting the use of growth hormone in children with MSUD revealed a single case report from 1968 which described MSUD metabolic crisis and states "The use of human growth hormone at such times has been considered. A fall in plasma amino acid levels has been observed following its administration but its value in clinical use is not yet established" [4]. More recently a physician William Nyhan published an article online for MSUD Family Support Group on the treatment of the acute crisis in MSUD. He described the use of insulin and glucose to promote anabolism and reverse catabolic states. He adds "More recently we have been using human growth hormone, a very powerful anabolic agent in this situation. At first, we only turned to growth hormone when amino acids plus insulin had not turned things around. More recently I have employed growth hormone earlier and have not needed to use insulin" [10].

Literature review of growth hormone in the treatment of other inherited disorders of metabolism revealed a few limited case series. D. Marsden et al. studied five patients with organic acidemias, two of which demonstrated decreased growth hormone secretion to stimulation challenge and reported increased protein tolerance of 20–60% with growth hormone treatment [5]. M. Al-Owain et al. report improved linear growth but no change in serum methylmalonic acid concentrations in two children with methylmalonic acidemia found to have growth hormone secretory deficiency [6]. C—H Kao et al. reports the use of growth hormone in four neonates with methylmalonic acidemia and observed weight gain and distinct improvement in skin erosions with indeterminant effect on serum propionyl carnitine levels [7]. H. Niinikoski et al. treated four patients with lysinuric protein intolerance with growth hormone for 3–4.5 years and reported improvement in height standard deviation scores and no episodes of hyperammonemias [8].

4. Conclusion

This case report demonstrates positive response to the use growth hormone as a pharmacologic rescue in MSUD metabolic crisis refractory to standard therapy. Literature search suggests that more research is needed into protein anabolic pharmacology in inherited metabolic disease and that studies performed in pediatric burn patients may be relevant to this inquiry. Randomized controls trials of protein anabolic pharmacotherapy have been performed in the pediatric burn population as reviewed by Diaz et al. [9]. Promising interventions from these studies could be assessed for application in inherited metabolic disease to reverse catabolic processes and improve nitrogen balance. Although metabolic disease and severe burns are not typically considered together, these apparently disparate catabolic conditions may unlock clinical and biochemical insight to understand their pathophysiology

and improve metabolic care for both populations. The use of protein anabolic pharmacotherapy in inherited metabolic disease could reduce the need for dialysis and other invasive interventions in the management of acute metabolic crisis. Thus, protein anabolic pharmacotherapy with acceptable safety profiles and improvement in net protein balance should be considered as candidates for further study as adjuvants to standard of care management in inherited disorders of amino acid metabolism.

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