Introduction

Inherited metabolic disorders present great challenges for patients, families, and healthcare professionals. In amino acidopathies, treatment is for life and dietary management consists of attempting to provide nutrition for growth and development while keeping serum concentrations of potential toxins to a minimum. Medical nutrition therapy for inherited metabolic disorders requires attention to more than just protein, calories, and micronutrient recommendations, as will be seen in this case study.
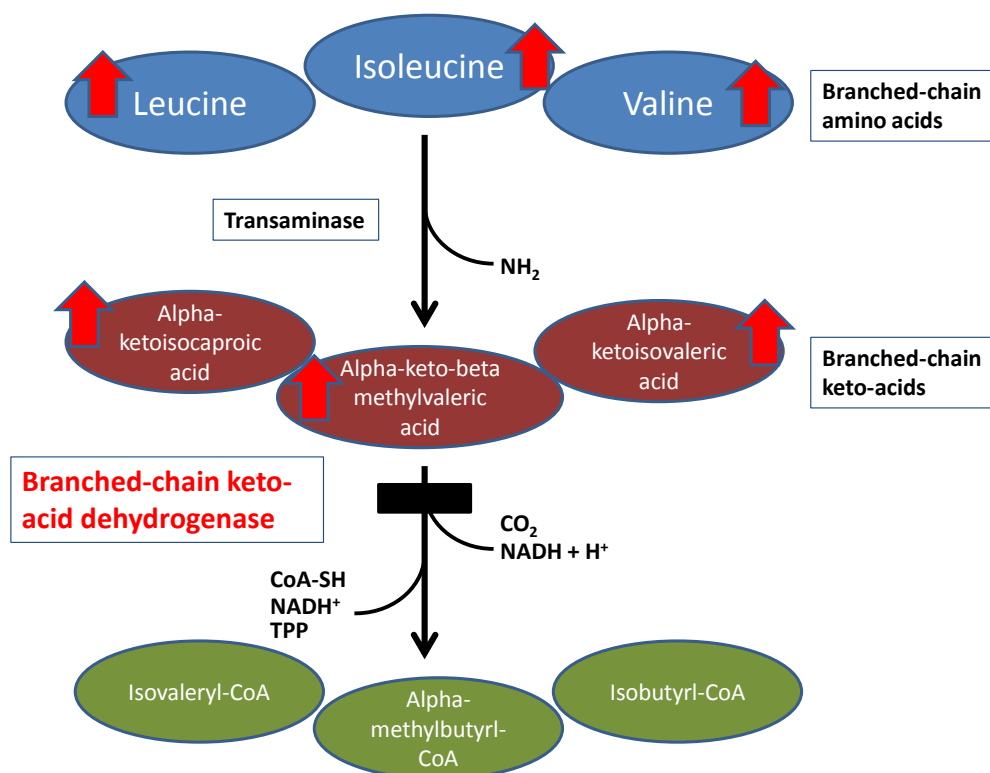
Maple syrup disease (MSUD), or branched-chain alpha-ketoaciduria, is a genetic disorder inherited in an autosomal recessive manner; both the mother and father of an affected infant must have passed on a defective gene for the branched-chain keto-acid dehydrogenase (BCKAD) enzyme[1]. They will each carry one copy of the defective gene but will nevertheless be unaffected[1]. Enzyme activity has to be reduced to perhaps less than five percent of "normal," requiring two defective copies, before toxic metabolites of MSUD can accumulate to dangerous concentrations (Joseph Muenzer, MD, PhD, personal communication, October 18, 2013). Therefore, many parents have no knowledge of their carrier status until an affected child is born. As approximately 1 in 215 persons carries a defective gene, MSUD has an estimated incidence ranging from 1 in 185,000 to 1 in 200,000 in the general population[2,6,8].

For treatment of Maple Syrup Disease (MSUD), metabolic dietitians must adjust relative amounts of protein, calories, and a special metabolic food containing all amino acids except for the branched-chain amino acids (BCAAs) in order to compensate for changes in weight or serum concentrations of BCAAs. Though the more common concern is for accumulation of toxic metabolites when BCAAs are elevated in the blood, metabolic dietitians are also aware of the danger of poor growth or deficiencies if all essential nutrients are not provided. They manage the MSUD diet in an attempt to keep serum concentrations of amino acids not too high, not too low, but "just right." It was unusual,

therefore, that a patient of UNC Department of Pediatrics, Division of Genetics and Metabolism came to present with an acrodermatitis enteropathica-like rash most likely due to a deficiency of isoleucine - one of the very amino acids whose elevation is a hallmark of MSUD.

MSUD is one of many inherited metabolic disorders in which impaired enzyme activity leads to accumulation of toxic substrates in untreated individuals[1]. The mitochondrial branched-chain ketoacid dehydrogenase complex (BCKAD) is responsible for irreversible oxidative decarboxylation of the three branched chain amino acids, leucine, isoleucine, and valine[1]. BCAAs are not metabolized properly and both branched-chain ketoacids and the BCAAs themselves accumulate in abnormally high amounts (Figure 1)[1]. MSUD is named for an accumulation of a volatile and odorous metabolite of branched-chain amino acid hydroxylation called sotolone that occurs only with impaired decarboxylation, and can be detected in an infant's cerumen and urine[3]. MSUD's consequences can be as severe as death in the first one to two weeks of life if untreated[1,6]. Damage occurs through leucinosis, the accumulation in the brain of leucine and its corresponding ketoacid alpha-ketoisocaproate[4]. The result is a complex neurochemical syndrome involving altered brain protein accretion, disturbed neurotransmitter synthesis, abnormal cell volume regulation, atypical neuron growth, and irregular myelin synthesis[4]. Abnormally high concentrations of leucine also cause neurotoxicity by interfering with the transport of other large neutral amino acids across the blood-brain barrier, namely tryptophan, methionine, tyrosine, phenylalanine, valine, histidine, and threonine[4]. The ketoacid alpha-ketoisocaproate may additionally deplete glutamate in the brain and diminish brain energy metabolism, causing damage[5].

Figure 1: MSUD Biochemical Pathway and Metabolite Accumulations

Leucine

Isoleucine

Valine

Branched-chain amino acids

Transaminase

NH_2

Alpha-ketoisocaproic acid

Alpha-keto-beta methylvaleric acid

Alpha-ketoisovaleric acid

Branched-chain keto-acids

Branched-chain keto-acid dehydrogenase

CO_2
$NADH + H^+$

CoA-SH
$NADH^+$
TPP

Isovaleryl-CoA

Alpha-methylbutyrl-CoA

Isobutyryl-CoA

Reports of the disorder first appeared in scientific literature in 1954 when four cases of a rapidly progressing lethal encephalopathy during the first week of life was noted to be accompanied by a peculiar odor of maple syrup in the urine[6]. By 1960, the enzymatic cause of MSUD was known and patients of the disorder were able to be treated before the disorder could result in death[6]. Today, because newborn screening can now implicate MSUD before clinical symptoms appear, proper treatment of MSUD can allow a benign neonatal course, normal childhood growth and development, and a low rate of hospitalization, although normal growth is not guaranteed[1,7]. There are many adult patients of MSUD currently followed and treated by metabolic clinics across the country that live full and healthy lives[8].

Acute decompensation from MSUD can occur at any age[7]. Risk for complications are due to excessive consumption of dietary protein; therefore, much of the lifelong treatment for the disorder focuses on avoiding problems caused by improper diet[7]. Nevertheless, most severe cases of MSUD

decompensation actually arise from catabolism of body tissues at times of fasting, injury, excessive exercise, surgery, or physical stress[9]. Best practices include immediate action taken during illness to minimize catabolism of body protein through intravenous provision of glucose and enteral or parenteral BCAA-free protein depending on the patient's ability to use the gastrointestinal tract[10]. Insulin may also be provided to stimulate anabolism[10]. Even when well, and especially during infancy when growth is rapid and illnesses can be common, medical nutrition therapy for the patient of MSUD will require regular alterations to nutrient content and amino acid balance.

Description of the Case

In early July 2013, the UNC Department of Pediatrics, Division of Genetics and Metabolism first saw a 22 day old boy diagnosed with MSUD in the state of Florida after an abnormal newborn screen with very elevated leucine and leucine-to-phenylalanine ratio, as well as elevated valine. When newborn screening results were available at 6 days of life, the patient had been admitted to the hospital and begun on IV glucose, BCAA-free formula, and supplemental isoleucine and valine. Isoleucine and valine are known to decrease in concentration at a much greater rate than leucine, thus supplementation is necessary for the protein anabolism that will lower leucine concentration. Confirmatory plasma amino acids demonstrated the presence of alloisoleucine, verifying the diagnosis. Serial amino acids were followed (Table 1) and he was restarted on dietary leucine at day 12 of life (Table 2). After a stay of nearly two weeks in the hospital in Florida, the infant was discharged and three days later was seen at the UNC Genetics' outpatient clinic. His mother had moved away from his father and nearer her own mother for support.

Table 1. Serum concentrations of BCAAs over time

Day of life	Weight (kg)	Leucine (umol/L)	Isoleucine (umol/L)	Valine (umol/L)	Day of life	Weight (kg)	Leucine (umol/L)	Isoleucine (umol/L)	Valine (umol/L)
2	3.02	1055	----	367	43	----	409	98	43
6	3.07	2665	675	654	58	----	500	159	64
8	----	1309	355	316	68	4.6	----	----	----
9	3.37	1123	----	----	69	----	350	18	72
10	----	421	355	316	69	----	444	60	65
11	3.32	25	1074	1460	78	4.68	39	249	57
13	3.42	25	1074	1460	79	4.6	43	190	66
14	----	72	695	1221	82	4.66	----	----	----
15	3.48	68	263	662	98	4.89	----	----	----
16	3.49	47	8	315	105	4.88	----	----	----
17	----	178	3	268	107	----	474	30	233
18	3.49	65	58	243	112	----	15	204	396
19	3.58	60	68	354	124	5.15	24	850	472
22	3.77	20	327	612	147	----	73	807	79

At his first clinic visit he was found to have gained weight, prompting a change in the most current formula prescription from Florida to increase calories and protein, both intact and BCAA-free (Table 2). His formula included BCAA-free formula, regular infant formula, and supplemental isoleucine and valine. His analysis of amino acids from day 19 of life showed leucine to be slightly low (Table 1), but otherwise the patient's BCAAs were within normal reference range and he clinically appeared healthy. The patient's mother was told that the prescribed volume of metabolic formula should be consumed in its entirety each day and that if more or less volume was required for two days in a row, contact with the UNC metabolic team would be necessary for a dietary adjustment. Metabolic formula prescriptions involve weighing by gram all of the components of the formula and it is important, especially in an outpatient setting, to know whether or not a patient like this one is receiving more or less of the calories, protein, and BCAAs that his team believes him to be receiving. Before he left his first

clinic visit, blood was taken for an amino acid analysis and the patient's mother was instructed to take a blood spot each week and mail it to the clinic for analysis. His next clinic visit was scheduled for three weeks later.
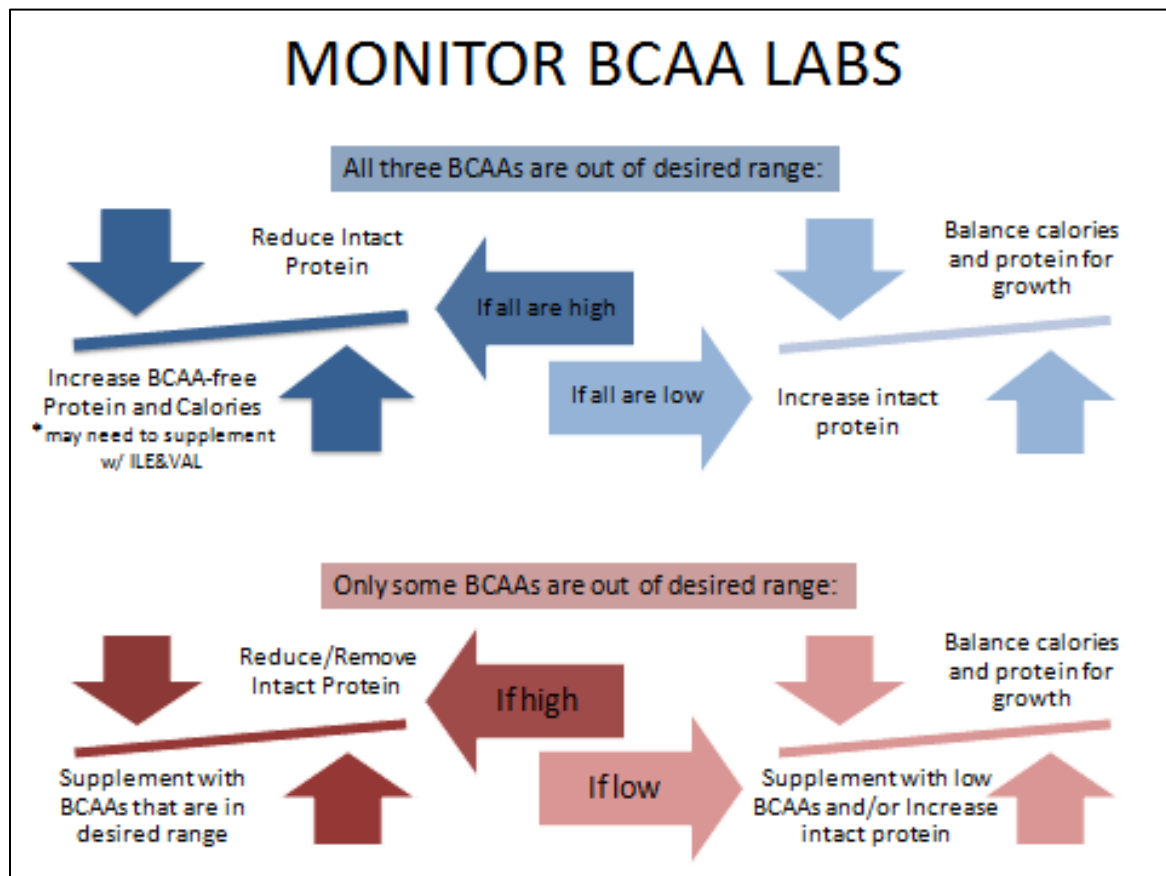
Table 2. Dietary Prescriptions with BCAAs Supplied as Compared with Recommendations

Day of Life	Leucine (mg/kg)	Isoleucine (mg/kg)	Valine (mg/kg)	BCAA-free formula (grams)	Regular infant formula (grams)	Protein-free calorie powder (grams)	Supplemental Isoleucine (mL of 1% solution)	Supplemental Valine (mL of 1% solution)	Supplemental Leucine (mL of 1% solution)
6	0	140	140	81	----	----	43	43	----
8	0	130	130	87	----	----	40	40	----
9	0	50.4	50.4	87	----	----	17	17	----
10	0	50.4	35.6	87	----	----	17	12	----
11	131	48.4	49	70	22	----	----	----	16
13	113	40.6	41.1	60	19	----	----	----	15
14	71.6	21.3	21.6	68	10	----	----	----	12
15	66.8	18.9	19.1	77	9	----	----	----	12
16	89.5	52.3	53	68	25	----	----	----	----
17	89.5	52.3	53	68	25	----	----	----	----
18	89.5	52.3	53	68	25	----	----	----	----
19	76.8	50.4	61.1	70	22	----	2	5	----
22	79.6	51.8	60.4	72	24	----	2	5	----
26	86	51	51	67	29	----	----	----	----
29	86	51	51	67	29	----	----	----	----
43	86	51	51	67	29	----	----	----	----
54	81.3	52.5	58	69	26	32	2	4	----
58	81.3	52.5	58	69	26	32	2	4	----
63	0	5	15	75	----	50	2	6	----
64	46.9	32.4	37.8	50	15	24	2	4	----
65	71.9	47	57.6	72	23	32	2	6	----
68	62.5	40.8	50	72	23	32	2	6	----
69	62.5	40.9	50	72	23	32	2	6	----
69	62.5	40.9	50	72	23	32	2	6	----
70	62.5	47.4	50	72	23	32	5	6	----
75	62.5	47.4	50	72	23	32	5	6	----
78	62	47	49	72	23	32	5	6	----
79	32.6	30	32.3	72	12	44	5	6	----
80	32.6	30	32.3	72	12	44	5	6	----
81	62.5	47.4	50	72	23	32	5	6	----
82	61.7	46.8	49.4	72	23	32	5	6	----
84	72	42	69	83	27	18	----	9	----
94	72	42	69	83	27	30	----	9	----
98	69	40	59.4	83	27	5	----	9	----
105	69	40.1	59.5	83	27	5	----	9	----
107	69	40.1	59.5	83	27	5	----	9	----
112	69	40.1	59.5	83	27	5	----	9	----
114	67.7	59.7	42.9	100	20	----	10	9	----
118	77.9	65.6	59.6	97	23	----	10	5	----
124	73.8	62.2	56.5	97	23	----	10	5	----
133	83.3	58.3	55	72	26	22	5	1	----
147	83.3	58.3	55	72	26	22	5	1	----

Recommendations for dietary amino acids[9]:   Leucine: 40-100 mg/kg   Isoleucine: 30-90 mg/kg   Valine: 40-95 mg/kg

When BCAAs are outside normal range, metabolic dietitians must make decisions to increase or decrease intact protein (protein containing all amino acids) and other diet components to ensure growth and development but bring potentially toxic compounds under control (Figure 2). Ten days after his visit, this patient's amino acid analysis from clinic was available, showing leucine was low but isoleucine and valine were elevated, as were several other amino acids. The patient's isoleucine and

valine supplementation were eliminated, but intact protein was increased in his diet to provide greater amounts of all three BCAAs.
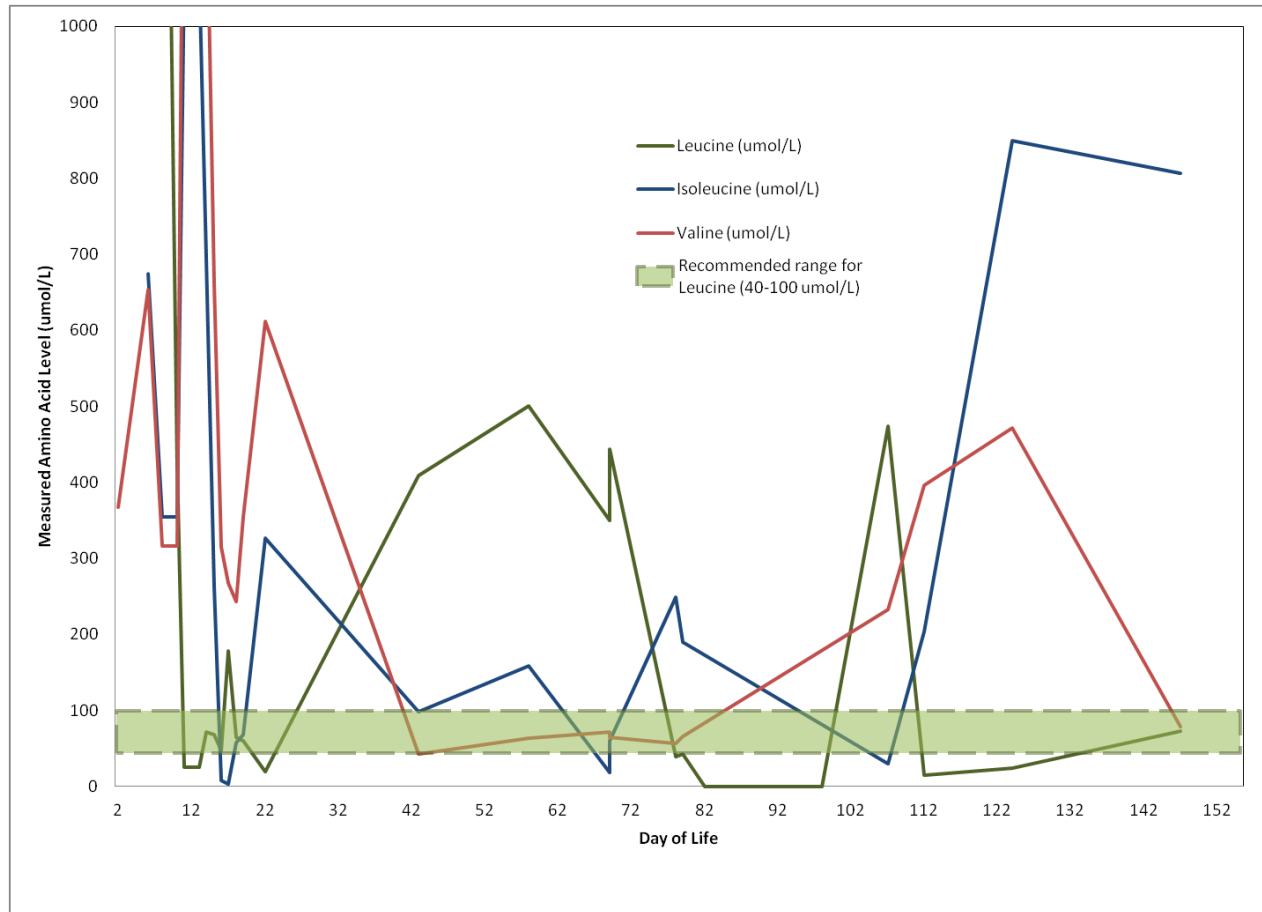
Figure 2: MSUD Decision Algorithm

MONITOR BCAA LABS

All three BCAAs are out of desired range:

Reduce Intact Protein

Balance calories and protein for growth

If all are high

Increase BCAA-free Protein and Calories *may need to supplement w/ ILE&VAL

If all are low

Increase intact protein

Only some BCAAs are out of desired range:

Reduce/Remove Intact Protein

Balance calories and protein for growth

If high

Supplement with BCAAs that are in desired range

If low

Supplement with low BCAAs and/or Increase intact protein

Blood spots sent by the patients' mother between clinic visits were never received, so the next time blood was taken for analysis of amino acids came eleven days after the adjustment to his diet at his clinic visit at 43 days of age. It was learned at this visit that he had been consuming 960 mL of formula, rather than the 720 mL he was prescribed, which would provide 165 kcal/kg if prepared as recommended. Despite this, he had had minimal growth since his last clinic visit. His formula was adjusted to decrease caloric density so that he could continue taking the volume he was demanding and protein-free calories were substituted for some of the BCAA-free protein he'd been receiving.

The next update on serum concentrations of amino acids came when the clinic amino acid analysis was returned at 54 days of age. His leucine was elevated and isoleucine slightly elevated, but valine was now low (Figure 3). Adjustments made by the metabolic dietitian involved reintroducing isoleucine and valine supplementation while decreasing intact protein (Table 2). Nine days later, results of a between-clinic blood spot amino acid analysis revealed that the patient's leucine had since gone higher as had isoleucine, and though valine had increased somewhat, it was still well outside a desirable range. As his leucine had remained high despite decreasing intact protein in his formula, a three-day correction regimen was attempted (Table 2). Over the three days, a removal and gradual reintroduction of leucine in the presence of adequate calories intended to reduce serum concentrations of leucine with protein turnover.

Two days after the completion of this correction regimen, however, the patient's mother contacted the on-call metabolic physician due to vomiting, diarrhea, and irritability. The physician recommended admission and made arrangements for measurement of plasma amino acids and urine ketones and for intravenous glucose to be started to avoid catabolism. A diaper rash and skin rash at the patient's neck were noted at admission that had reportedly started that day. After a stay of two days, the patient was discharged with a diagnosis of viral enteritis and dehydration. A positive urine culture prompted a ten day course of antibiotics and antifungal cream was prescribed for the neck rash.

Figure 3. Serum concentrations of BCAAs over time with target range for leucine

During the inpatient stay, a dried blood spot and blood for plasma amino acid analysis isolated on the same day were sent to Mayo Clinic because the analyzer at UNC was in need of repair. The blood spot amino acid analysis was available first, at day 70 of life, and showed elevated leucine and low isoleucine and valine. His supplemental isoleucine was increased. Five days later, however, the plasma amino acid analysis from Mayo Clinic was reported and concentrations of amino acids were significantly different from the earlier blood spot and isoleucine was in normal range. Blood had been taken the same day, however, so such a difference was unexpected. No further adjustments to the diet were made at this time; the next clinic visit was 3 days away.

On day 78 of life, the patient was once again seen in the UNC metabolic outpatient clinic as well as in general pediatric clinic, with whom his primary care had recently been established. His general pediatric team reported that he was acting normally, feeding appropriately, and afebrile but having frequent, watery diarrhea. The general pediatric team also noted the patient had an erythematous macular rash within his neck folds that appeared to be caused by yeast, a systolic murmur, and small fingernail scratches on his right cheek and nose. The patient's mother reported that the neck rash had previously resolved but had returned with recent illness and antibiotic use. Antifungal cream was again prescribed for his rash to be applied until two days after the rash cleared. His metabolic dietitian reported the patient was adequately receiving his metabolic formula, so blood for plasma amino analysis was drawn and he was scheduled to return three weeks later.

Unfortunately, just three days later he was again admitted to the hospital due to vomiting at the on-call metabolic physician's recommendation. He had been able to consume only half of his prescribed formula, was unable to tolerate liquids, had continuing diarrhea, and the rash in his diaper area was worsening. He was found to have multiple small sores on his face, right thumb, and left great toe. His mother reported that the diarrhea had not resolved since discharge from his last hospital stay. His stool was *Clostridium difficile* negative but his urine grew the same bacteria present on his last admission. Due to normocytic anemia, he was given a transfusion of red blood cells. His previously noted systolic murmur resolved post-transfusion. He was again provided intravenous glucose to avoid catabolism with his illness and after three days was discharged with a diagnosis of urinary tract infection and diarrhea possibly secondary to gastroenteritis due to antibiotic use. The rash was considered by his inpatient medical team to be consistent with fungal infection. He was again prescribed antifungal and barrier creams for the rashes.

Plasma amino acids taken at the last clinic visit and during his inpatient stay were available at day 83 of life (Table 1). Leucine and valine were low, isoleucine was high (Figure 3). Dietary adjustment

was made: intact protein and BCAA-free protein were increased, non-protein calories decreased, valine supplementation increased, and isoleucine supplementation discontinued (Table 2). Ten days later, the patient's mother reported spitting up to the metabolic dietitian, hence the formula was concentrated with the addition of non-protein calories.

On day 98 of life, he was seen in metabolic outpatient clinic, where his mother reported large volumes of spitting up and frequent loose stools. He had reportedly received only 600-720 mL of his metabolic formula over the previous several days and was having about five small, loose green stools each day. Reflux was reported after feeding. His dietary prescription was decreased in volume to 720 mL to ensure that he received the nutrition his team believed him to be getting. The patient's mother reported that his rash had spread from his bottom to lower back, scalp, face, torso, and extremities in the previous five to seven days and had been peeling for the past three or four days. Upon examination of the rash by his physicians, an urgent appointment was scheduled with a pediatric dermatologist in a nearby, but off-site, location. Blood for plasma amino acid analysis was not drawn in the rush to get him to his dermatology appointment, but unfortunately due to car trouble, his mother was unable to get him there and his appointment was rescheduled.

Figure 4. Peeling erythematous rash on patient's neck, back, arms, and buttocks

Figure 5. Peeling erythematous rash on patient's ear and neck

Seven days later he had not yet been seen by a dermatologist and the patient was admitted for

his worsening rash (Figures 4,5). As the rash had the appearance of acrodermatitis enteropathica,

serum concentrations of zinc were analyzed and the zinc content of his metabolic formula was

calculated. His formula was found to contain more than adequate zinc and his blood concentration was

adequate. However, plasma amino analysis revealed that isoleucine was mildly depressed (Table 1, day

107 of life). With reintroduction of isoleucine supplementation, the rash quickly improved. As the

patient was MRSA positive on skin cultures, mupirocin was started and saline soaks and petrolatum

ointment were recommended for infection prophylaxis. Low serum IgA, IgM, and IgG concentrations

were also noted and suspected to be due to GI losses from chronic diarrhea. At discharge, the patient was prescribed a new dietary formula with increased isoleucine and valine supplementation, increased BCAA-free protein, and a reduced amount of a complete, but elemental, amino acid formula (Table 2). His dietary management continues to struggle to stabilize all three BCAAs in desirable range, but increased supplemental isoleucine is provided to ensure that he will not become deficient again.

Discussion

MSUD itself is rare, so infrequently encountered rashes similar to acrodermatitis enteropathica in this population warrant reporting. In 1993, Giacoia and Berry described the presentation of a severe rash in an infant that evolved over three weeks of dietary treatment consisting of protein only from BCAA-free formula[11]. Concurrent with the rash were loose stools and depressed hemoglobin and hematocrit, as were seen in this case study patient before his transfusion at day 81 of life. Zinc sulfate therapy failed to resolve Giacoia and Berry's patient's rash, but within seven days of isoleucine supplementation the rash had healed. Koch et al. reported on recurrent eruptive dermatitis in two patients with MSUD who were fed only BCAA-free formulas after diagnosis until low amino acid concentrations of leucine, isoleucine, or both were noted and supplementation initiated[12]. These rashes also healed with increased dietary BCAAs. De Raeve et al., Bosch et al, and Tabanlioglu et al. all described patients of various metabolic disorders with acrodermatitis enteropathica-like rashes corresponding with low concentrations of BCAAs[13,14,15]. Tabalioglu et al. stated that the mechanism for the rash is as yet unknown but suggest it to be most likely related to a deficiency of one or more amino acids and proposed the name "acrodermatitis dysmetabolica" for the condition[15].

Many previous cases of isoleucine deficiency in the literature were reported to be iatrogenic, resulting from total exclusion or severe restriction of dietary BCAAs for an extended period of time[11-14]. Koch et al. state, "In MSUD the dermatitis occurs as a complication of treatment," highlighting the fact

that in an attempt to ensure that BCAAs are not in a toxic range, dietitians may cause a deficiency[12].
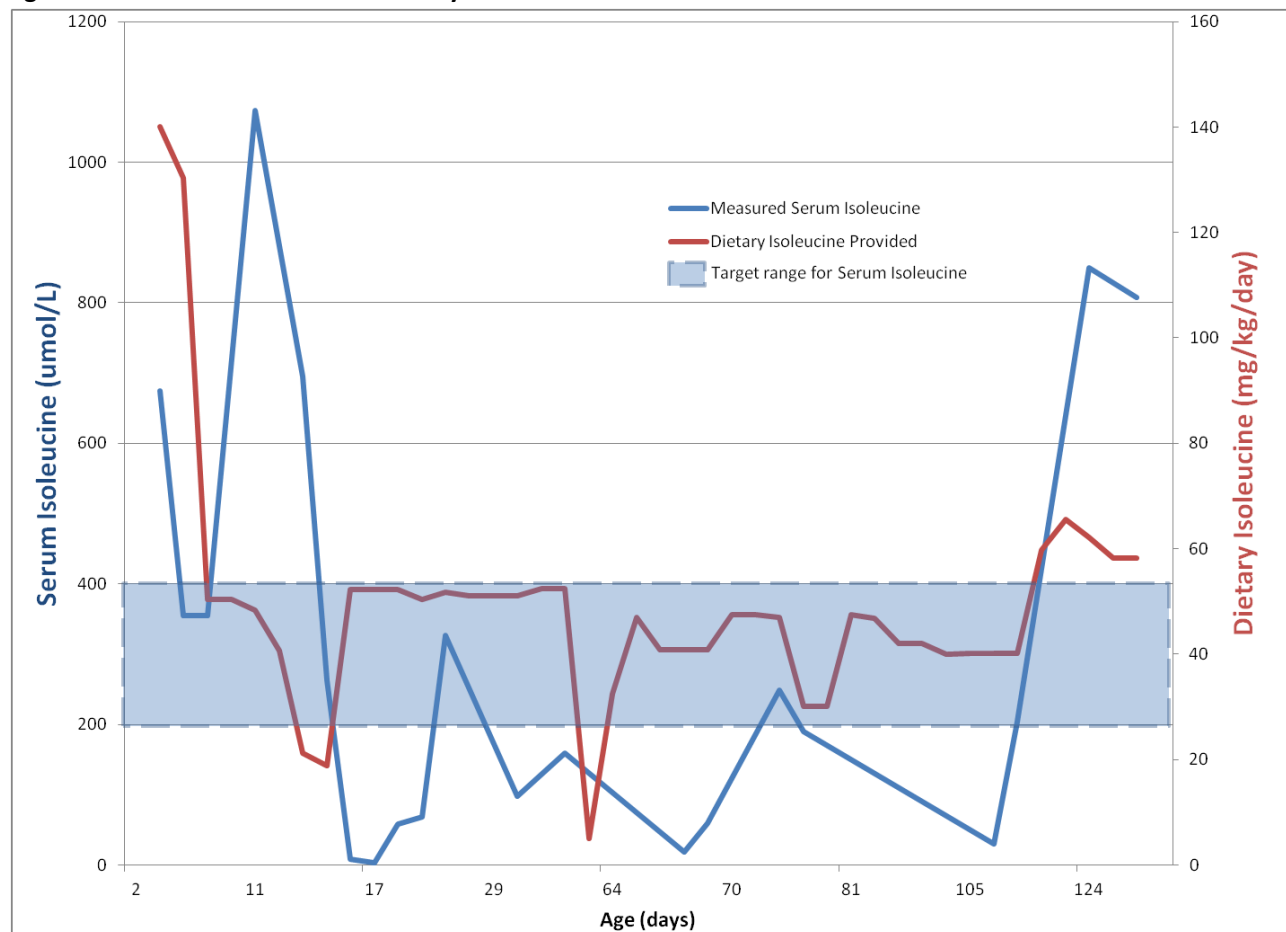
Getting treatment "just right" can be quite difficult. Though the exact mechanism of the development

of "acrodermatitis dysmetabolica" rashes seen in patients of inherited metabolic disorders has not been

fully elucidated, the correlation between manifestation of rash and deficiency of amino acids, especially

isoleucine, is strong enough to necessitate special attention from metabolic dietitians.

Might the medical team have taken different steps that would have prevented this patient's

experience? There are guidelines for medical nutrition therapy for MSUD set forth this year by GMDI

and SERC to ensure that MSUD patients receive adequate but not excessive BCAAs for growth and

development[10]. Discussion of a few of these guidelines compared with this patient's management are

pertinent. GMDI/SERC recommendations are that infants have daily amino acid analysis until

concentrations stabilize, once to twice weekly until the infant is six months of age, and weekly from the

age of six months to one year. The guidelines recommend providing 30-90 mg/kg of isoleucine for

infants. The guidelines also suggest managing serum concentrations of BCAAs differently from following

the reference ranges for individuals without the disorder. "Normal" serum concentrations of isoleucine

should range between 40-90 umol/L while GMDI/SERC recommend concentrations of 200-400 umol/L

for a patient of MSUD[10].

The suspicion is that this patient's rash developed due to isoleucine deficiency. Discharge

documentation from his last inpatient visit made note of the fact that supplemental isoleucine was

discontinued four weeks prior when his plasma amino acid analysis indicated elevated isoleucine. At the

time, he was receiving 50 mg of supplemental isoleucine as 5 mL of a 1% isoleucine solution added to his

metabolic formula. However, the same dietary prescription that discontinued his supplemental

isoleucine also increased his intact protein in formula, resulting in a decrease of only 20.8 mg of dietary

isoleucine, a drop from 46.8 mg/kg to 42 mg/kg and still within the recommended range of dietary

provision of isoleucine for a medically stable patient of MSUD. This particular case study patient was

never without isoleucine from diet or supplement before the development of his rash, in contrast with some previously described patients[11-14]. Additionally, as compared to GMDI/SERC recommendations, this patient's dietary prescription for isoleucine intake was below recommendations for only a single day during his time in North Carolina, regardless of having to change his diet over a dozen times in less than four months (Table 2, Figure 5).

Figure 5. Serum Isoleucine versus Dietary Isoleucine over time

Analyses of this patient's amino acid concentrations reveal that all three of the BCAAs have fluctuated from below normal to well above normal (Figure 2). Before his admission for his progressively worsening rash at day 105 of life, in fact, the most recent amino acid analysis showed high serum isoleucine, but unfortunately that was an analysis of blood drawn 26 days earlier. In retrospect,

the medical team might have had the patient come in for a blood draw before so much time elapsed. Opportunities for amino acid analysis were missed on days 82 and 98 of life, when the patient was either in the hospital or in clinic. An additional complication with regular, serial amino acid analysis occurred when machine regularly used by the UNC metabolic team needed repair on two separate occasions during the time span covered by this case.

Obtaining the frequency of amino acid analysis recommended by GDMI/SERC is certainly possible in an inpatient scenario but becomes much more complicated when the patient is managed through an outpatient clinic. Following the protocol from the recommendations might have allowed an isoleucine deficiency to be avoided, but this patient did not have a primary care provider for an extended period of time after moving to North Carolina and coming to clinic involved hours of travel. The metabolic team opted to try to avoid hardship for the family by having the patient's mother provide blood spots by mail for analysis, though when blood spots were not received it is unknown whether they were lost in the mail or never truly taken by the patient's mother.

This patient's serum concentrations of isoleucine were infrequently below the "normal" reference range but were below GMDI guidelines for 45% of the measurements (10 of 22 analyses). The metabolic dietitians have had a very difficult time attempting to stabilize amino acid concentrations within recommended ranges for this patient. MSUD presents a particularly great challenge because serum concentrations of three BCAAs must be balanced and the priority is often stabilization of leucine, since it and its ketoacid can lead to toxicity if elevated while elevations of isoleucine and valine are not known to be toxic[4].

Though this patient was not monitored as regularly as recommended (sometimes for reasons outside the medical team's control) and serum concentrations of isoleucine were not able to be maintained at concentrations recommended by GMDI, neither of these issues are the direct cause of the rash that developed. This patient developed diarrhea and vomiting that persisted for several weeks and

was likely a strong contributor to development of isoleucine deficiency. Irritation of the gastrointestinal tract over time can result in a diminished ability to absorb nutrients[16]. Therefore, though his dietary prescriptions were thought to have supplied ample isoleucine, the amount absorbed was possibly less than adequate to avoid deficiency. It is also possible that the great fluctuations in his amino acid concentrations over time (Figure 3) were contributory to the development of rash.

The metabolic dietitians and his metabolic physicians considered a deficiency-induced rash to be a possibility for this patient well before his diagnosis. However, as he was assumed to be receiving adequate dietary isoleucine and his most recent labs at the time showed elevated isoleucine concentrations, the team discounted the idea and believed his rash to have been induced by diarrhea and yeast infection, as had been diagnosed in the hospital. Their assumptions were faulty, however, partly because the information available was outdated or incomplete.

Perhaps the most important lesson that can be drawn from the experience with this patient is the reminder that the care a metabolic dietitian can provide is only as good as the information available to the dietitian. In an outpatient setting, considerations of a family's resources and social situation might lead a medical team to forgo an amino acid analysis or be understanding of a missed clinic appointment. Surekha Pendyal, MSc, MEd, RD, a member of his metabolic team, states, "The over restriction [of isoleucine] can occur intentionally or unintentionally due to various problems: difficult social situation, communication difficulty, discrepancy between what is recommended and how much the child has consumed, and inadequate monitoring" (personal communication November 2, 2013). Most of those concerns, however, can be ameliorated with frequent patient-dietitian communication. This patient's experience demonstrates that the need for regular follow-up is critical and social support should have been implemented.

The GMDI/SERC guidelines are new and may not yet be the standard of care for many metabolic teams across the country and globe; however, strict adherence to these new recommendations may

have changed the outcome for this patient. In an outpatient setting, though, strict adherence may be improbable or even impossible. Regardless, the experience with this patient can teach that any time deviation from nutrition management guidelines is considered, the risk and benefit of different actions should be weighed against one another and the ultimate decision should be the one that will most likely result in getting medical nutrition therapy for the patient "just right."

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