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Hyperleucinosis during infections in maple syrup urine disease post liver transplantation

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ABSTRACT

Maple syrup urine disease (MSUD) is due to biallelic variants in one of the three genes: *BCKDHA*, *BCKDHB*, and *DBT*. Branched-chain alpha-ketoacid dehydrogenase complex deficiency and elevated leucine, valine, isoleucine and alloisoleucine in body fluids are the results. We report hyperleucinosis during intercurrent illnesses in six patients with MSUD post liver transplantation. Patient charts were retrospectively reviewed. Data was entered into an Excel Database. Literature was reviewed. Six patients with MSUD were included who had post liver transplantation hyperleucinosis during an intercurrent illness. Five had encephalopathy. One received hemodialysis for the management of hyperleucinosis. All patients had unrestricted diet. Additionally, there were five patients (one patient included into the current study) reported in the literature. We suggested management considerations for the follow-up of patients with MSUD post liver transplantation after the first episode of unexplained encephalopathy or signs of acute hyperleucinosis during intercurrent illness due to our clinical experience: 1) Healthy: Unrestricted diet and monitoring of leucine levels; 2) Illness: a) home illness management: increased carbohydrate intake b) illness management at hospital: intravenous dextrose, intravenous lipid and daily plasma amino acid monitoring. We report hyperleucinosis and/or encephalopathy as a rare event post liver transplantation in MSUD as a multicenter case series. Hyperleucinosis and/or encephalopathy may occur in both related and unrelated donor liver transplantation. Based on the long-term follow-up of those patients, these suggested management considerations may be revised as per the patients' needs.

1. Introduction

Maple syrup urine disease (MSUD) is due to biallelic variants in one of the three genes including *BCKDHA* (MIM#608348), *BCKDHB* (MIM#248611), and *DBT* (MIM#248610). Biallelic variants in one of these genes result in branched-chain alpha-ketoacid dehydrogenase complex (BCKDC) deficiency and thus elevated leucine, valine, isoleucine and alloisoleucine levels in body fluids [1]. Its estimated incidence is 1 in 185,000 live births. Due to a pathogenic founder variant in *BCKDHB* (c.548G > C; p.Arg183Pro) [2], its prevalence is 1 in 113 in Ashkenazi Jewish population. Due to a pathogenic founder variant in *BCKDHA* [c.1312 T > A; p.Tyr438Asn (Alias p.Tyr393Asn)] its estimated incidence is 1 in 380 live births in Swiss Mennonite population [3].

The disease severity, age of onset and phenotypes range from classical, intermediate, intermittent and thiamine responsive MSUD [1]. The early neonatal onset of classical MSUD presents with feeding intolerance, encephalopathy, and seizures in the first week of life. Maple syrup

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odor in cerumen can be detected as early as 12 h of age [1]. Untreated, patients progress to coma or death secondary to brain edema. Intermediate and intermittent forms can manifest from infancy to adulthood. Intermediate form can present with global developmental delay, failure to thrive, maple syrup urine smell, and intermittent episodes of encephalopathy during intercurrent illnesses [1]. Patients with the intermittent form and thiamine responsive form present with early normal development and growth and acute onset of ataxia and/or encephalopathy during an incurrent illness [1].

MSUD is included into expanded newborn screening programs, thus allowing identification of newborns either asymptomatically or in the early stage of their symptom onset. Elevated leucine, alloisoleucine, valine and isoleucine in plasma amino acid analysis are the biochemical hallmark of the disease. Metabolic acidosis is the result of elevated branched chain ketoacids. Despite normal ammonia levels in the majority of patients, there are cases of hyperammonemia during acute metabolic decompensations [4]. Newborn screening may not identify intermediate, intermittent and thiamine responsive forms [5]. Plasma amino acid analysis can be normal or mildly elevated in intermittent forms of MSUD outside of metabolic decompensations. Acute ataxia episodes during intercurrent illness warrants plasma amino acid analysis.

Dietary restriction of leucine, branched chain amino acid free medical formula and supplementation of valine and isoleucine are the mainstay of the treatment. High caloric intake is required during intercurrent illness to prevent catabolism and hyperleucinosis. If high leucine levels are not decreased with medical treatment, hemodialysis is recommended to remove leucine and to prevent coma and death [1]. If there are frequent hospital admissions due to hyperleucinosis and acute encephalopathy during intercurrent illnesses, non-related orthotopic liver transplantation is required to manage frequent episodes of hyperleucinosis and encephalopathy [1].

2. Methods

Corresponding author (S.M-A) sent an e-mail to Metab-L mailing list on Inborn Errors of Metabolism (https://www.daneel.franken.de/metab-l/) to discuss MUSD post liver transplant hyperleucinosis during intercurrent illness in February 2020. All co-authors included into this study responded with their experience. The co-authors decided to present all cases together as a small case series. There were no other known cases to the authors.

All parents and/or patients signed informed case report consent forms. Patient charts were reviewed retrospectively. Leucine intakes were calculated by metabolic dieticians in each center as per their clinical diet management practices using either diet recalls or by food records for 1–3 days provided by parents. All information was entered into an Excel Database.

We reviewed the literature using liver transplantation, maple syrup urine disease, MSUD, leucinosis, hyperleucinemia, and hyperleucinosis keywords. We included patients with MSUD who underwent liver transplantation and presented with hyperleucinosis during intercurrent infections. Based on our study results, we suggested management considerations for patients with MSUD post liver transplantation.

3. Results

3.1. Patients

There were six patients from six different centers across North America. All had diagnosis of classical MSUD, presented in the newborn period, and were identified by positive newborn screening for MSUD. Patient 6 was previously reported [6]. We summarized biochemical features, leucine levels, leucine intakes, number of hospital admissions prior to liver transplantation and genotypes of all patients with MSUD in Table 1. We summarized liver transplantation and monitoring of patients with MSUD prior to hyperleucinosis in Table 2. Mean age of liver transplantation was 23 months (range 14–29 months). Three patients received deceased donor liver, two patients received living non-related donor liver and one patient received living related donor liver. Mean duration of follow-up was 5.8 years (range 1.7–15 years). The mean hyperleucinosis level was 1865 μmol/L (range 546–2784 μmol/L). Number of admissions, type of infections, management and monitoring of patients with MSUD during hyperleucinosis are summarized in Table 3. Five patients had signs and symptoms of encephalopathy. Hemodialysis was applied to one patient. A second patient was attempted to receive hemodialysis, but due to clotting of the dialysis catheter, hemodialysis was not initiated, and his leucine level was improved. A further patient had encephalopathy requiring intensive care unit admission and one patient was listless with the maximal leucine of 546 μmol/L, however this was resolved by intravenous fluids.

Mild to moderate elevation of liver enzymes were reported in two patients (Table 4). One of them had a low-grade Epstein-Barr virus hepatitis in liver biopsy performed due to persistent mild transaminitis.

Table 1
Biochemical features, leucine levels, leucine intakes, number of hospital admissions prior to liver transplantation and genotypes of all patients with MSUD are summarized in Table 1. Patients 1–6 are current study patients. Patients 6–10 are patients that reported in the literature.

Patient#: age at diagnosis/current age [Reference]	NBS Leu + Iso (cut off; μmol/L)	1st PAA leu (μmol/L)	Leu range (healthy-illness; μmol/L)	Leu intake (mg/kg/d)	Number of hospital admissions	Genotype
1: 4 d/3 y 3 m	517 (⟨300)	1705	24–1156	42–53	16	HMZ; c.1312T>A (p.Tyr438Asn) in *BCKDHA*; NM_000709.4
2: 1 w/7 y 3 m	1209 (<300)	NA	23–3768	19–80	4	HMZ c.205C>T (p.Gln69[a]) in *BCKDHA*; NM_000709.4
3: Newborn/4 y	951 (<300)	1713	13–1713	10	2	Cmp HTZ c.485G>A (p.Gly162Asp) and c.1110-1119del (p.Gln371Glyfs[a]17) in *BCKDHA*; NM_000709.4
4: 7 d/5 y 10 m	658 (<300)	2601	16–2601	34	8	HMZ c.1312T>A; (p.Tyr438Asn) in *BCKDHA*; NM_000709.4
5: 6 d/11 y	1304 (<300)	2022	18–809	30–50	4	NA
6: 1 w/17 y [6]	80 (<20)	NA	17–45	15	1	NA
7: 9 d/NA [8]	NA	5281	<380–541	25–30	1	Cmp HTZ p.Gly135Arg and p.His206Arg in *BCKDH*
8: 10 d/NA [7]	NA	1950	48–1000	NA	7	HMZ c.1281+1G>T in *DBT*
9: 9 d/NA [10]	NA	685	NA	0.5[a]	NA	NA
10: 5 d/NA [9]	2086	3445	NA	30–40	NA	Cmp HTZ c.1330dupA and c.1169A>G in *DBT*

Abbreviations: Cmp = compound; HMZ = homozygous; HTZ = heterozygous; leu = leucine; leu + iso = leucine + isoleucine combined; m = months; NA = not available; NBS = newborn screening w = weeks; y = years.
[a] Natural protein intake as g/kg/d.

Table 2
Liver transplantation and monitoring of patients with MSUD prior to hyperleucinosis are summarized in Table 2. Patients 1–6 are current study patients. Patients 6–10 are patients that reported in the literature.

Patient#: age at tx/follow-up [reference]	Donor type	Leu level (time collected; μmol/l)	Leu intake (mg/kg/d)/ protein (g/kg/d) intakes	Frequency of leucine measurements
1: 1 y 8 m/1 y 7 m	Deceased	374 (6 h)	366/4.2	Every 2 m
2: 3 y 5 m/3 y 10 m	Living non-related	181 (1 d)	117/1.7	Every 3 m
3: 2 y 1 m/1 y 11 m	Living related (mother)	470 (2 d)	41–54/1.1–1.3	Every m (n = 3); Every 6 m
4: 2 y 2 m/3 y 9 m	Living non-related	106 (1 d)	NA/1.5–1.8	Every m
5: 14 m/10 y	Deceased	216 (1 d)	100–130/2.5	Every 6–12 m
6: 2 y/15 y [6]	Deceased	16 (30 d)	150/1.8	Annually
7: 1 y/1 y 4 m [8]	Living related (father)	NA	150/NA	NA
8: 1 y 3 m/ 11 m [7]	Living related (mother)	NA	Unrestricted	NA
9: 38 m/3 y 3 m [10]	Living non-related	NA	NA/2–2.5	NA
10: 10 m/8 m [9]	Living related (mother)	NA	NA/2	

Abbreviations: d = day(s); hr = hour; Leu = leucine; m = month(s); NA = not available; tx = transplantation; w = week(s); y = years.

Average leucine intake increased from 31 mg/kg/day (range 10–80 mg/kg/day) pre-transplantation to 188 mg/kg/d (range 41 mg/kg/d – 366 mg/kg/day) post liver transplantation. All patients were managed during illness based on the centers' experience applying different monitoring and illness management plans. All managements are summarized in Table 3. None of the patients had failure to thrive. None of the patients were on thiamine therapy. During the acute metabolic decompensation, ketonuria (n = 4), metabolic acidosis (n = 4), elevated isoleucine and valine (n = 5) and elevated alloisoleucine (n = 4) were present. None of the patients had urine organic acid analysis.

3.2. Literature Review

Using our search criteria, we identified five patients (one of them included in our current study) with MSUD and post liver transplantation hyperleucinosis during intercurrent illness. We summarized those patients in Tables 1–4 together with the patients in the current study.

Three patients with MUSD, who underwent living related donor liver transplantation from one of their heterozygous parents, presented with moderate to severe hyperleucinosis during acute infections [7–10]. All patients achieved good metabolic control on an unrestricted diet.

4. Discussion

We report six patients with MSUD, who underwent liver transplantation and presented with hyperleucinosis during intercurrent illnesses post liver transplantation. The leucine levels were markedly elevated in five of those patients. We identified five additional patients reported in the literature with similar episodes, and one of those patients were included into our current study with additional details. Our study highlights that despite good metabolic control on unrestricted diet, there is still a potential risk of significant metabolic decompensation post liver transplantation during intercurrent illnesses. It is not clear, if this is a rare finding or is underdiagnosed as there are no monitoring or management recommendations for patients with MSUD post liver transplantation. Families and patients should be informed for the risks of hyperleucinosis during intercurrent illnesses post liver transplantation and be monitored and managed appropriately to prevent hyperleucinosis, encephalopathy, hemodialysis or even death.

The liver contributes to 9%–13% of the total body BCKDC activity [11]. Liver transplantation in MSUD has been an effective treatment to prevent hyperleucinosis and liberalize leucine or protein restricted diet and decreases the number of severe metabolic decompensations [1,12–15]. Several patients with MUSD received related living liver donor transplants from their carrier parents who had no history of hyperleucinosis post liver transplantation [16–21]. Hyperleucinosis and encephalopathy was reported in only three patients with MSUD who received related living liver donor transplants from their carrier parents [7–9]. For this reason carriers for MSUD do not serve as liver transplant donors for patients with MSUD in the recent years. Interestingly in our study, four patients with MSUD received unrelated donor liver transplantation, but still presented with hyperleucinosis and/or encephalopathy. We think that hyperleucinosis and/or encephalopathy should be monitored in patients with MSUD post liver transplantation for the acute management of the patients. The genotyping is not part of pre-liver transplant preparations in liver donors. Liver transplant donors would have been carrier for MSUD. MSUD carrier testing may be

Table 3
Number of admissions, type of infections, management and monitoring of patients with MSUD during hyperleucinosis and after the first episode of hyperleucinosis are summarized in Table 3. Patients 1–6 are current study patients. Patients 6–10 are patients that reported in the literature.

Patient#	# of admissions	Type of infections	# of EP	Home illness management		Management during admission			Frequency of leu measurements
				Intake	Uket measurements	IV fluids (rate)	IV lipids	Medical formula	
1	4	GE, RTI	1	10% CHO	Yes	D10 (1.5×)	No	No	Every 2 w
2	2	GE, RTI	1	Medical formula	No	D10 (1×)	No	Yes	Every 3 m
3	3	GE, RTI	1	10% CHO	No	D10 (1.5×)	Yes	Yes	Every 6 m
4	6	NA	1	10% CHO	No	D10 (1×)	No	No	Every m
5	1	GE	1	10% CHO	No	D10 (1×)	No	No	Every 3–4 m
6 [6]	1	GE	0	None	No	D10 (1×)	No	No	Every 12 m
7 [8]	1	RTI	0	NA	NA	NA	NA	NA	NA
8 [7]	3	GE	3	NA	NA	Yes	NA	Yes	NA
9 [10]	1	CMV, acute rejection	0	NA	NA	NA	NA	NA	NA
10 [9]	1	Ascites	0	NA	Na	D10	NA	NA	Every 2 w

Abbreviations: CHO = carbohydrate; EP = encephalopathy; GE = gastroenteritis; IV = intravenous; NA = not available; RTI = respiratory tract infection; Uket = urine ketones;

Table 4
Biochemical investigations of patients with MSUD during hyperleucinosis are summarized in Table 4. Patients 1–6 are current study patients. Patients 6–10 are patients that reported in the literature.

Patient#: [References]	BCAA during hyperleucinosis				Liver enzymes			CKU/L	Blood gas			Urine ketones (mmol/L)
	Leu (μmol/L)	Ileu (μmol/L)	Val (μmol/L)	AIleu (μmol/L)	ALT U/L	AST U/L	GGT U/L		pH	HCO3	BE	
1	2088	868	1422	177	113	122	NA	NA	7.38	18	-6	>15.6
2	1672	442	689	139	41	58	39	57	7.29	15	−12	Moderate
3	2784	1128	1459	NA	297	76	NA	77	7.34	20	−15	>80
4	546	524	284	86	NA	NA	NA	NA	7.34	18	0.9	NA
5	1930	835	1430	161	53	53	NA	33	NA	NA	NA	+4
6 [6]	2170	1009	1483	NA	N	N	NA	NA	NA	NA	NA	NA
7 [8]	450	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
8 [7]	2001	877	1653	NA	N	NA	NA	NA	NA	NA	NA	NA
9 [10]	865	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
10 [9]	340	NA	NA	NA	NA	NA	NA	NA	N	N	N	pos

Abbreviations: AIso = alloisoleucine; Ileu = isoleucine; Leu = leucine; NA = not available; N = normal; pos = positive; Val = valine.

included into the pre-liver transplant preparations in liver donors for MSUD patients to prevent risks of hyperleucinosis post liver transplantation.

So far more than 250 patients with MSUD have received liver transplantation: 1) patients reported in the literature (n = 107) worldwide and summarized in Table S1; 2) patients in the United Network for Organ Sharing (unos.org) data base (n = 60, accessed in 2017) and patients followed by one of the authors in this study (n = 100, personal communication by Dr. Mazariegos in US). The number of patients has been increasing in the recent years, whereas age of liver transplantation has been decreasing for liver transplantation in MSUD [22–28]. It appears that patients with MSUD maintain normal or marginally elevated leucine levels on the unrestricted diet post liver transplantation, when they are well. However, they may have increased risk of hyperleucinosis and/or encephalopathy, when they have intercurrent illnesses, especially if those are associated with diarrhea and dehydration, which is likely secondary to the decreased hepatic blood flow. Acute liver rejection was not observed in our small case series and 37 patients reported by Mazariegos et al. previously [6]. Unfortunately, there are no nutrition or illness management recommendations for MSUD post liver transplantation. Due to the increasing number of patients receiving liver transplantation for the treatment of MSUD in the recent years, we think that there is a necessity to develop monitoring and management recommendations for MSUD post liver transplantation. These recommendations will likely prevent catabolism, encephalopathy, and even death. Based on our small case series, we suggested management considerations for the follow-up of patients with MSUD post liver transplantation and summarized in Table 5: 1) no leucine- or protein-restricted diet post liver transplantation; 2) after the first episode of unexplained encephalopathy and hyperleucinosis post liver transplantation; a) high carbohydrate intake and monitoring of blood dot spot leucine levels during intercurrent illness as home management; b) intravenous fluids and lipids and plasma amino acid analysis during hospital admission. Branched chain amino acid free medical formula and valine and isoleucine supplementation might be necessary. Parents and patients should be informed for the risks of hyperleucinosis during intercurrent illness post liver transplantation during liver transplantation preparation meetings.

In conclusion, we report hyperleucinosis and/or encephalopathy post liver transplantation in MSUD as a multicenter small case series. Hyperleucinosis and/or encephalopathy occur in related and unrelated donor liver transplantation. Based on our group's experience and review of the literature, the incidence of hyperleucinosis in MSUD post liver transplantation seems low. We think that there is a need for a prospective multicenter MSUD liver transplantation registry study to identify the prevalence of hyperleucinosis in MSUD post liver transplantation. There is also a need for the evidence-based expert consensus recommendations for the management of patients with MSUD post liver transplantation. The first episode of unexplained encephalopathy during intercurrent illness warrants monitoring and management of patients with MSUD post liver transplantation.

Table 5
Suggested management considerations for patients with MSUD post liver transplantation are summarized in Table 5.

Conditions post liver transplantation	Healthy	After first episode of unexplained encephalopathy and hyperleucinosis	
Monitoring parameters depending on sign and symptoms	No episodes of unexplained encephalopathy during intercurrent illness	Intercurrent illness able to tolerate illness management at home	Intercurrent illness not able to tolerate illness management at hospital
Leucine or protein intake/ illness management	Unrestricted	Unrestricted[a]/ 10%–15% carbohydrate solutions 1–1.5 maintenance	Unrestricted[a]/ D10-NS at 1.5 maintenance, IV lipids (2–3 g/kg/d)
Monitoring of leucine levels by blood dot spot	None	Daily	None
Plasma amino acids	• 1st day of post liver transplantation • Prior to hospital discharge • 1st or 2nd outpatient visit • Yearly afterwards	None	Every 2–3 days
Urine ketones	None	Daily	Daily

Abbreviations: IV = intravenous; D10-NS = 10% dextrose and 0.9% sodium chloride.
[a] 50%–100% reduction of natural protein and BCAA-free medical formula, if elevated leucine levels during intercurrent illness.

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Author statements

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