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Natural history of children and adults with maple syrup urine disease in the NBS-MSUD Connect registry

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1. Introduction

Maple syrup urine disease (MSUD) is a rare autosomal recessive metabolic disorder (OMIM #248600) in which affected individuals cannot metabolize branched-chain amino acids (BCAA) (leucine, isoleucine, and valine) due to pathogenic variations in one of three genes: *BCKDHA, BCKDHB,* and *DBT* encoding the E1α, E1β, and E2 subunits of the branched-chain α-ketoacid dehydrogenase (BCKDH) enzyme complex [1]. Consequently, these amino acids and their corresponding α-ketoacids accumulate in the body. In the United States of America (USA), the incidence of MSUD is approximately 1:198,000 [2], although it is considerably higher in some populations such as Old Order Mennonite (1:358) [3] and Ashkenazi Jewish populations (1:26,000) [4].

Without treatment, MSUD can lead to feeding difficulties, lethargy, seizures, urine and cerumen that smell like maple syrup, vomiting, coma, and death [5]. Early diagnosis and treatment can optimize outcomes, although treated individuals have an increased rate of anxiety, depression, attention deficit hyperactivity disorder (ADHD), movement disorders, and small reductions in intelligence and global function [5].

Treatment consists of a protein-restrictive diet that limits the amount of branched-chain amino acids consumed, along with synthetic formula consisting of the other amino acids and various micronutrients [6]. The goal of treatment is to maintain plasma leucine concentrations, with frequent monitoring, between 75 and 200 μmol/L for infants and children age five years and younger, and between 75 and 300 μmol/L for individuals older than five years of age [7]. Even with dietary treatment, metabolic decompensation can occur during times of stress (e.g., infection) and must be treated promptly [5]. Liver transplants may allow for relaxation of the diet, and can help prevent further brain damage but cannot reverse existing damage [8,9].

Because treatment must be initiated as soon as possible after birth, screening for MSUD was first included in newborn screening (NBS) programs in the USA in 1964 [10]. In 1999, MSUD was included on the American College of Medical Genetics list of recommended diseases for inclusion in tandem mass spectrometry-based NBS panels [11], and is currently screened for in all states in the USA [2].

In order to add to the literature on outcomes of this rare condition, we report the characteristics of a group of respondents with MSUD from NBS-MSUD Connect, the first self-reported patient registry for metabolic NBS disorders. NBS Connect was launched in 2012 with NBS-PKU Connect for phenylketonuria (PKU) as the pilot registry, and NBS-MSUD Connect was added in 2013 [12]. The purpose of this report is to provide a snapshot of respondents with MSUD, including management techniques employed, clinical symptoms, and factors potentially associated with metabolic control of plasma leucine levels.

2. Materials and methods

NBS-MSUD Connect is a web-based self-report patient registry that collects information on current diagnosis, management, and treatment practices from respondents with MSUD or their caregivers. NBS-MSUD Connect registry development has previously been described [12]. Data collection and analysis via the NBS-MSUD Connect registry has been approved by the Emory University Institutional Review Board.

Data from the following questions were analyzed for this report. For a list of possible responses to these questions, please see the supplementary file.

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- What was the affected person's blood leucine level at diagnosis? (Please enter either μmol/L OR mg/dL)
- What is the current level of leucine? (Please enter either μmol/L OR mg/dL)
- What were the symptoms in the affected person at diagnosis?
- What are the symptoms in the affected person currently?
- Does the affected person have any family members with inborn errors of metabolism?
  ○ If yes, choose all that apply
- Has the affected person had symptoms of a psychological condition?
- Has the affected person ever taken any of the following medications for depression or anxiety?
- Has the affected person taken medication for ADHD or ADD?
- Does the affected person ever use a Ketostik to check amount of ketones in urine?
- If Ketostiks are used to check amount of ketones in urine, how often are they used?
- Does the affected person ever use a DNPH kit to check amount of ketones in urine?
- If DNPH kits are used to check amount of ketones in urine, how often are they used?
- Has the affected person ever had symptoms of a skin condition? Is the affected person taking any other supplements?
- Which of the following best describes the affected person's current prescribed diet?
- Is the affected person following the prescribed diet?
- Does the affected person use specially modified low protein food products?
- Is the affected person currently taking medical food/formula? If yes, please choose appropriate formula?
- At what age was the affected person started on diet?
- Has the affected person had a liver transplantation?
- Has the affected person had a problem getting reimbursed for any of the following? Medical food (formula), Specially modified low protein foods, Free amino acids (Isoleucine and/or Valine)

Height-for-age z-scores were calculated using an online program based on the Centers for Disease Control and Prevention (CDC) growth charts [13,14]. Height-for-age data was discarded for three individuals with biologically-implausible values for height-for-age (z-score < -5 or $> +3$).

For the question on symptoms of a psychological condition, we collapsed bipolar disorder, dysthymic disorder, major depressive disorder, and mood disorder choices into one category of mood disorders. A few respondents reported “depression” in the “other” category. These respondents were also categorized as having symptoms of a mood disorder.

For the questions about plasma leucine levels, answers given in the mg/dL format were converted to the μmol/L format. Current plasma leucine levels were dichotomized relative to 6 mg/dL or 308 μmol/L [7] (higher or lower) and cross-tabulated with the variables described in Table 5. Fisher's exact test was used to test for significant associations.

3. Results

At the time of this report, the NBS-MSUD Connect registry included data on 39 respondents (Table 1), with an age range of four months to 41 years. Data were self-reported by eight respondents, and reported by a parent or other caregiver for 31 individuals. The respondents who self-reported ranged in age from 18 years to 41 years (mean = 30.4 - years). The respondents for whom data was entered by a caregiver ranged in age from 4 months to 32 years (mean = 11.3 years). Registry respondents were largely from the USA (n = 35), with four respondents from other countries.

Two of the respondents (age 16 and 27 years) were reported to have had a liver transplant. Four of the respondents had a family history of MSUD, and one reported a family history of PKU. Twenty-two respondents reported having had genetic testing, 11 reported no genetic testing, and six reported “unknown.” Of those with genetic testing, 12 (54.5%) indicated that they would be willing to share the test results with the registry, but only one respondent did so. Twelve reported that enzyme testing had been done, 14 reported that enzyme testing had not been done, 12 were unknown, and one did not answer. Twenty respondents reported plasma leucine levels at the time of diagnosis (Table 1). Approximately half (n = 11) had plasma leucine levels in excess of 1538 μmol/L at diagnosis.

Table 1
Characteristics of study population.

Sex, n (%)	(N = 39)
Male	22 (56.4%)
Female	17 (43.6%)
Age, years	(N = 39)
Mean	15.3
SD	12.2
Median	13
Minimum	0
Maximum	41
Race/ethnicity, n (%)	(N = 35)
Asian	3 (8.6%)
Black, African American	6 (17.1%)
Caucasian Hispanic or Latino	4 (11.4%)
Caucasian not Hispanic or Latino	19 (54.3%)
Other	1 (2.8%)
Multiple races or ethnicities	2 (5.7%)
Plasma leucine level at diagnosis (μmol/L), n (%)	(N = 20)
< 154	1 (5.0%)
154–308	1 (5.0%)
309–462	1 (5.0%)
463–769	2 (10.0%)
770–1077	2 (10.0%)
1078–1538	2 (10.0%)
> 1538	11 (55.0%)

Height, age and gender were available for 31 respondents, allowing for calculation of z-scores for height-for-age. Of these, 16 (51.6%) had z-scores of less than -1, 11 (35.5%) had z-scores of -1 to $+1$, and four (12.9%) had z-scores of greater than $+1$. Respondents who were diagnosed by NBS were more likely to achieve a height-for-age z-score of greater than -1 (11/19, 57.9%) than were respondents who were not diagnosed by NBS (1/8, 12.5%) ($p = 0.038$).

Twenty-four respondents were reportedly diagnosed via NBS, 23 of whom were USA respondents. Of those diagnosed by NBS, the age at diagnosis was less than one week for 12 respondents, one to two weeks for nine respondents, three to four weeks for two respondents, and prenatally for one respondent. Eight were not diagnosed by NBS, and their age at diagnosis was one to two weeks for five respondents, three to four weeks for one respondent, four to six months for one respondent, and 10–12 months for one respondent. Of those with unknown NBS status, age at diagnosis was one to two weeks for one respondent, three to four weeks for four respondents, and five years for one respondent.

All respondents except two (liver transplant recipients) reported having a prescribed diet. Of these, twenty-eight (75.7%) were prescribed medical food and protein restriction, and nine (24.3%) were prescribed protein restriction alone. Likewise, 35 of 37 respondents reported the use of formula; the two “no” respondents were liver transplant recipients. Thirty-one of the respondents started their diet at 1–60 days of age, six at 2–12 months, one at one year of age, and one at five years of age.

Three respondents were not following a prescribed diet at the time of the report, 24 were following a prescribed diet all of the time, and nine were following a prescribed diet sometimes (two were unknown). Twenty-six respondents reported that they had never been off of the diet. Three were off diet for less than three months, one for 6–12 months, three for 1–5 years (including one liver transplant

Table 2
Supplement use among participants with MSUD (N = 37).

No supplements	3[a]
At least one supplement	34
Thiamine	21
L-valine	22
L-isoleucine	22
L-leucine	1
Multivitamin	10
Other minerals	0
Omega-3 fatty acids (DHA)	3
Omega-6 fatty acids	1
Carnitine	1
Other[b]	5

[a] Includes one liver transplant recipient.
[b] Two Vitamin D, one carbocal, one ketonex-2, one Complex Essentials MSD.

recipient), and two for 5–10 years (including one liver transplant recipient). Most respondents (91.9%) reported taking one or more supplements, with thiamine, L-valine and L-isoleucine being the most common (Table 2).

Ketostiks were reportedly being used by 24 respondents to measure ketones in the urine: one daily, four weekly, three monthly, 14 only during illness, and two at unspecified time intervals. Seven respondents reported the use of 2,4-dinitrophenylhydrazine (DNPH) kits to check urine ketones: one weekly, two monthly, two only during illness, and two at unspecified time intervals. Six of the respondents reported use of both Ketostiks and DNPH kits.

At the time of diagnosis, 36 (n = 38) respondents had one or more symptoms of MSUD, with the most common being maple syrup odor, lethargy/irritability/weakness, and poor feeding (Table 3). At the time of report, 15 (n = 39) respondents had one or more of the symptoms of MSUD, with current age cross-referenced with symptoms in Table 3. Maple syrup odor and poor concentration were the most commonly reported symptoms currently affecting respondents. Those with one or more current symptoms had an age range of 0 to 37 years.

Ten respondents reported that they had experienced rashes, six reported other skin conditions, and one reported both rash and another skin condition. The other conditions reported were: dry scalp (n = 1), acne (n = 1), psoriasis (n = 1), and eczema (n = 4).

Of the 38 respondents for whom a neuropsychological history was available (Table 4), 14 (36.8%) reported a mental health disorder, use of anti-anxiety or antidepressant medication, or use of Attention Deficit Disorder (ADD) or ADHD medication. The mean age was higher among respondents who reported evidence of a neuropsychological comorbidity (19.1 years) than respondents who reported no such comorbidity (16.0 years). Nine respondents reported ADD/ADHD disorder or medication history. Seven reported a mood disorder, two of whom also reported anxiety, and nine reported a history of use of anxiety or mood disorder medication. Obsessive compulsive disorder was reported by four respondents.

Table 3
Symptoms at diagnosis and at current age.

Symptoms	At diagnosis (N = 38)	Currently (N = 39)	Current age (years)
None	2	24	Mean = 16.2, sd = 12.4
Lethargy, irritability, weakness	25	4	10, 10, 20, 37
Poor feeding	30	3	1, 2, 10
Nausea, vomiting	9	0	
Hypotonia	9	3	4, 10, 10
Hypertonia	8	1	1
Dystonia	6	1	2
Ataxia	6	3	1, 4, 10
Poor concentration	4	6	0, 1, 10, 10, 19, 32
Seizures	7	2	9, 10
Coma	9	0	
Maple syrup odor (urine, ear wax)	23	7	2, 3, 9, 19, 20, 24, 30
No weight gain	8	2	10, 30
Skin rash	6	2	0, 20
Hair loss	2	1	0
Other[a]	3	0	

[a] Weight loss, high-pitched cry, apnea.

Table 4
Neuropsychological comorbidities.

Mental health disorder (N = 31)	Number of subjects reporting	Current age (years)
None	20	Mean = 16.0, sd = 14.1
Unknown	4	1, 10, 17, 28
Anxiety Disorder	2	30, 32
ADD/ADHD	8	0, 9, 10, 15, 20, 24, 30, 32
Autism	1	0
Mood disorder	7	4, 15, 16, 19, 24, 30, 32
Obsessive Compulsive Disorder	4	10, 20, 30, 32
Specific Phobia	1	16
Medication History		
Anxiety or depression (N = 34)	6	15, 19, 30, 32, 37, 37
ADD/ADHD (N = 36)	5	0, 5, 15, 20, 32
Any disorder or medication (N = 38)	14	Mean = 19.1, sd = 12.3

Of the respondents with a neuropsychological comorbidity, only 2 out of 13 (15.4%) were diagnosed before the age of one week, compared to 10 out of 24 (41.7%) among those without a neuropsychological comorbidity (p = 0.10). Evidence of a neuropsychological disorder was reported by 9 of 31 (29.0%) respondents who started the diet before the age of 60 days, and by 5 of 7 (71.4%) respondents who started the diet after the age of two months (p = 0.050).

Twenty-nine respondents reported on their most recent plasma leucine level (Table 5). Levels varied and did not appear to correlate with the use of low protein modified foods; prescribed dietary strategy; trouble getting access to formula, low protein foods or free amino acids; use of Ketostiks; use of DNPH kits; or following their prescribed diet at all times. Respondents who had evidence of a neuropsychological condition had comparable recent plasma leucine levels to those who did not. Likewise, respondents who reported current MSUD symptoms or a history of skin conditions showed a wide range of recent plasma leucine levels. The aforementioned variables did not appear to segregate according to most recent plasma leucine levels being within (< 308 umol/L or < 6 mg/dL) or above the therapeutic range [7].

Fourteen (36.8%) respondents were hospitalized in the prior year, with a mean age of 10.5 years (sd = 13.0). This group included three of the five individuals in the registry who were under the age of one year. Eight of the hospitalized respondents (57.1%) reported current MSUD symptoms. Among the 24 respondents who had not been hospitalized in the past year, the mean age was 18.3 years (sd = 10.8), and eight (33.3%) reported current symptoms of MSUD.

4. Discussion

This paper presents a snapshot of NBS-MSUD Connect registry respondents currently living with MSUD. The respondents included here range in age from four months to 41 years. Except for the individual who was diagnosed at five years of age, all reportedly began dietary management before the age of two years, with most (81.6%) initiating dietary management before the age of two months. There is a high burden of disease among respondents with MSUD, with 15 (38.5%) having been hospitalized in the prior year. This includes three of five

Table 5
Plasma leucine levels (μmol/L) at time of most recent test (N = 30).

Leu level (μmol/L)	< 154	154–308	309–462	463–769	770–1077	1078–1538	> 1538
Most recent (N = 30)	5[a]	8	9	5	2	1	0
Uses modified low protein foods							
No	4[a]	2	0	1	0	1	0
Yes	1	6	9	4	2	0	0
Prescribed diet	3	7	8	4	1	0	0
Medical food and protein restriction							
Protein restriction only	0	1	1	1	1	1	0
No prescribed diet	2[a]	0	0	0	0	0	0
Barriers							
No trouble getting formula, low protein foods, or free amino acids	5[b]	4	7	2	2	1	0
Has trouble getting at least one of these	0	4	2	3	0	0	0
Follows diet (two missing)							
All of the time	2	4	7	3	1	1	0
Some of the time	1	3	1	2	1	0	0
Does not follow diet	0	1	1	0	0	0	0
Uses ketosticks (one missing)							
No	3[a]	5	2	1	0	1	0
Yes	2	3	7	4	1	0	0
Uses DNPH kits (one missing)							
No	5[a]	7	5	5	0	1	0
Yes	0	1	4	0	1	0	0
Neuropsychological comorbidity							
No	3	7	6	3	1	1	0
Yes	2[a]	1	3	2	1	0	0
Current symptoms of MSUD							
No	5[a]	5	4	4	2	0	0
Yes	0	3	5	1	0	1	0
History of a skin condition							
No	4[a]	7	4	4	0	0	0
Yes	1[b]	1	5	1	2	1	0
Hospitalized in past year							
No	3[b]	3	8	3	1	0	0
Yes	2	5	1	2	1	1	0

[a] Includes two liver transplant recipients.
[b] Includes one liver transplant recipient.

(60.0%) infants under the age of one year in the registry. It is possible that as children with MSUD age, they become more tolerant to increased levels of branched-chain amino acids and are therefore less likely to require hospitalization.

Consistent with treatment, the most recent plasma leucine levels were lower than at the time of diagnosis, but still vary widely among respondents with 56.7% having levels above 308 μmol/L (6 mg/dL). This may reflect difficulty maintaining the prescribed dietary regimen, although a range of levels was also seen in the subset who reported following the diet at all times. Alternatively, reported leucine levels could be a reflection of different therapeutic thresholds used at different clinics. Despite treatment, 38.5% of respondents reported one or more current symptoms of MSUD, with maple syrup odor and poor concentration being the most common. Current symptoms were reported by respondents across all ages, and did not appear to correlate with current plasma leucine levels.

In addition, current plasma leucine levels did not correlate with use of modified low-protein foods, prescribed approach to dietary management (protein restriction and medical foods versus protein restriction only), or how often respondents followed their prescribed diet (all of the time versus some of the time). These results suggest that respondents experience difficulty in maintaining therapeutic levels of plasma leucine.

Respondents reported taking a variety of supplements, the most common being thiamine, L-valine, L-isoleucine, and multi-vitamins. Thiamine is recommended for the subset of MSUD patients who have some residual enzyme activity and have been shown to be responsive to thiamine supplementation [7]. It is not known if the respondents in this study who take thiamine had been previously tested for thiamine-responsiveness, or if the thiamine supplementation was recommended by a clinician. There is very little consensus for the use of supplements, and recommendations vary across clinics. The issue of supplementation has begun to be addressed by evidence- and consensus-based nutrition management guidelines [7], and further research regarding supplements is necessary to inform harmonization of treatment regarding supplement use in patients with MSUD.

Two of the respondents in the registry were liver transplant recipients. Neither one followed a prescribed diet at the time of survey completion. Generally, individuals with MSUD who receive a liver transplant from a deceased donor are able to follow an unrestricted diet, as evidence by two studies of long-term outcomes [8,9]. As the liver represents only 9–13% of BCKDH activity in the body [15], liver transplantation does not provide a complete cure. Indeed, BCAA levels in MSUD liver transplant recipients remain approximately two-fold greater than normal [9], and transient leucine elevations following an illness have been reported [9]. Recently, there have been reports of living donor liver transplants from parents (who are carriers of MSUD) to their affected children [16–21]. Although these patients may also return to a normal diet, they may still have a risk of metabolic decompensation during illness [21]. More data are needed on the long-term outcomes of MSUD patients who receive a living donor liver transplant from a carrier relative.

In this sample, 36.8% of respondents reported having had symptoms of a neuropsychological condition, or reported a history of taking medication for anxiety, depression or ADD/ADHD. Neuropsychological comorbidities were more common among respondents with a delayed onset of diet than among those who started their diet within 60 days of birth. Likewise, those with neuropsychological comorbidities were less likely to have been diagnosed before the age of one week. These results highlight the importance of NBS and early diagnosis and treatment for MSUD.

The rate of neuropsychological comorbidities in this analysis was

lower than that reported in Muelly et al., who found that the cumulative lifetime incidence of mental illness (depression, anxiety disorders, ADHD) among MSUD patients reached 83% by age 36 years [22]. However, their population was slightly older than ours (age 5–35 years). If we exclude the 11 respondents under the age of five years in our sample, the rate of symptoms or medications for a neuropsychological comorbidity increases to 42.8%, which is still lower than their estimate. While our estimates are based on self-report, Muelly et al. based their estimates on neuropsychological testing. Therefore, it is possible that our rate is an under-estimate of the true rate in the MSUD population.

Abi-Wardé et al. also reported on the rate of neuropsychological conditions in an MSUD population, with eight out of 34 (23.5%) having a diagnosis of externalizing disorders, mood or emotional disorders, or anxiety disorder [23]. Their estimate was based on a diagnosis in a psychiatric setting, but not all individuals in the study had a full psychiatric evaluation, which likely contributes to their lower estimate. Their rate may also be lower because they only included individuals who were diagnosed in the first month of life, while our sample included some respondents who did not commence diet until after two months of age.

Due to the high rate of neuropsychological conditions in patients with MSUD, patients may benefit from routine screening for symptoms. Screening tools have the advantages of being short, easy to use, and easily administered by non-psychologists. Patients who are identified as being at risk based on screening results can be referred to specialists for further assessment. Recent research supports the use of screening tools for cognitive functioning for children with metabolic disorders [24]. A similar approach may benefit patients with behavioral symptoms, leading to early recognition and treatment of symptoms.

About half of the respondents reported a history of rash or other skin conditions, including eczema and psoriasis. Only two respondents reported current skin rash, and both had plasma leucine levels above 308 μmol/L (6 mg/dL). Dermatitis has previously been reported in patients with MSUD and is associated with low levels of isoleucine [25–27]. Therefore, it was not unexpected that current skin conditions did not correlate with current levels of leucine. Isoleucine and valine levels are not always reported to families. Therefore, we did not ask respondents for data on these amino acids. However, these results highlight the importance of reporting valine and isoleucine levels to patients so that they can maintain these amino acids in the therapeutic range as well as leucine, as indicated in guidelines [7]. Questions about isoleucine and valine will be added to the NBS-MSUD Connect registry survey in the future.

Little has been published about growth profiles in individuals with MSUD. In one report of nine individuals with MSUD, three (33.3%) had growth less than the average range (z-score < -1) [28]. However, in our larger sample, half of the respondents had height-for-age z-scores of less than -1. In theory, growth may be restricted by chronic protein restriction and frequent catabolic events [28]. In our analysis, growth to at least average range (z-score of > -1) was more often achieved by respondents who were diagnosed by NBS, suggesting that early damage sustained by delays in treatment may also be a contributing factor. More studies are needed to characterize the growth profiles of individuals with MSUD, with particular focus on the impact of NBS and early treatment.

The primary strength of this study is that it included respondents from across the country, and even internationally, so the sample was not restricted to patients from a single clinic. We obtained a wealth of information from a relatively large sample of the rare condition MSUD. However, there are several important limitations to this study. First, our data are based on self-report with no validation of laboratory test values or confirmation of diagnosis, though data curation is currently underway. For questions about leucine levels, it is not clear if respondents are consulting their own records or are relying on memory. Likewise, it is possible that reported heights were based on the last recorded height of the respondent, rather than the height on the day that the survey was completed. Therefore, height values may be underestimates. Responses to dietary adherence may also be biased if respondents are misreporting their practices or if caregivers are unaware of the true practices of the patient.

Second, we do not know the timing of the most recent reported plasma leucine level relative to completion of survey, so the most recent plasma leucine level may not be an accurate representation of the current plasma leucine level. This may be an important distinction in the analysis of current symptoms. Third, we were unable to classify respondents based on types of MSUD as these data were not collected as part of the registry survey. There are several methods of classification of MSUD, based on clinical presentation, gene involved, and enzyme activity level [5]. Because classification can be ambiguous, and usually not clearly reported to patients, we elected not ask respondents for their MSUD type. We did ask for information about enzyme activity levels and genotype, although very few registrants shared this information. Genotype data was only reported by one respondent, even though 22 reported having undergone genetic testing. Further research is needed to explore the barriers that patients face in reporting genotype information. Obtaining genotype information via a patient-reported registry is therefore a challenge that may require alternative approaches, such as assistance from a genetic counselor.

Additional data curation efforts for NBS Connect are currently underway to clarify inconsistent responses, verify outlying data points, and obtain additional information such as data from genetic testing, enzyme activity, and other laboratory reports. These efforts will improve the accuracy of the self-report data for future studies using NBS Connect registry data. In addition, yearly update of data by respondents will allow for longitudinal analysis of data from the registry in the future.

5. Conclusions

Our NBS-MSUD Connect registry respondents reported a range of plasma leucine levels with over half having levels above the therapeutic range. Difficulty with maintenance of therapeutic plasma leucine levels was seen even in those who follow diet all of the time, reflecting the difficulties in managing MSUD. Despite treatment, there was a high rate of hospitalizations, MSUD symptoms, comorbid neuropsychological symptoms, and skin conditions. Newborn screening and early treatment may help reduce the rate of neuropsychological comorbidities and optimize growth. These results highlight the value of self-report registry data for rare diseases such as MSUD.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2018.01.001.

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