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ORIGINAL ARTICLE

Long-term metabolic follow-up and clinical outcome of 35 patients with maple syrup urine disease

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Abstract

Background Maple syrup urine disease (MSUD) is a rare disease that requires a protein-restricted diet for successful management. Little is known, however, about the psychosocial outcome of MSUD patients. This study investigates the relationship between metabolic and clinical parameters and psychosocial outcomes in a cohort of patients with neonatal-onset MSUD.

Methods Data on academic achievement, psychological care, family involvement, and biochemical parameters were collected from the medical records of neonatal MSUD patients treated at Necker Hospital (Paris) between 1964 and 2013.

Results Thirty-five MSUD patients with a mean age of 16.3 (2.1–49.0) years participated. Metabolic decompensations (plasma leucine >380 μmol/L) were more frequent during the first year of life and after 15 years, mainly due to infection and dietary noncompliance, respectively. Leucine levels increased significantly in adulthood: 61.5% of adults were independent and achieved adequate social and professional integration; 56% needed occasional or sustained psychological or psychiatric care (8/19, with externalizing, mood, emotional, and anxiety disorders being the most common). Patients needing psychiatric care were significantly older [mean and standard deviation (SD) 22.6 (7.7) years] than patients needing only psychological follow-up [mean (SD) 14.3 (8.9) years]. Patients with psychological follow-up experienced the highest lifetime number of decompensations; 45% of families had difficulty coping with the chronic disease. Parental involvement was negatively associated with the number of lifetime decompensations.

Conclusion Adults had increased levels of plasma leucine, consistent with greater chronic toxicity. Psychological care was associated with age and number of decompensations. In addition, parental involvement appeared to be crucial in the management of MSUD patients.

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Keywords Decompensation · Maple syrup urine disease · MSUD · Psychosocial outcome · Leucine

Introduction

Maple syrup urine disease (MSUD) is due to a defect in the branched-chain alpha ketoacid dehydrogenase enzyme

complex (EC 1.2.4.4) with accumulation of branched-chain amino acids (BCAAs) and the corresponding branched-chain keto acids (Clow et al. 1981). Delayed treatment is associated with irreversible neurological impairment (Hilliges et al. 1993). Hemofiltration is often required at diagnosis, together with glucose and lipids IV and a BCAA-free medical diet (Clow et al. 1981; Morton et al. 2002; Strauss and Morton 2003; Hoffmann et al. 2006). Management associates a leucine-restricted diet and a mixture of amino acid supplements and caloric support.

Early diagnosis and treatment significantly improved prognosis, resulting in patients reaching adulthood (Aoki and Wada 1988; Hilliges et al. 1993; Hoffmann et al. 2006; Walterfang et al. 2013; Herber et al. 2015; Couce et al. 2015). This study investigates the long-term follow-up of patients with neonatal-onset MSUD, with particular focus on the relationship between metabolic and clinical parameters and psychosocial outcomes.

Patients and methods

Patients

Between 1964 and 2013, 41 MSUD patients were diagnosed at Necker Hospital (Paris). Inclusion criteria were biochemical diagnosis within the first month of life and follow-up in the same clinical department. Exclusion criteria were late-onset MSUD ($n = 4$) and <1.5 years old at the time of chart review ($n = 2$). In most patients, the diagnosis was confirmed by molecular genetic analysis. All patients were treated with a leucine-restricted diet combined with adjusted doses of a BCAA-free MSUD mixture (0.5–2 g/kg day). Valine and isoleucine (200–600 mg/day) were given on a case-by-case basis according to plasma levels. No patient was responsive to thiamine when given.

Methods

Data collection

Charts were retrospectively reviewed, including physical examinations, psychological tests, nutritional and biochemical parameters, decompensations, and medical treatments.

Biochemical parameters and decompensations

Plasma amino acids were measured by a Jeol aminotac analyzer; measurements on dried blood were done by tandem mass spectrometry (MS/MS) from 2012 onward. Since May 2007, all plasma leucine levels were stored in a database. In MSUD patients, the recommended goal for amino acid levels are leucine 76–205 μmol/L, isoleucine 40–90 μmol/L, and valine 200–425 μmol/L (Morton et al. 2002; Hoffmann et al. 2006; Servais et al. 2013). In practice, leucine values between 76 and 380 μmol/L were considered acceptable. Leucine levels were followed up every week during the first year of life then every other week until 15 years of age and monthly thereafter. Emergency metabolic analysis was performed when a patient had any unusual symptom (e.g., fatigue or signs of infection). Details on emergency metabolic crises were also collected. A metabolic decompensation was defined by a plasma leucine level > 380 μmol/L, usually due to a catabolic state (e.g., infection) or excess leucine in the diet. Decompensation was treated by a leucine-free and high-caloric diet (principally including carbohydrates and lipids) combined with an a mixture of BCAA-free amino acid supplements orally or IV. Metabolic decompensation events were managed as follows:

- At home, with treatment orally when leucine levels were between 380 and 760 μmol/L in the absence of gastrointestinal or neurological symptoms.
- In the hospital, with continuous enteral feeding and/or infusion IV when leucine levels were >760 μmol/L and/or when patients presented with gastric intolerance.
- In the intensive care unit, if leucine levels were >1140 μmol/L; hemodialysis was considered based on neurological signs, kinetics of leucine levels, and clinical context (i.e., whether the patient was in a catabolic state, such as resulting from gastroenteritis).

Treatment options: amino acid mixture orally versus IV

Since 2010, we have used a mixture of BCAA-free amino acid supplement delivered IV for MSUD patients (called hereafter IVAA, Agence Générale des Equipements et Produits de Santé or AGEPS, France) when enteral feeding was impossible (e.g., vomiting, refusal). IVAA is composed of all amino acids except valine, leucine, and isoleucine and is a critical part of the treatment. AGEPS synthesized an formula for IV delivery at our request for specific use in MSUD patients with gastroenteritis. Fourteen patients have been treated with IVAA since 2011. We compared the orally prepared mixture of amino acids (OAA) from 2008 until 2010 and IVAA for visits from 2011 through 2013.

Psychomotor and neurological assessments

a. Psychomotor and development tests

The psychomotor evaluation was performed using standardized psychometrics tests:

- Developmental quotient (DQ) by the Brunet-Lézine test, 6–30 months. The DQ measures a developmental age and ratio for children and includes four main features: postural development, hand–eye coordination, language, and socialization.
- Intellectual quotient (IQ) by Wechsler Preschool and Primary Scale of Intelligence (WPPSI-R or WPPSI-III) 30 months to 6 years and by Wechsler Intelligence Scale for Children (WISC-III or WISC-IV) 6–16 years. These tests measure intellectual ability (verbal and intelligence performance) compared with healthy children of the same age. The total IQ is calculated from four principal indexes: verbal comprehension, perceptive reasoning, working memory, and processing speed.

Both IQ and DQ in the general population follow a normal distribution (normal scores: 80–120).

b. Academic achievement

Patients were classified according to their schooling level, as follows:

- Normal academic achievement;
- Delayed academic achievement (learning difficulties needing scholarly support and/or repeating an academic year);
- Specialized schooling (special classes in classical schools dedicated to the education of children with mild developmental delay);
- Medico-educational institute (specialized institutes for the education of children with severe developmental delay).

c. Psychological follow-up and psychiatric care

Patients were also classified by whether a psychological follow-up was thought to be necessary. Any suspicion of a psychiatric pathology by our psychologist (the same for 20 years) led to intervention of a psychiatrist.

- No psychological or psychiatric follow-up;
- Occasional psychological or psychiatric follow-up;
- Continuous psychological and/or psychiatric care.

d. Autonomy in adulthood

Professional integration and autonomy were investigated by reviewing social and medical files. Patients were classified as follows:

- Independent living with adequate socioprofessional integration: patient normally integrated into society, living and working independently, having a normal emotional and social life;
- Partial dependence (usually familial support);
- Living in an institution.

e. Family involvement

A multidisciplinary evaluation by social workers, psychologists, and dieticians was performed to define families involvement in the treatment and their understanding of the chronic disease (respect for particularities of diet and medical treatment, management of catabolic crises, difficulties coping with the chronic disease, patient education):

- Adapted involvement and compliance;
- Negligence or overprotection;
- Complete lack of involvement or denial requiring intervention of social workers.

Data analysis

We determined the number of metabolic decompensations in each age range (<1 year, 1–5 years, 6–9 years, 10–14 years, 15–19 years, and >20 years). As a parameter for leucine toxicity severity, the area under the curve (AUC) for leucine values >380 μmol/L was calculated. Linear trapezoidal method was used, and all AUCs were summed for each patient. Maximum leucine values were defined as the highest plasma leucine values during a decompensation. We calculated hospital stay and recovery speed by dividing the difference between maximal leucine level and the first level < 380 μmol/L by the number of days associated with this decrease.

Descriptive statistics such as percentages, range (min-max), median with 25th and 75th percentiles (P25–P75), and arithmetic mean with standard deviation (SD) were used to summarize patient characteristics. Comparisons were based on nonparametric tests. Fisher's, Mann–Whitney, Kruskal–Wallis, and Wilcoxon tests were used to investigate relationships between clinical and biochemical parameters. Post hoc Bonferroni–Dunn tests were performed when appropriate. Associations between decompensations and psychosocial outcome were assessed using logistic regression models with adjustment for plasma leucine levels. Results were expressed as odds ratios (OR) with 95% confidence intervals (95% CI).

Since available follow-up amino acid data was complete only for patients born after May 2007, calculations were also stratified by date of birth (i.e., before versus after May 2007). Statistical analyses were performed with STATA statistical software (release 13.0; Stata Corporation, College Station, TX, USA).

Results

Our study involved 35 patients (32 families, 21 females, 14 males) who were, on average, 16.3 years old (median 14; P25–P75 8.0–24.0; min–max 2.1–49.0 years). Six patients were <6 years, six between 7 and 10 years, eight between 11 and 16 years, six between 16 and 20 years, and nine ≥20 years (Table 1).

Consanguinity was found in 23% of cases. Pregnancies were uneventful, with normal birth parameters at delivery. Survival rate was 97% (34/35). One patient died at age 22 while in a coma due to inappropriate voluntary intake of proteins consecutive to suicidal ideation and dangerous behavior.

Diagnosis

Failure to thrive and vomiting were the most common clinical presentations, with lethargy leading to coma in 26 of 32 neonates for whom the data was available. The diagnosis was made on average (SD) at 10.3 (4.5) days, with median plasma leucine levels of 3378.2 μmol/L (P25–P75: 2926–3800 μmol/L). Siblings were treated prophylactically after birth. Two presymptomatic neonates were diagnosed based on familial history. No difference in plasma leucine levels was detected between patients born before and after May 2007 (median levels: 3378.2 μmol/L versus 3389.6 μmol/L, Kruskal–Wallis test, $p = 0.911$); 78.1% of patients (25/32) required hemodialysis; one required additional exchange transfusion. Plasma leucine levels normalized in the neonatal period for all patients.

Table 1 Characteristics of the study population: 35 patients with neonatal maple syrup urine disease

Characteristic	No.* (%) or mean (SD)
Sex, *n* (%)	
Male	14 (40.0)
Female	21 (60.0)
Consanguinity, *n* (%)	8 (22.9)
Patients born after May 2007, *n* (%)	6 (17.1)
Age in 2013 (in years), mean (SD)	16.3 (11.3)
Diagnostic parameters	
Prenatal diagnosis, *n* (%)	2 (5.7)
Age at diagnosis (days), mean (SD)	10.3 (4.5)
Leucine levels (μmol/L) at diagnosis, mean (SD)	
All patients	3302.7 (939.6)
Born before May 2007	3327.1 (723.2)
Born after May 2007	3123.5 (1599.5)
Hemodialysis, *n* (%)	25 (78.1)
Exchange transfusion, *n* (%)	2 (6.3)
Coma, *n* (%)	26 (81.3)

SD standard deviation

*Number of patients may vary because of missing information

Long-term dietary management

Mean (SD) leucine tolerance evolved as follows: 359.5 (58.2) mg/day before age 1, 492.2 (93.3) mg/day between 1 and 6 years, 587.8 (123.0) mg/day between 6 and 10 years, 725.0 (209.0) mg/day between 10 and 15 years, and 1134.6 (1170.0) mg/day after 15 years. Apart from episodes of decompensation, nasogastric or gastrostomy tube feeding was used daily in patients with feeding difficulties (10/34), anorexia (7/10), or brain damage (3/10).

Acute metabolic events

Table 2 summarizes the metabolic events by age. Patients <1 year had the highest number of yearly decompensations, followed by those between 15 and 19 years. Mean leucine levels were similar across all age groups.

Triggers for decompensation were mainly infectious, especially in infants; lack of diet compliance in adolescents; and onset of menstruation in girls. Clinical presentations during decompensations were variable: asymptomatic (diagnosed solely by plasma leucine level), reports of fatigue or digestive symptoms, and alterations in consciousness or hallucinations. One patient described transient visual problems, along with a failure to recognize his mother's face (he reported seeing a ghost). His maximal plasma leucine level during this acute episode was 1649.2 μmol/L. Two other patients described distorted vision or visual hallucinations (max. leucine levels 934.8 μmol/L and 744.8 μmol/L).

Plasma leucine levels

Medians of plasma leucine levels averaged over the period 2007–2013 differed by age groups (Kruskal–Wallis test, $p = 0.002$), (Fig. 1). In all age groups except ≥20 years, median plasma leucine levels were <380 μmol/L, whereas in patients ≥20 years, the median was 522.3 μmol/L (P25–P75: 370.5–586.6 μmol/L; p value of post hoc Bonferroni–Dunn test <0.05). The difference was still significant when comparing patients from the 15- to 20-year group with those aged ≥20 years, although both groups had similar follow-up with regular leucine level evaluations (post hoc Bonferroni–Dunn test, $p < 0.05$).

Table 2 Acute metabolic decompensations and plasma leucine levels during decompensations by age range

Age	< 1 year	1–5 years	6–9 years	10–14 years	15–19 years	≥ 20 years
Number of patients	26	31	26	19	13	9
Number of years	1	5	4	5	5	*
Decompensations, mean (SD)						
Total number	6.8 (3.7)[a]	18.5 (14.2)[a,b]	11.3 (9)[a,b,c]	12.9 (13.8)[a,d]	22.1 (11.4)[a,c,d]	21.4 (15.2)[a,c]
Total number per year	6.8 (3.7)[a]	4.4 (3.2)[a,d]	3.6 (3.0)[a,e]	3.1 (2.9)[a,b,d]	5.5 (2.2)[b,e,c]	2.5 (1.4)[a,c]
Total number of hospitalizations per year	2.3 (2.4)	1.4 (1.3)	1.1 (1.2)	1.2 (1.5)	1.7 (1.4)	1.4 (1.4)
Total number treated at home per year	4.5 (2.9)[a]	3.0 (2.3)[a,b]	2.3 (1.8)[a,c]	1.8 (2.2)[a,b,d]	3.7 (2.4)[c,d,e]	1.0 (1.0)[a,b,e]
Total number treated by hemodialysis per year	0.1 (0.3)	0.1 (0.1)	0.1 (0.2)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)
Leucine levels (μmol/L), median (P25–P75)						
Mean level	687.0 (539.6–760.0)	585.2 (532.0–676.4)	608.0 (528.2–771.4)	646.0 (551.8–836.0)	671.1 (549.5–725.8)	738.7 (570.0–836.8)
Maximum level	1067.8 (661.2–1459.2)	1067.8 (858.8–1596.0)	1048.8 (752.4–1322.4)	980.4 (792.7–1321.6)	1238.8 (912.0–1504.8)	1140.0 (752.4–1605.9)

Number of patients may vary because of missing information

P25–P75 25th and 75th percentiles, *SD* standard deviation

*Years after 20 years varies depending on patient age

a, b, c,d, e : $p < 0.05$, p values from post hoc Bonferroni–Dunn test

Psychomotor evaluation, schooling, psychological follow-up, independence, and family involvement in the disease

Psychomotor development tests

Brunet–Lézine's psychomotor developmental test [n = 9, mean age (SD) = 1.7 (0.8) years] showed a mean (SD) DQ of 82.6 (16.4) (min–max: 53–104). The WPPSI-III test [n = 3, 4.3 (0.9) years] showed an IQ of 80.6 (15.6) (min–max 65–102), and the WISC-III or IV test [n = 20, 9.1 (3.2) years] showed an IQ of 88.6 (16.8) (min–max 53–126) (Table 3).

Academic achievement

Academic achievement was normal in 19/35 patients (54.3%) and delayed in 11 (31.4%). Four patients (11.4%) went to a specialized school (ages 16, 24, 34, and 49 years in 2013), and one patient went to a medicoeducational institute (2.9%). Speech therapy and/or occupational therapy was required in 57.1% of patients with normal or delayed schooling.

Psychological follow-up and psychiatric care

For patients with available data (n = 34), 15 (44%, median age 12 years) did not need psychological consultation. Patients with maladapted social behavior or major difficulties coping with their diet were referred for psychological consultation. Nineteen patients (56%) needed either occasional counseling/psychotherapy (n = 14, 13.5 years) or sustained psychological follow-up (n = 5, 24 years). Patients' ages differed significantly across groups (p = 0.034), with those who required a sustained psychological follow-up plan being older. Among patients requiring a psychological consultation, eight needed psychiatric care. Retrospective data from the psychiatric follow-up showed externalizing disorders in three, mood or emotional disorders in four (one of whom had a manic episode), and anxiety disorder in one. Patients who required psychiatric care were significantly older [median (P25–P75) age 21.0 (17.0–31.0) years] than those who required only psychological follow-up [12.0 (8.0–19.0) years; Mann-Whitney test, p = 0.047].

Independence at adult age

Eight of 13 (61.5%) adult patients (25 years) were completely independent and able to achieve adequate professional integration, whereas three patients were still dependent on their parents. After enrollment in a specialized school during childhood, two adults lived in an institution due to severe neurodevelopmental disabilities.

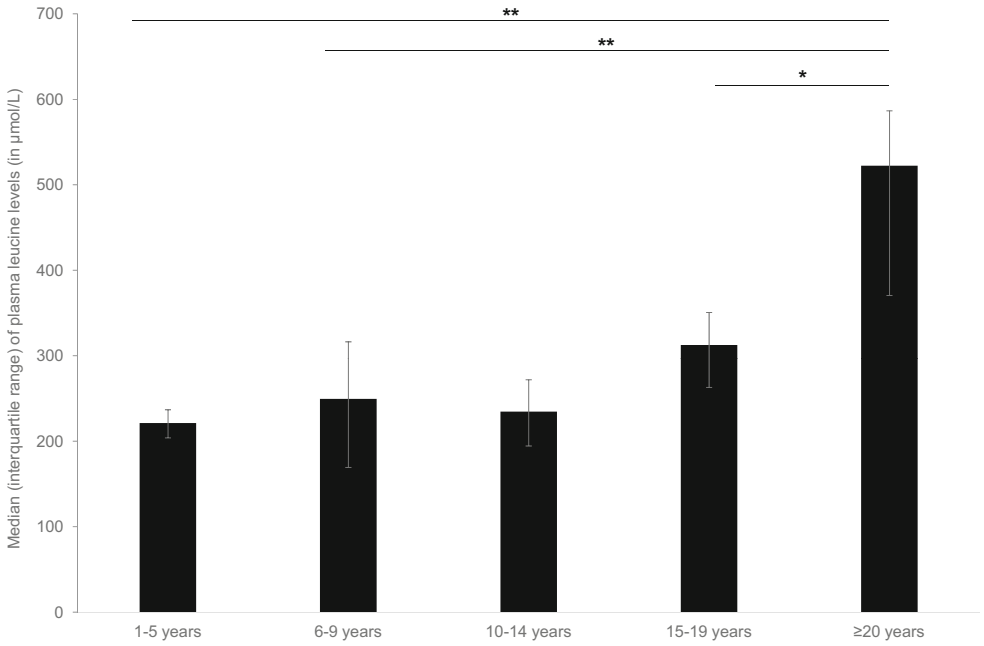

Fig. 1 Median values of plasma leucine levels (in μmol/L) averaged between 2007 and 2013 by age group. Each *bar* represents the median value with interquartile ranges over the corresponding age interval. *P* values are from posthoc Bonferroni–Dunn test (*p* value from Kruskal–Wallis test = 0.002). *$P < 0.05$, **$p < 0.01$

Family involvement

Eighteen families (18/33, 55%) proved to be compliant with diet and treatment. Six families (18%) had difficulties coping with the chronic disease, either neglecting or overprotecting their children, and needed educational advice by a psychosocial team. For nine patients (27%), families were described as completely reckless and negligent, denying the patient's chronic condition, leading to risky behavior; these families needed intervention by social workers and sustained follow-up.

Outcomes in relation to clinical and biochemical parameters

Table 3 summarizes the relation between each type of outcome (academic, psychological, independence), parental involvement in the disease, age, plasma leucine levels at diagnosis, hemodialysis, lifetime and yearly number of decompensations, and leucine AUC. Academic achievement did not differ with age or plasma leucine levels at diagnosis, whether or not hemodialysis was performed, or with the number of decompensations. This remained true after stratification for year of birth (before/after 2007). Leucine AUC tended to be higher in patients who required specialized schooling or in those who went to a medicoeducational institute (Kruskal–Wallis test, $p = 0.127$).

Need for psychological follow-up did not differ with age, plasma leucine level, and treatment at diagnosis. Conversely, the need for psychological follow-up was significantly associated with the number of lifetime metabolic decompensations (treated at home and at hospital). Some associations with leucine AUC were found (Kruskal–Wallis test, $p = 0.061$). For each increase in maximum leucine levels (+1 μmol/L), a 20% increase in psychological referral or care was estimated, with borderline significance [OR (95% CI) 1.20 (1.00–1.44), $p = 0.053$]. This relationship attained statistical significance for children born before 2007 [1.58 (1.10–2.25), $p = 0.012$]. Independence was not associated with age at diagnosis, initial plasma leucine level, hemodialysis, decompensation, or leucine AUC.

The number of lifetime decompensations was associated with parental involvement (Kruskal–Wallis test, $p = 0.035$). Appropriate parental involvement in the treatment tended to lower leucine AUC (Kruskal–Wallis test, $p = 0.056$). This association was significant in patients born before 2007 (Kruskal–Wallis test, $p = 0.021$). Family involvement was also positively associated with higher initial leucine levels (Kruskal–Wallis test, $p = 0.031$).

Treatment options

Hospital stay and time needed for normalization of leucine levels differed according to treatment. On average, patients with OAA spent 4.1 (1.4) days [median (P25–P75) = 4.2 (3.0–4.9) days] at the hospital, whereas IVAA patients spent 3.6 (1.3) days [median (P25–P75) = 3.0 (2.6–4.5) days, Wilcoxon test, $p = 0.030$]. Leucine level normalization was faster when patients were treated IV rather than orally (Wilcoxon test, $p = 0.015$).

Discussion

This study investigated the outcomes of 35 patients with neonatal-onset MSUD. Patients who needed psychological—

Table 3 Relationship between academic achievement, psychological and independence outcomes, parental involvement and diagnostic age (in days), plasma leucine at diagnosis (in μmol/L), hemodialysis, decompensations, area under the curve (AUC, in μmol/L/day) for plasma leucine levels >380 μmol/L during follow-up, and age in 2013 (in years)

	Diagnostic age, median (P25–P75)	Initial plasma leucine, median (P25–P75)	Hemodialysis *n* (%)	Decompensations		AUC, median (P25–P75)	Age in 2013, median (P25–P75)
				Lifetime, median (P25–P75)	Yearly, median (P25–P75)		
Schooling (*n* = 35)							
Normal academic achievement (*n* = 19)	9 (8–13)	3298.4 (2812.0–3765.8)	13 (72.2)	33 (19–85)	4.6 (2.8–6.5)	31,818.1 (14,533.1–116,968.8)	12 (8–18)
Delayed academic achievement (*n* = 11)	9.5 (9.0–14.5)	3446.6 (3226.2–3963.4)	6 (60.0)	30 (14–68)	2.9 (2.3–4.5)	54,438.6 (24,063.4–165,069.8)	14 (9–24)
Specialized schooling (*n* = 4)	8 (8–10)	2736 (2432–3800)	2 (66.7)	71.5 (11–147)	3.0 (0.7–5.2)	77,451.5 (52,165.8–363,711.5)	29 (20–41.5)
Medico-educational Institute (*n* = 1)	16 (−)	3648 (−)	1 (100.0)	75.0 (−)	10.7 (−)	203,443.3 (−)	7 (−)
Psychological care (*n* = 34)							
Not needed (*n* = 15)	9 (7–13)	3306 (2660–3800)	11 (84.6)	21 (14–27)[b]	3.8 (2.0–6.5)	22,996.3 (14,533.1–75,860.4)	12 (3–14)[a]
Occasional consultations (*n* = 14)	10 (9–16)	3446.6 (3116.0–3777.2)	7 (50.0)	71 (33–85)[b]	3.9 (2.9–5.3)	47,092.0 (31,818.1–190,325.0)	13.5 (8–19)[a]
Sustained follow-up (*n* = 5)	9 (8–10)	3040.0 (2736.0–3412.4)	4 (80.0)	90 (89–126)[b]	4.9 (2.9–5.0)	60,796.2 (57,843.3–547,087.8)	24 (18–31)[a]
Independence (*N* = 13)							
Independent life (*n* = 8)	15 (10–17)	3355.4 (3040.0–3587.2)	3 (50.0)	79.5 (41–95)	3.2 (2.5–4.6)	148,606.5 (40,866.4–216,405.3)	25 (18.5–31)
Partial dependence (*n* = 3)	9 (9–9)	3769.6 (3412.4–4126.8)	1 (50.0)	55 (5–89)	2.9 (0.2–2.9)	94,106.8 (51,033.8–547,087.8)	31 (19–49)
Living in an institution (*n* = 2)	9 (8–10)	3268 (2736–3800)	2 (100.0)	147 (126–168)	5.2 (4.9–5.5)	347,056.3 (60,796.2–633,316.3)	29 (24–34)
Parental involvement in the disease (*n* = 33)							
Involvement and compliance (*n* = 18)	9 (8.5–11.5)	3587.2 (3290.8–3906.4)[a]	14 (82.4)	23 (14–74)[a]	3.5 (2.4–5.0)	31,818.1 (16,436.8–46,159.4)	12 (8–17)
Negligence or overprotection (*n* = 6)	10 (9–17)	3420 (3040–3800)[a]	3 (50.0)	61.5 (36.0–90.0)[a]	3.9 (2.8–5.5)	51,033.8 (18,023.9–60,796.2)	18.5 (13–24)
Complete lack of involvement or denial (*n* = 9)	9.5 (8.0–16.5)	2850.0 (2238.2–3188.2)[a]	5 (55.6)	75 (45–99)[a]	5.0 (3.6–6.6)	184,256.6 (61,649.6–381,086.4)	15 (9–31)

No statistical difference in initial plasma leucine levels in stratified analysis (before/after May 2007)

No statistical difference in AUC in stratified analysis (before/after May 2007), except for parental implication (before May 2007, $p = 0.021$; after May 2007, $p = 0.675$)

P25–P75 25th and 75th percentiles, *AUC* area under the curve

[a] $p < 0.05$, [b] $p < 0.01$, *p*-value from Kruskal–Wallis test or Fisher's exact test

and in particular, psychiatric—follow-up were the oldest. Adult patients had significantly higher median plasma leucine levels compared with children, suggesting that patients become less compliant with diet as they enter adulthood. Adult patients also had a higher number of lifetime metabolic decompensations. Leucine levels tended to be associated with psychological outcome. This may suggest that a long period of leucine toxicity, as well as recurrent acute decompensations, exposes patients to psychological comorbidity. It is noteworthy that acute decompensations during psychiatric episodes and the metabolic disorder per se are interdependent, causing mutual instability and making patient rehabilitation more complicated. Among the eight patients with psychiatric follow-up, bipolar disorder was diagnosed in one patient without acute metabolic decompensation. These neuropsychiatric comorbidities have rarely been described in MSUD, and the frequency of such symptoms is not well known. In addition to a long period of leucine toxicity, the diagnosis of MSUD itself seems to be a trigger for the development of psychiatric symptoms, as the risk of decompensation and burden of strict diet is an important stress factor in vulnerable patients. Muelly et al. reported that 83% of patients (mean age 36 years) suffer from depression and anxiety, especially when they presented with neonatal coma. On another hand, patients were prone to hyperactivity and had less favorable cognitive outcome when lifetime metabolic control was poor (Muelly et al. 2013). Moreover, dietary treatment per se and the risk of life-threatening decompensation may play a role in psychological morbidity, as these issues are also associated with higher perceived burden for the family (Packman et al. 2007; Weber et al. 2012; Fabre et al. 2013; Gramer et al. 2014). The importance of long-term endogenous or exogenous leucine excess, but also the importance of specialized management to avoid nutritional deficiencies that can influence mood and behavioral disorders appearing later in life, was emphasized (Flores et al. 2016).

In our study, familial adaptation to treatment led to a better metabolic equilibrium over time, emphasizing the importance of parental involvement in the treatment of chronic pediatric diseases. Although patients can continue to live a normal life into adulthood without any serious complications (le Roux et al. 2006), long-term compliance to such a strict diet is difficult (Kowalik et al. 2007) and requires intensive therapeutic education, sometimes complicated by cultural peculiarities and language difficulties (Simon et al. 2007). A holistic approach that incorporates the family's social context is essential (Weber et al. 2012). Moreover, educating teenagers about their diet and lifestyle requirements represents a challenge to balancing achievement of independence and limiting decompensations that will impact employment and social life (Packman et al. 2012).

We found that plasma leucine levels at diagnosis (similar in patients born before and after 2007) were not associated with either psychological outcome or academic achievement. Normal academic achievement was observed in 54.3% of patients, with IQ and ID between borderline values of 80 and 90. Whatever their academic levels, 57.1% needed speech therapy or psychomotor/occupational therapy at school age, suggesting specific learning disorders, as recently reported in a national cohort of primary schoolchildren (Bouchereau et al. 2017). All adults in our study who attended a mainstream school (5/13) were independent; 60% who needed assistance at school (n = 3/5) became independent; the remaining 40% (2/5) became partially independent. The impact of early diagnosis on cognitive outcome was previously reported: notably, time after birth with plasma leucine levels >1000 μmol/L (Hilliges et al. 1993; Morton et al. 2002; Ibarra-González et al. 2007) or long-term metabolic control assessed by plasma leucine levels (Clow et al. 1981; Simon et al. 2005; Hoffmann et al. 2006; Couce et al. 2015). Even if the relation was controversial (Yoshino et al. 1999; le Roux et al. 2006), the quality of long-term metabolic control may affect IQ (Hilliges et al. 1993), as shown in 37 classic MSUD patients aged 5–35 years (Muelly et al. 2013). It was suggested that plasma leucine should not exceed 200 μmol/L in infants and preschool children to obtain the best intellectual outcome (Hoffmann et al. 2006). Independent of baseline leucine levels, the risk of metabolic decompensation at any time and any age, especially during common childhood infections (Clow et al. 1981), may impair neurologic function (Morton et al. 2002).

The possible mechanisms involved in brain deterioration may include the monoaminergic neurotransmitter system (Walterfang et al. 2013), particularly glutamate (Yudkoff et al. 2005; Haroon et al. 2016), cerebral depletion of essential amino acids (Yudkoff et al. 2005), toxicity of branched-chain keto acids on astrocytes and glial cells (Funchal et al. 2004, 2007; Sitta et al. 2014), resulting in brain energy depletion (Sgaravatti et al. 2003; Ribeiro et al. 2008; Strand et al. 2014) and oxidative stress.

Liver transplantation was reported as an interesting alternative to dietary treatment (Barshop and Khanna 2005; Strauss et al. 2006; Yasui et al. 2016), although neurological sequelae are not corrected by transplantation (Mazariegos et al. 2012) because neurostructural changes are relatively irreversible (Muelly et al. 2013). However, liver transplantation reduces the risk of further neurological damage and might maintain neurological functionning at the pretransplantation level (Soltys et al. 2015).

MSUD patients can develop normally. However, the medical diet is strict, young adults are less compliant, and decompensations from catabolic crises can be frequent. Increased leucine levels during follow-up and the burden of chronic disease may account for the observed unsatisfactorily high psychological/psychiatric comorbidity. Studies focusing on this topic could reveal new strategies of care for the metabolic specialist and psychiatrists alike. Psychological follow-up

over the years has remained the same in our metabolic unit, and there is a crucial need for identifying and evaluating psychological problems early. There is also an emerging need for a holistic approach, since psychosocial support for patients and families should be initiated early and focus on familial adaptation to the disease.

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Compliance with ethical standards

Conflict of interest M.-T. Abi-Wardé, C. Roda, J.-B. Arnoux, A. Servais, F. Habarou, A. Brassier, C. Pontoizeau, V, Barbier. M. Bayart, V. Leboeuf, B. Chadefaux-Vekemans, S. Dubois, M. Assoun, C. Belloche, J.-M. Alili, M.-C. Husson, F. Lesage, L. Dupic, B. Theuil, C. Ottolenghi, and P. de Lonlay declare that they have no conflict of interest.

References

Aoki K, Wada Y (1988) Outcome of the patients detected by newborn screening in Japan. Acta Paediatr Jpn Overseas Ed 30:429–434

Barshop BA, Khanna A (2005) Domino hepatic transplantation in maple syrup urine disease. N Engl J Med 353:2410–2411. https://doi.org/10.1056/NEJM200512013532220

Bouchereau J, Leduc-Leballeur J, Pichard S et al (2017) Neurocognitive profiles in MSUD school-age patients. J Inherit Metab Dis. https://doi.org/10.1007/s10545-017-0033-7

Clow CL, Reade TM, Scriver CR (1981) Outcome of early and long-term management of classical maple syrup urine disease. Pediatrics 68: 856–862

Couce ML, Ramos F, Bueno MA et al (2015) Evolution of maple syrup urine disease in patients diagnosed by newborn screening versus late diagnosis. Eur J Paediatr Neurol 19:652–659. https://doi.org/10.1016/j.ejpn.2015.07.009

Fabre A, Baumstarck K, Cano A et al (2013) Assessment of quality of life of the children and parents affected by inborn errors of metabolism with restricted diet: preliminary results of a cross-sectional study. Health Qual Life Outcomes 11:158. https://doi.org/10.1186/1477-7525-11-158

Flores K, Chikowski R, Morrell DS (2016) Acrodermatitis dysmetabolica in an infant with maple syrup urine disease. Clin Exp Dermatol 41: 651–654. https://doi.org/10.1111/ced.12876

Funchal C, Gottfried C, De Almeida LMV et al (2004) Evidence that the branched-chain alpha-keto acids accumulating in maple syrup urine disease induce morphological alterations and death in cultured astrocytes from rat cerebral cortex. Glia 48:230–240. https://doi.org/10.1002/glia.20072

Funchal C, Tramontina F, Quincozes dos Santos A et al (2007) Effect of the branched-chain alpha-keto acids accumulating in maple syrup urine disease on S100B release from glial cells. J Neurol Sci 260: 87–94. https://doi.org/10.1016/j.jns.2007.04.011

Gramer G, Haege G, Glahn EM et al (2014) Living with an inborn error of metabolism detected by newborn screening-parents' perspectives on child development and impact on family life. J Inherit Metab Dis 37:189–195. https://doi.org/10.1007/s10545-013-9639-6

Haroon E, Fleischer CC, Felger JC et al (2016) Conceptual convergence: increased inflammation is associated with increased basal ganglia glutamate in patients with major depression. Mol Psychiatry 21(10): 1351–1357

Herber S, Schwartz IVD, Nalin T et al (2015) Maple syrup urine disease in Brazil: a panorama of the last two decades. J Pediatr 91:292–298. https://doi.org/10.1016/j.jped.2014.08.010

Hilliges C, Awiszus D, Wendel U (1993) Intellectual performance of children with maple syrup urine disease. Eur J Pediatr 152:144–147

Hoffmann B, Helbling C, Schadewaldt P, Wendel U (2006) Impact of longitudinal plasma leucine levels on the intellectual outcome in patients with classic MSUD. Pediatr Res 59:17–20. https://doi.org/10.1203/01.pdr.0000190571.60385.34

Ibarra-González I, Fernández-Lainez C, Belmont-Martínez L, Vela-Amieva M (2007) Increased mortality and disability in a cohort of Mexican children with maple syrup urine disease. Gac Med Mex 143:197–201

Kowalik A, Narojek L, Sykut-Cegielska J (2007) Compliance of the diet restricted with leucine, isoleucine and valine in maple syrup urine disease (MSUD) children. Rocz Państw Zakł Hig 58:95–101

le Roux C, Murphy E, Hallam P et al (2006) Neuropsychometric outcome predictors for adults with maple syrup urine disease. J Inherit Metab Dis 29:201–202. https://doi.org/10.1007/s10545-006-0223-1

Mazariegos GV, Morton DH, Sindhi R et al (2012) Liver transplantation for classical maple syrup urine disease: long-term follow-up in 37 patients and comparative united network for organ sharing experience. J Pediatr 160:116–121.e1. https://doi.org/10.1016/j.jpeds.2011.06.033

Morton DH, Strauss KA, Robinson DL et al (2002) Diagnosis and treatment of maple syrup disease: a study of 36 patients. Pediatrics 109: 999–1008

Muelly ER, Moore GJ, Bunce SC et al (2013) Biochemical correlates of neuropsychiatric illness in maple syrup urine disease. J Clin Invest 123:1809–1820. https://doi.org/10.1172/JCI67217

Packman W, Henderson SL, Mehta I et al (2007) Psychosocial issues in families affected by maple syrup urine disease. J Genet Couns 16: 799–809. https://doi.org/10.1007/s10897-007-9114-3

Packman W, Mehta I, Rafie S et al (2012) Young adults with MSUD and their transition to adulthood: psychosocial issues. J Genet Couns 21: 692–703. https://doi.org/10.1007/s10897-012-9490-1

Ribeiro CA, Sgaravatti AM, Rosa RB et al (2008) Inhibition of brain energy metabolism by the branched-chain amino acids accumulating in maple syrup urine disease. Neurochem Res 33:114–124. https://doi.org/10.1007/s11064-007-9423-9

Servais A, Arnoux JB, Lamy C et al (2013) Treatment of acute decompensation of maple syrup urine disease in adult patients with a new parenteral amino-acid mixture. J Inherit Metab Dis 36:939–944. https://doi.org/10.1007/s10545-012-9570-2

Sgaravatti AM, Rosa RB, Schuck PF et al (2003) Inhibition of brain energy metabolism by the alpha-keto acids accumulating in maple syrup urine disease. Biochim Biophys Acta 1639:232–238

Simon E, Wendel U, Schadewaldt P (2005) Maple syrup urine disease-treatment and outcome in patients of Turkish descent in Germany. Turk J Pediatr 47:8–13

Simon E, Schwarz M, Wendel U (2007) Social outcome in adults with maple syrup urine disease (MSUD). J Inherit Metab Dis 30:264. https://doi.org/10.1007/s10545-007-0475-4

Sitta A, Ribas GS, Mescka CP et al (2014) Neurological damage in MSUD: the role of oxidative stress. Cell Mol Neurobiol 34:157–165. https://doi.org/10.1007/s10571-013-0002-0

Soltys KA, Mazariegos GV, Strauss KA (2015) Living related transplantation for MSUD–caution, or a new path forward? Pediatr Transplant 19:247–248. https://doi.org/10.1111/petr.12423

Strand JM, Skinnes R, Scheffler K et al (2014) Genome instability in maple syrup urine disease correlates with impaired mitochondrial

biogenesis. Metabolism 63:1063–1070. https://doi.org/10.1016/j.metabol.2014.05.003

Strauss KA, Morton DH (2003) Branched-chain Ketoacyl Dehydrogenase deficiency: maple syrup disease. Curr Treat Options Neurol 5:329–341

Strauss KA, Mazariegos GV, Sindhi R et al (2006) Elective liver transplantation for the treatment of classical maple syrup urine disease. Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg 6:557–564. https://doi.org/10.1111/j.1600-6143.2005.01209.x

Walterfang M, Bonnot O, Mocellin R, Velakoulis D (2013) The neuropsychiatry of inborn errors of metabolism. J Inherit Metab Dis 36:687–702. https://doi.org/10.1007/s10545-013-9618-y

Weber SL, Segal S, Packman W (2012) Inborn errors of metabolism: psychosocial challenges and proposed family systems model of intervention. Mol Genet Metab 105:537–541

Yasui T, Suzuki T, Hara F et al (2016) Successful living donor liver transplantation for classical maple syrup urine disease. Pediatr Transplant 20:707–710. https://doi.org/10.1111/petr.12738

Yoshino M, Aoki K, Akeda H et al (1999) Management of acute metabolic decompensation in maple syrup urine disease: a multi-center study. Pediatr Int 41:132–137

Yudkoff M, Daikhin Y, Nissim I et al (2005) Brain amino acid requirements and toxicity: the example of leucine. J Nutr 135:1531S–1538S