

Management of maple syrup urine disease in the Intensive Care and Neonatal Medicine in Monastir

Prise en charge de la leucinoïse dans le service de Réanimation et de Médecine Néonatale de Monastir

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ABSTRACT

Background: Leucinosi (maple syrup urine disease, MSUD) is a rare autosomal recessive aminoacidopathy with a severe neurological and vital prognosis. We aimed to describe its clinical and therapeutic features and identify short- and long-term prognostic factors. **Patients and Methods:** We conducted a retrospective descriptive study in the Intensive Care and Neonatal Medicine Department of the Maternity Center at CHU Fattouma Bourguiba in Monastir from January 2012 to December 2023. All newborns with leucinosi confirmed by amino acid and organic acid chromatography were included. **Results:** Ten neonates were included, mainly from central-western Tunisia (N=5), with consanguinity in 9 cases and a familial history in 8. Neurological symptoms developed after a mean symptom-free interval of 6.5 days, with admission at 12.7 days. Central respiratory distress (N=6), digestive symptoms (N=4), and a characteristic fenureek odor (N=9) were observed. Initial abnormalities included metabolic acidosis (N=6), hyperlactatemia (N=5), hyperammonemia (N=4), and acute renal failure (N=3). Magnetic resonance spectroscopy confirmed the diagnosis at a mean age of 19.4 days. Management included neurological resuscitation and emergency dietary therapy; peritoneal dialysis was required in one patient. Major complications were metabolic decompensation, healthcare-associated infections, respiratory distress, and metabolic acrodermatitis. Four patients died during short-term follow-up, mainly from infections. Among survivors, long-term outcomes included psychomotor delay (N=2), intellectual disability (N=2), and epilepsy (N=1). Genetic testing identified two different BCKDHB mutations. **Conclusion:** Early diagnosis and appropriate management may reduce complications and improve the functional and vital prognosis of patients with MSUD.

Keywords: Maple syrup urine disease; Newborn; Diagnosis; Intensive Care; Prognosis

INTRODUCTION

Maple syrup urine disease (MSUD), also known as leucinosi, is a rare inborn error of metabolism characterized by impaired catabolism of branched-chain amino acids (BCAAs): leucine, isoleucine, and valine. The disease results from a defect in the branched-chain α -ketoacid dehydrogenase (BCKDH) complex, responsible for the oxidative decarboxylation of the corresponding α -ketoacids [1]. In Tunisia, where consanguinity remains frequent, the incidence of MSUD has been estimated between 1/13,716 and 1/66,000 live births [2,3]. Among aminoacidopathies diagnosed in the country, leucinosi represents one of the most frequently diagnosed metabolic disorders.

The classic neonatal form is the most severe and most prevalent phenotype of MSUD, accounting for approximately 75–90% of cases. This form is characterized by a profound enzymatic deficiency, with residual BCKDH complex activity ranging from 0 to 2%. Clinical manifestations typically develop during the first week of life, following a symptom-free interval of approximately 2–5 days [4]. Early signs include poor feeding, vomiting, lethargy, and

progressive neurological deterioration caused by the accumulation of toxic metabolites, particularly leucine and its corresponding α -ketoacids. If untreated, the disease rapidly progresses to acute encephalopathy, cerebral edema, and death [5].

The prognosis of affected newborns remains closely related to the timeliness of diagnosis and treatment. Early metabolic intervention can prevent severe neurological damage and improve survival [6]. However, the management of neonatal MSUD remains challenging in settings where systematic newborn screening is not widely available and access to specialized metabolic investigations is limited. In Tunisia, these challenges may contribute to delays in diagnosis and initiation of treatment. Furthermore, the long-term management of affected infants requires strict dietary control based on specialized BCAA-free or BCAA-restricted metabolic formulas, with carefully adjusted BCAA supplementation when indicated. Limited availability and accessibility of these specialized nutritional products may complicate the implementation of individualized dietary therapy. In addition, optimal management requires regular biochemical monitoring, particularly serial measurement of

plasma BCAA concentrations, to guide dietary adjustments and prevent both metabolic decompensation and excessive nutritional restriction. Limited access to frequent biochemical monitoring may therefore represent an additional challenge in the follow-up of patients with MSUD.

Although MSUD is relatively well studied worldwide, few data are available regarding its clinical presentation and management in developing countries [7]. In Tunisia, only a limited number of studies have described the epidemiological and clinical characteristics of affected patients [2,3,8]. However, data specifically addressing the practical challenges of diagnosing and managing the classic neonatal form, as well as the long-term outcomes of affected infants, remain limited.

The objective of the present study was therefore to describe the epidemiological, clinical, biological, radiological, and therapeutic characteristics of newborns diagnosed with classic neonatal MSUD and to analyze their short- and long-term outcomes.

PATIENTS AND METHODS

Study design and setting

We conducted a retrospective descriptive study in the Neonatal Intensive Care Unit (NICU) of the Maternity and Neonatal Center of Monastir University Hospital, Tunisia. The study covered a 12-year period from January 2012 to December 2023.

Study population and diagnostic criteria

All neonates admitted during the study period with a confirmed diagnosis of MSUD were considered for inclusion, irrespective of whether they were inborn or referred from another institution.

The diagnosis of MSUD was established based on biochemical investigations, including plasma amino acid chromatography and urinary organic acid chromatography, performed at the specialized biochemical laboratory of La Rabta Hospital in Tunis. The diagnosis was based on markedly elevated plasma leucine and other branched-chain amino acids (BCAAs), with or without elevation of their corresponding α -ketoacids. When available, molecular genetic testing was performed to identify pathogenic variants in genes encoding components of the branched-chain α -ketoacid dehydrogenase (BCKDH) complex.

Inclusion criteria

Neonates presenting with the classic neonatal form of MSUD, defined by clinical onset during the neonatal period and confirmed biochemically by amino acid chromatography, with markedly elevated plasma leucine and BCAAs, were included in the study. The classic neonatal phenotype was distinguished from intermediate and intermittent forms by early clinical presentation and marked, persistent elevation of plasma leucine and other BCAAs.

Exclusion criteria

Patients with intermediate, intermittent, or thiamine-responsive forms of MSUD were excluded, as were patients without biochemical confirmation of the diagnosis. Two patients were excluded because of incomplete medical records.

Data collection

Clinical and laboratory data were retrospectively extracted from medical records using a standardized data collection form. Collected variables included demographic and epidemiological characteristics (sex, geographic origin, consanguinity, and family history of MSUD); clinical presentation and age at symptom onset; laboratory and metabolic findings, including biochemical and genetic investigations; neuroimaging findings; therapeutic management, including supportive care, nutritional therapy, and extracorporeal detoxification; and complications and outcomes, including survival, neurological sequelae, and psychomotor development during follow-up.

Definitions of clinical outcomes

Metabolic decompensation was defined as an acute deterioration in clinical status associated with a significant increase in plasma leucine and/or other BCAAs, occurring in the context of an intercurrent illness, fasting, inadequate nutritional intake, or another precipitating factor, and requiring intensification of metabolic treatment.

Healthcare-associated infection was defined as an infection occurring during hospitalization that was not present at the time of admission, based on clinical and/or microbiological findings documented in the medical record.

Neurological sequelae were defined as persistent neurological abnormalities documented after the acute metabolic episode or during follow-up, including seizures, abnormal muscle tone, movement disorders, or other neurological deficits attributable to MSUD-related encephalopathy.

Psychomotor delay was defined as delayed acquisition of age-appropriate developmental milestones, as documented during follow-up visits.

Dermatological complications were defined as clinically documented skin abnormalities occurring during hospitalization or follow-up and recorded in the medical records.

Outcomes

Short-term outcomes included survival, age at death, clinical condition at hospital discharge, occurrence of metabolic decompensation, healthcare-associated infections, and other documented complications during hospitalization. Long-term outcomes included growth parameters, neurological and psychomotor development, recurrence of metabolic decompensation, neurological sequelae, and neurosensory complications documented during follow-up visits.

Statistical analysis

Data were analyzed using SPSS version 22. Continuous variables were expressed as means with standard deviations or medians with ranges, while categorical variables were presented as frequencies and percentages. Due to the small sample size, only descriptive statistical analysis was performed.

Ethical considerations

The study was conducted in accordance with the ethical standards of Monastir University Hospital. Patient anonymity and confidentiality were strictly maintained.

RESULTS

Ten newborns with confirmed MSUD were included during the study period. They represented 0.02% of all hospitalized

neonates and 0.21% of NICU admissions.

Epidemiological characteristics

Of the 10 patients included in the study, seven were female and three were male. The patients originated from several regions of Tunisia, with a predominance from the central-western region.

Parental consanguinity was present in nine cases. Four newborns had a family history of neonatal deaths attributed to MSUD in siblings. In two families, multiple neonatal deaths had previously occurred due to undiagnosed metabolic disease (Figure 1). The demographic and familial characteristics of the 10 neonates are summarized in Table 1. Despite the presence of confirmed cases of MSUD in siblings, prenatal diagnosis had not been performed due to parental refusal.

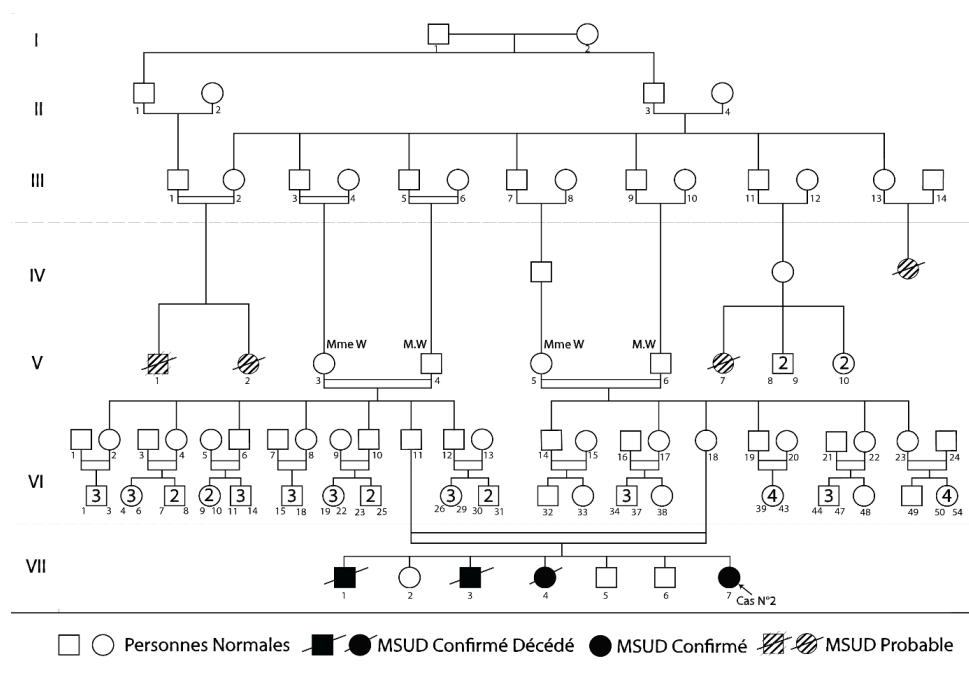


Figure 1. Family pedigree, case No. 2 (VII-7) demonstrating multiple neonatal deaths due to undiagnosed metabolic disease. * MSUD was suspected based on information obtained from the family history, which revealed a severe neurological presentation progressing to coma, followed by early neonatal death, in the absence of definitive biochemical or molecular confirmation.

Table 1. Epidemiological characteristics of neonates in our cohort

Case (n=10)	Gender	Place of birth	Origin	Consanguinity	History of familial leucinosi	Hospitalization within the first 24 hours
1	F	Out born	Gafsa	Yes	No	No
2	F	Out born	Kairouan	Yes	Among siblings	Yes, for surveillance
3	F	Out born	Kairouan	No	No	Yes, for NRD and LBW
4	F	In born	Monastir (Bekalta)	Yes	Within the family	No
5	F	In born	Monastir (Bekalta)	Yes	Among siblings	Yes, for surveillance
6	F	Out born	Sidi Bouzid	Yes	Within the family	No
7	M	Out born	Sidi Bouzid	Yes	Within the family	No
8	F	Out born	Monastir (Moknine)	Yes	Among siblings	Yes, for surveillance
9	M	Out born	Gafsa	Yes	Possible	No
10	M	Out born	Sidi Bouzid	Yes	Within the family	No

M: male; F: female; NRD: neonatal respiratory distress; LBW: low birth weight.

Clinical presentation and laboratory abnormalities

The mean age at onset of symptoms was 6.5 days (range 2–

16 days). Parents sought medical attention after a mean delay of two days following the onset of symptoms.

Neurological manifestations were present in all neonates at admission and included peripheral hypertonia, abnormal movements described as "pedaling" or "boxing," axial hypotonia, feeding refusal, and seizures. Respiratory distress was observed in six newborns, mainly characterized by apnea or bradypnea. Hemodynamic instability was present in one patient.

Digestive symptoms such as vomiting occurred in four newborns and resulted in moderate to severe dehydration in three cases. Hypoglycemia and acetonuria were documented in four patients. A characteristic fenugreek-like odor of urine was detected in all cases. The same odor was also noticed in ear cerumen.

Initial metabolic evaluation revealed hypoglycemia in four neonates, metabolic acidosis in six, hyperlactatemia in five, and hyperammonemia in four. Plasma amino acid chromatography confirmed elevated levels of branched-chain amino acids in all patients. The presence of allo-isoleucine, considered a diagnostic marker of MSUD, was detected. Urinary organic acid chromatography demonstrated increased excretion of branched-chain α -ketoacids.

The di-nitro-phenyl-hydrazine (DNPH) screening test was performed in eight newborns and was positive in seven cases. Table 2 summarizes the main clinical manifestations and laboratory abnormalities observed in the 10 neonates.

Table 2. Main clinical and biological abnormalities in the 10 neonates

Case	Vital distress	Dehydration	Hypoglycemia	AU	ARF	Dysnatremia	Metabolic acidosis (pH)	Lactacidemia (mmol/l)	Ammoniaemia (μ mol/l)
1	Respiratory	Yes	Yes	-	Yes	No	7.23	2.4	136
2	No	No	No	-	No	No	7.45	2.4	<100
3	Respiratory / Hemodynamic	No	No	-	Yes	Hyper	7.15	28	891
4	No	No	Yes	-	No	No	7.42	<2.2	<100
5	Respiratory	No	No	+	No	No	7.42	<2.2	<100
6	No	Yes	Yes	+	Yes	No	7.17	3.1	<100
7	No	No	Yes	4+	No	Hypo	7.05	3	219.6
8	Respiratory	No	No	4+	No	Hypo	7.43	<2.2	<100
9	Respiratory	Yes	No	-	No	Hypo	6.84	<2.2	355
10	Respiratory	No	No	-	No	No	7.18	<2.2	<100

AU: acetonuria; ARF: acute renal failure; Hyper: hypernatremia; Hypo: hyponatremia.

Radiological abnormalities

Head ultrasound revealed increased echogenicity of the periventricular white matter and basal ganglia in four patients. Brain magnetic resonance imaging was performed

in seven cases and showed bilateral symmetrical abnormalities affecting the cerebellar white matter, brainstem, and basal ganglia (Figure 2). Magnetic resonance spectroscopy demonstrated a characteristic peak corresponding to branched-chain amino acids.

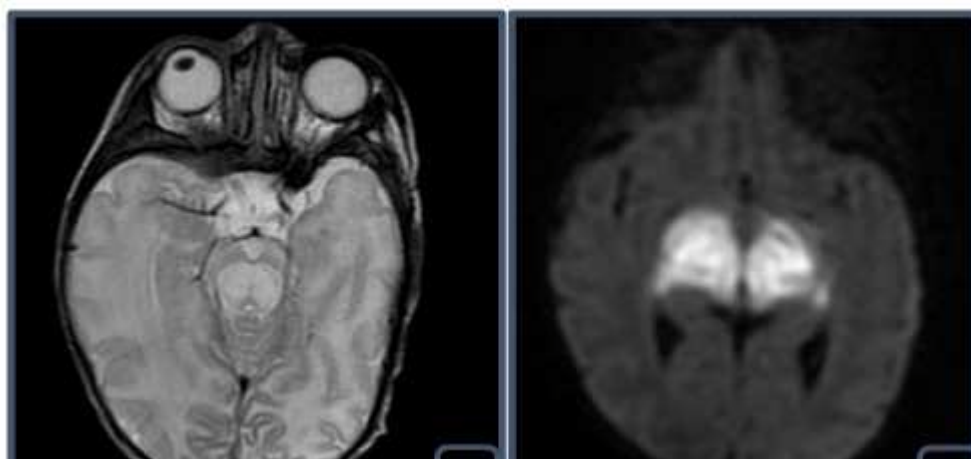


Figure 2. Magnetic resonance imaging, T2 (A) and diffusion (B) sequences, axial section showing a bilateral hypersignal in the mesencephalic region.

Genetic testing

Genetic testing was performed in two patients and identified homozygous mutations in the BCKDHB gene, confirming type 1B MSUD. Two different variants were identified: NM_183050.4(BCKDHB): c.502C>T, p.(Arg168Cys) (case

No. 4) and NM_183050.4(BCKDHB): c.532G>T, p.(Gly178Ter) (case No. 9).

Therapeutic management

Anticonvulsant therapy using phenobarbital was administered in all cases. Mechanical ventilation was

required in seven patients due to severe neurological or respiratory distress.

Given the clinical presentation suggestive of an intoxication-type metabolic disorder, metabolic investigations were initiated immediately upon admission. Although biochemical confirmation of MSUD was obtained after approximately two weeks, specific metabolic treatment was initiated from the first day of hospitalization based on the strong clinical suspicion of MSUD. Metabolic management consisted of initiating an emergency diet devoid of branched-chain amino acids with high caloric intake to prevent catabolism. This regimen was hypercaloric, providing 120–130% of the usual energy requirements, with a carbohydrate- and lipid-based composition and a balanced carbohydrate-to-lipid ratio. Carbohydrates accounted for approximately 60% of the total caloric intake. Protein equivalents, provided as a BCAA-free amino acid mixture (COMIDA MSUD A), were essential and administered at a dose of 2 g/kg/day.

Adequate supplementation with electrolytes, trace elements, minerals, and vitamins was also required during this phase, as these micronutrients are essential for maintaining optimal metabolic function.

The emergency dietary regimen was continued for only 48 hours, as prolonged restriction of BCAAs may lead to deficiencies in essential amino acids. The route of administration was determined according to the severity of the clinical presentation, gastrointestinal tolerance, and the availability of the nutritional products and equipment

required for management, including 20% lipid emulsions, BCAA-free amino acid mixtures, and central venous access.

In our cohort, parenteral nutrition administered through either a central or peripheral venous catheter was initially used in six neonates. Gradual reintroduction of amino acids was attempted once clinical stabilization was achieved. However, supplementation with valine and isoleucine was possible in only two patients because these products were not available in our country.

Peritoneal dialysis was performed in one neonate presenting with severe metabolic intoxication (neurological deterioration) on day 46 of life, and very high leucine levels of 1795 $\mu\text{mol/l}$. The procedure resulted in rapid biochemical improvement (the leucine level decreased to 85 $\mu\text{mol/l}$).

Complications

Several complications occurred during hospitalization. Healthcare-associated infections were recorded in seven patients and represented the main cause of mortality. Hyperammonemia occurred in four neonates and was treated with carbamyl glutamate (Carbaglu®) or sodium benzoate. Table 3 specifies the molecule used and the clinical and biological outcome for neonates with hyperammonemia.

Metabolic acrodermatitis developed in five patients. Skin lesions were located in periorificial and intertriginous areas and were attributed to deficiencies in branched-chain amino acids due to dietary imbalance. Treatment consisted of local care with urea-based Vaseline, antiseptic baths, and essential amino acid supplementation.

Table 3. Management and evolution of hyperammonemia in maple syrup urine disease

Case	Ammonia before treatment ($\mu\text{mol/l}$)	Ammonia purifier used / dose*	Ammonia after treatment ($\mu\text{mol/l}$)	Clinical significance of post-treatment ammonia level	Clinical course
1	136	Sodium benzoate 300 mg/kg/day	63	Decreased	Death 19 days after admission
3	891	Carbamyl glutamate 50 mg/kg/dose	777	Severe persistent hyperammonemia despite treatment, indicating inadequate metabolic control**	Death 1 day after admission
7	219.6	Carbamyl glutamate 50 mg/kg/dose	131.6	Partial reduction in ammonia	Death 9 days after admission
9	355	Carbamyl glutamate 50 mg/kg/dose	54	Marked reduction in ammonia	Death 97 days after admission

* Timing of treatment at admission, immediately after the initial ammonia level was obtained. ** The patient presented with multiorgan failure.

Outcomes

Four patients died during hospitalization, mainly due to severe infections and metabolic decompensation. Among the six surviving patients, the mean duration of hospitalization was 54 days.

Long-term follow-up was available for four children. Two developed spastic encephalopathy with psychomotor delay and visual impairment. One patient developed epilepsy. Table 4 summarizes the psychomotor development and the results of various neurosensory and radiological examinations for the four children.

Table 4. Psychomotor development and neurological impairments in children under observation

Case	Psychomotor delay	Neurological sequelae	Intellectual disability	Epilepsy	Neurophysiological explorations		
					EEG	MRI	AEP / VEP
2	Yes, moderate to severe	Spastic encephalopathy; convergent esotropia; nystagmus	Yes, moderate	No	Normal	Unrequested	Normal
4	No	No	No	No	Normal	Unrequested	Normal
5	No	No	No	No	Normal	Unrequested	Unrequested
6	Yes, moderate	Extrapyramidal syndrome; convergent esotropia; nystagmus	Yes, light	Yes, under levetiracetam; myoclonus with focal seizures	Myoclonus with focal seizures	Cortical and subcortical parenchymal atrophy	Normal

EEG: electroencephalogram; MRI: brain magnetic resonance imaging; AEP, VEP: auditory and visual evoked potentials.

DISCUSSION

MSUD is a rare metabolic disorder but represents one of the most frequent aminoacidopathies in Tunisia, accounting for 32.5% of cases according to a study conducted by the Biochemistry Laboratory at La Rabta Hospital in Tunis [2]. The higher incidence observed in the country is mainly related to the high prevalence of consanguineous marriages.

Our study confirmed the strong association between MSUD and parental consanguinity, which was present in nearly all families. The geographic clustering of several cases raises the possibility of founder variants, although broader molecular studies are required to confirm this hypothesis [2,3,8]. The clinical presentation observed in our cohort is consistent with that described in the literature for classical neonatal MSUD. Symptoms generally appeared during the first week of life after a short asymptomatic period [9].

Neurological manifestations were the most prominent signs and were present in all patients [10]. These neurological symptoms result from the neurotoxic effects of leucine and its metabolites, which cause cerebral edema and neuronal dysfunction [11].

The characteristic odor of urine, often described as resembling maple syrup, was present in all newborns in our study. In Mediterranean populations, however, the odor is more commonly compared to fenugreek [12]. Several metabolic abnormalities were observed in our patients, including metabolic acidosis, hyperlactatemia, and hyperammonemia. Although hyperammonemia is not a typical feature of MSUD, it has been reported in cases with delayed diagnosis and severe metabolic intoxication [13].

Brain MRI proved to be a valuable diagnostic tool. The typical radiological pattern observed in MSUD corresponds to intramyelinic edema affecting specific brain structures such as the cerebellar white matter, brainstem, and basal ganglia [14,15].

Two patients underwent genetic testing, which confirmed the diagnosis of MSUD by identifying the causative variant, whereas in four other patients, the variant was presumed to be present based on the identification of a known genetic variant in an affected relative from the same family. Overall, three variants in the BCKDHB gene (branched-chain 2-keto

acid dehydrogenase E1, β -polypeptide), which encodes the E1 β subunit of the mitochondrial BCKDH complex, were identified in our cohort and were responsible for MSUD type 1B. These variants were NM_000056.3(BCKDHB):c.716A>G, p.(Glu239Gly) (presumed), NM_183050.4(BCKDHB):c.502C>T, p.(Arg168Cys) (identified and presumed), and BCKDHB:c.532G>T (identified).

The NM_000056.3(BCKDHB):c.716A>G, p.(Glu239Gly) variant was first described in the literature by Jaafar et al. [16] in two patients with MSUD originating from Sidi Bouzid and belonging to different families. The authors therefore suggested a founder effect for this variant in the Sidi Bouzid region. Since three patients in our cohort belonged to these two families and given the high frequency of consanguineous marriages within these families, the presence of the same variant was presumed in these three patients.

The second variant, NM_183050.4(BCKDHB):c.502C>T, p.(Arg168Cys), was identified in patient No. 4 and presumed to be the same for his sister (patient No. 5), both of whom belonged to a family from Monastir. Finally, the third variant, NM_183050.4(BCKDHB):c.532G>T, p.(Gly178Ter), was identified in patient No. 9 from Gafsa.

All patients were homozygous for the identified variants. Thus, each patient carried two identical alleles, one inherited from the mother and the other from the father. This finding clearly highlighted the contribution of consanguinity and was consistent with findings from other Arab cohorts [16-18], in which affected individuals were homozygous for the variants, while both parents were heterozygous carriers.

Early metabolic management remains essential for improving the prognosis of MSUD. Treatment aims to reduce the concentration of toxic metabolites through dietary restriction of branched-chain amino acids and prevention of catabolism [19,20]. Metabolic resuscitation, consisting of diet therapy and extracorporeal detoxification [21], must be initiated in parallel with the treatment of this neurological distress.

The suppression of catabolism and promotion of anabolism consisted of introducing an emergency diet with the following objectives [19]: to avoid the exogenous intake of toxic precursors (BCAAs), and to inhibit catabolism to limit

the endogenous production of BCAAs and boost protein anabolism. This is a high-calorie (120 to 130% of usual energy intake), carbohydrate-lipid diet with a balanced carbohydrate/lipid ratio (60% of caloric intake in the form of carbohydrates). The introduction of protein equivalents in the form of a mixture of amino acids lacking BCAAs (e.g., COMIDA MSUD A) is essential and is administered at a rate of 2 g/kg/day [22]. This diet should not generally exceed 48 hours, as prolonged use would lead to a deficiency in essential amino acids [22].

Since valine and isoleucine stimulate protein synthesis, promote the use of leucine, and competitively prevent the latter from crossing the blood-brain barrier, gradual supplementation with these two BCAAs at a rate of 20-50 mg/kg/day is necessary before introducing leucine [20]. In our cohort, only two newborns benefited from the introduction of these two BCAAs due to the unavailability of corresponding capsules in our country. In theory, supplementation was carried out gradually while monitoring plasma BCAA levels. However, this biological monitoring of supplemented patients in our series was not technically feasible (testing not available in our country). Thus, the use of international recommendations concerning the maximum tolerance of these two BCAAs (20-50 mg/kg/day for isoleucine and 30-60 mg/kg/day for valine) [20] and the clinical evolution of the newborns were the parameters that allowed us to adjust the doses.

The introduction of the third BCAA, leucine, is indicated as soon as its plasma level falls below 250-300 $\mu\text{mol/l}$ and is done gradually with an initial dose of 50 mg/day in the form of 40-50 ml of breast milk (1 ml of breast milk $\approx$ 1 mg of leucine). The dose was then gradually increased in 50 mg increments, depending on the leucine level and the maximum tolerance of leucine, which was around 250-300 mg/day (60-90 mg/kg/day), thus defining the maintenance regimen. In our study, biological monitoring of leucine was impossible, so we relied on clinical status. Extracorporeal detoxification techniques such as dialysis may be required in cases of severe intoxication [23].

Several therapeutic difficulties were encountered in our context, particularly the limited availability of specialized metabolic formulas and amino acid supplements. Healthcare-associated infections represented a major complication and were responsible for most deaths in our

series. Neurological sequelae observed in surviving patients were mainly related to delayed diagnosis and prolonged exposure to toxic metabolites. Indeed, several studies have demonstrated that early diagnosis through newborn screening significantly improves neurological outcomes [24-26]. In countries where screening programs are implemented, treatment can be initiated before the onset of severe neurological damage [26].

This study has several limitations that should be acknowledged. First, its retrospective, single-center design limits the generalizability of the findings. Second, the small sample size limits the statistical power of the study and precludes robust subgroup analyses. Genetic testing was incomplete in some patients, which may have limited the molecular characterization of the cohort. In addition, serial plasma leucine measurements were not systematically available, preventing a detailed assessment of the evolution of biochemical control over time. Long-term follow-up data were also incomplete, limiting the evaluation of long-term neurological, developmental, and nutritional outcomes. Finally, the retrospective nature of the study may have introduced selection and missing-data biases. These limitations should be considered when interpreting the findings and highlight the need for larger, prospective, multicenter studies with standardized genetic testing, serial biochemical monitoring, and long-term follow-up.

CONCLUSION

MSUD is a rare but severe metabolic disorder with a relatively higher incidence in Tunisia due to the high rate of consanguinity. Our study highlights the clinical severity of neonatal MSUD and the challenges related to its diagnosis and management in resource-limited settings.

Delayed diagnosis likely contributed to the unfavorable neurological outcomes observed and is a recognized prognostic factor in previous studies. The implementation of newborn screening programs and improved access to specialized metabolic treatments could significantly improve patient outcomes.

Finally, systematic genetic counseling and prenatal diagnosis should be proposed to families with a history of MSUD in order to prevent recurrence in future pregnancies.

Conflicts of interest: none.

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