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Relevance of Expanded Newborn Screening in Maple Syrup Urine Disease: A Case Report

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Keywords:

Syrup Urine Disease; Expanded Newborn Screening; Encephalopathy

Abbreviations:

MSUD:Maple Syrup Urine Disease; ENS: Expanded Newborn Screening; Leu Leucine; Val Valine; Ile Isoleucine; BCAAs:Branched-Chain Amino Acids; CT: Computed Tomography Scan; EEG:Electroencephalogram; MRI:Magnetic Resonance Imaging; INP: National Institute of Pediatrics (Instituto Nacional de Pediatria); IMSS:Mexican Social Security Institute (Instituto Mexicano del Seguro Social); CBC: Complete Blood Count

1. Abstract

1.1. Background

Maple Syrup Urine Disease (MSUD) is a rare inherited metabolic disorder that, if not diagnosed and treated promptly, can lead to severe complications in newborns, including encephalopathy, irreversible neurological damage, and even death.

1.2. Case Report

We present the case of a 6 day old male infant who showed symptoms such as irritability and feeding difficulties. Despite undergoing various diagnostic evaluations, the diagnosis of MSUD was delayed until Expanded Newborn Screening (ENS) was performed. By then, signs of encephalopathy were already evident.

1.3. Conclusion

This case emphasizes the severity of MSUD and the need for early diagnosis, expanded newborn screening, and dietary management to prevent neurological damage. Genetic counseling and ongoing follow-up are essential to support patients and families.

2. Introduction

MSUD is an autosomal recessive disorder classified among inborn errors of metabolism [1]. It is characterized by elevated levels of three specific amino acids: leucine, valine, and isoleucine (Leu, Val, and Ile)[2]. The disease occurs at approximately 1 in every 86,800 to 185,000 live births [3], with an incidence as high as 1 in 200 in certain Mennonite populations in Pennsylvania [4]. MSUD is inherited in an autosomal recessive manner, meaning that a child must inherit a non-functional gene from both parents to manifest the disease. When both parents are carriers, the risk of having an affected child is 25% in each pregnancy, the chance of having a carrier child is 50%, and the likelihood of having an unaffected, non-carrier child is 25%. This risk is the same for both males and females [1].Clinically, MSUD is characterized by neurological and developmental delays, encephalopathy, feeding difficulties, and a distinctive maple syrup odor in the urine [5]. There are five recognized clinical subtypes: classic, intermediate, intermittent, thiamine-responsive, and E3-deficient forms (linked to pyruvate dehydrogenase deficiency) [2]. In the classic and most severe form [6],

plasma concentrations of branched-chain amino acids (BCAAs) begin to rise within hours (h) after birth. If untreated, symptoms typically appear within the first 24 to 48 h of life [7]. Initial clinical presentation includes nonspecific signs of neurological dysfunction, such as lethargy, irritability, and poor feeding, followed by more specific neurological manifestations like abnormal movements, increased spasticity, seizures, and coma. A distinctive sign of MSUD is the development of a characteristic maple syrup odor, detectable in the urine and earwax within the first one or two days after birth. Without treatment, the disease leads to inevitable progressive brain damage and is fatal within weeks or months[8,9]. Nutritional management is a critical component of treatment. It consists of restricting the intake of Leu, Val and Ile while providing a specialized metabolic formula free of these amino acids. In mild forms of the disease, where tolerance to branched-chain amino acids is greater, breastfeeding may be feasible. However, in patients with severe forms, breast feeding presents significant challenges and must be closely monitored [6].ENS is an essential strategy for the early detection of metabolic disorders in newborns [10]. When performed within the first two weeks of life ideally between the fourth and seventh day, it allows for timely intervention and the prevention of serious complications. In the case of MSUD, early diagnosis is critical, as delays can lead to rapid neurological deterioration and even death[11].This report presents the case of a newborn who developed significant complications due to a delayed diagnosis of MSUD. The disease was not confirmed until the results of the ENS became available, by which point signs of encephalopathy had already emerged. This case highlights the crucial role of ENS in guiding the diagnostic approach in newborns with clinical features suggestive of metabolic disorders like MSUD and reinforces its value in preventing irreversible complications through timely identification and intervention.

3. Case Report

Male patient, on his sixth day of life, born at term at 40 weeks via an uncomplicated vaginal delivery, the product of the third pregnancy, and from parents with positive consanguinity. The pregnancy was adequately monitored with proper prenatal care and no evidence of gestational pathologies. The Apgar score was 8/9, SA 0, with a birth weight of 3.580 kg and a length of 52 cm. After delivery, the newborn was discharged without complications and was exclusively breastfed.One day before admission, he presented with irritability and oral intolerance. Upon arrival at the emergency room (day 7), he exhibited apnea (duration and reversal interventions unknown), along with seizures, which were treated with phenobarbital 1.5 mL orally every 12 h, without discontinuation. Additionally, calcium gluconate ($C_{12}H_{22}CaO_{14}$) was administered, primarily to restore calcium levels, stabilize cell membranes, exert a vasopressor effect, and prevent or treat magnesium toxicity. Magnesium sulfate ($MgSO_4$) was also used to reduce neuronal excitability and neuromuscular transmission. It participates in numerous enzymatic reactions and is an essential element, with half of the body's magnesium stored in the bones.

Encephalopathy was evident on day 28, and by day 30, a characteristic maple syrup odor was detected in the urine, which is the hallmark indicator of MSUD.Other findings included: episodes of cyanosis associated with feeding and gastroesophageal reflux at 25 days; and by 28 days, symptoms such as hypoactivity, hyperactivity, hypertonia, weak sucking, and psychomotor delay were observed, resulting from encephalopathy as a complication of the underlying condition. These clinical findings emerged during the progression of the disease in patients with MSUD (Table 1).During hospitalization, multiple studies were performed to provide appropriate follow up. On day 9, a lumbar puncture was done, showing a clear appearance, no signs of pathological development, and a yellowish color. On day 15, a cranial CT scan showed generalized hypodensity in the cerebral and cerebellar parenchyma. A transfontanellar ultrasound revealed no evidence of hemorrhagic or tumoral events. On day 25, an esophagogastroduodenal series showed a normally sized esophagus with adequate transit and gastroesophageal reflux reaching the mouth. On day 28, an electroencephalogram showed cortical irritation in the right parieto-occipital region. A second EEG on day 29 showed persistent generalized burst-suppression pattern, predominantly frontal, suggestive of encephalopathy. Finally, on day 63, a cranial MRI revealed extensive, symmetrical global demyelination, consistent with probable leukodystrophy and cortico-subcortical atrophy (Table 2).The EEG showed consistent burst-suppression patterns across all brain regions with high-voltage sharp and slow waves, suggestive of encephalopathy (Figure 1&2).The diagnostic suspicion of MSUD was based on clinical presentation and confirmed by newborn screening performed at 58 days, which showed elevated levels of Leu and Ile, among other metabolites. This test was crucial for confirming the MSUD diagnosis (Table 3).Following the diagnosis, the patient was referred to the Genetics Department of the National Institute of Pediatrics (INP), where metabolic management was initiated using formulas free of Leu, Val, and Ile, adjusted according to their limited market availability. He also received continuous care through speech therapy, physical rehabilitation, and neuropsychology from 2006 to 2015.Currently, the patient is 19 years old and follows a diet based on Ketonex-2 formula, consuming one can every two days. His diet is supplemented with unrestricted fruits and vegetables, except for potatoes, as they increase triglyceride levels. He is not on any regular pharmacological treatment, although he occasionally takes thiamine (100 mg every 24 h) as prescribed by the INP.The patient completed secondary school and finished the second semester of high school. Due to writing difficulties, he opted for oral exams and used the same approach for submitting assignments. He later studied barbering and has worked as a stylist and transport assistant. He currently maintains a high level of dietary awareness and is fully informed about the foods he can

and cannot consume.Every trimester, he visits the Gastroenterology Department of the Mexican Social Security Institute (IMSS) for medical follow-up. During these visits, he undergoes routine tests including Complete Blood Count (CBC), Blood Chemistry Panel, General Urinalysis, and liver and kidney ultrasounds every six months to monitor his health status at the INP. He also attends monthly psychology sessions.

Table 1: Chronological order of appearance of signs and symptoms in the MSUD clinical case.

Postnatal day	Signs and symptoms
6	Oral feeding intolerance and irritability
7	Dehydration, apnea, and seizures
25	Cyanosis
	Gastroesophagealreflux
28	Hypoactivity, hyperactivity, hypertonia, weak suck, and psychomotor delay
	Encephalopathy
30	Presence of a maple syrup-like odor

Table 2: Imaging studies performed for diagnosis in the MSUD clinical case.

Study	Postnatal day	Findings
Lumbar puncture	9	No development, transparent appearance, yellow color.
Cranialcomputedtomography	15	Mapped hypodensity throughout the cerebral and cerebellar parenchyma.
Transfontanelleultrasound	15	No sonographically identifiable images compatible with hemorrhagic and/or tumoral event.
Electroencephalogram	28	1. First EEG: Cortical irritation in the right predominant parieto-occipital region.
	29	2.Segundo EEG: Persistent generalized burst-suppression pattern, predominantly frontal. Thismaycorrespondtoencephalopathy.
Esophagogastroduodenal series	25	Esophagus of normal length and caliber, with normal transit; presence of gastroesophageal reflux reaching the mouth.
Cranialmagneticresonanceimaging	63	Findings of extensive, symmetric, global demyelination, consistent with probable leukodystrophy with corticosubcortical atrophy.

Table 3: Biochemical findings in the MSUD clinical case.

Test	Result	Reference values
Neonatal thyroid-stimulating hormone	<30ulU/mL	<30ulU/mL
Aminoacid profile Icludes: Phenylketonuria, Maple syrup urine disease, Homocystinuria, Arginase deficiency, Acute neonatal citrullinemia, Ornithine transcarbamylase deficiency	Presumptive Positive	Phenylalanine less than 130 uM Leu+Ile<400uM Val <400 uM Methionine<60uM Citrulline<55uM
17-Hydroxyprogesterone	Within Normal Limits	400-600ng/dL
Trypsinogen	<90ng/dL	<90ng/dL

Acylcarnitine Profile Includes: Organic aciduriasFatty acid oxidation defects and others)	Within Normal Limits	Free Carnitine >5uM Acylcarnitine >10uM Carnitine >15uM
Biotinidasa	Detected	Detected
Glucose-6-phosphate Dehydrogenase (G6PD)	Detected	Detected
Galactose-1-phosphate Uridyltransferase (ClassicGalactosemia)	Detected	Detected
TotalGalactose	<15mg/dL	<15mg/dL
DNA for Hemoglobin S, C, and E	Within normal limits	Within normal limits

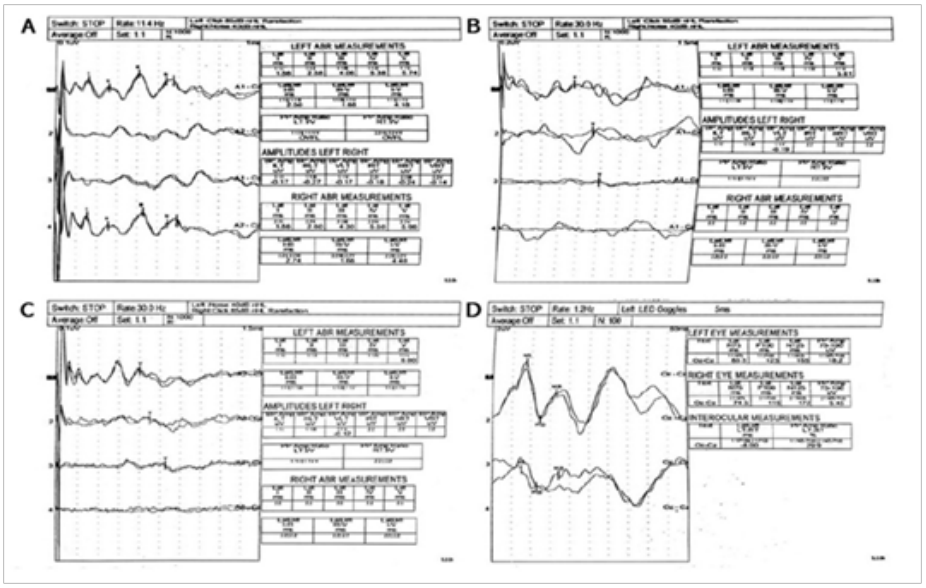

Figure 1. Electroencephalogram of clinical case: Shows a burst-suppression pattern in all regions, at times more evident frontally. The suppression with periods of very low voltage lasts between 2 and 4 seconds (s) during sleep. A) Burst of α activity; B and C) Burst of β activity; D) Burst of δ activity.

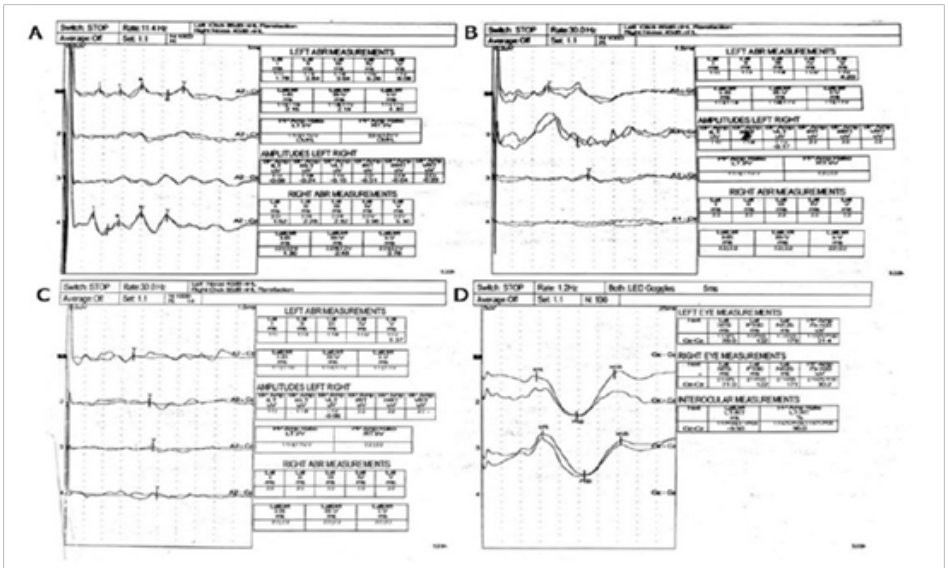

Figure 2. Electroencephalogram of clinical case: Shows persistent generalized burst-suppression tracing, predominantly frontal. A) Burst of α activity; B and C) Burst of β activity; D) Burst of δ activity.

4. Discussion

The clinical case described corresponds to a male patient diagnosed with MSUD, a rare inherited metabolic disorder that affects the metabolism of branched-chain amino acids: Leu, Val and Ile. This condition manifested early in the neonatal period, presenting severe neurological symptoms such as apnea, seizures, and irritability common indicators of an underlying metabolic disorder in otherwise healthy appearing newborns.The diagnosis of MSUD was confirmed through expanded newborn screening, which revealed elevated levels of Leu and Ile, findings that are characteristic of this disorder. The presence of the typical maple syrup odor in the urine, along with progressive neurological symptoms, further supported the diagnostic suspicion prior to biochemical confirmation.It is important to highlight the patient's genetic background, as he was born to consanguineous parents, a factor that significantly increases the risk of autosomal recessive conditions such as MSUD. This underscores the relevance of genetic counseling in populations with a history of consanguinity.Throughout the clinical course, progressive encephalopathy was evident, as documented by neuroimaging findings (cerebral hypodensity, symmetrical demyelination, and cortico-subcortical atrophy) and electroencephalographic patterns showing generalized burst-suppression, suggesting severe neurological damage likely related to the toxicity of accumulated amino acids.Early multidisciplinary management was essential in improving the patient's prognosis. The implementation of a strict diet free of branched-chain amino acids, along with continuous follow-up by genetics, neurology, psychology, and physical rehabilitation teams, contributed to an improved quality of life. Despite evident neurological and academic sequelae, the patient achieved a functional level that allowed him to complete part of his formal education and engage in vocational activities as a barber and assistant.The clinical evolution up to 19 years of age demonstrates that, although MSUD is a serious condition with potential for irreversible neurological damage, early diagnosis and strict dietary management can improve survival and promote partial social and occupational integration. Nonetheless, significant challenges remain, including limited access to specialized formulas, psychological impact, and the need for continuous medical monitoring to prevent metabolic decompensation.This case highlights the critical importance of reinforcing expanded newborn screening programs across all healthcare systems, especially in at-risk populations, as well as the need for continuous, patient-centered medical care that addresses both clinical and psychosocial aspects over time.

5. Conclusion

In conclusion, this clinical case demonstrates that MSUD is a severe hereditary metabolic disorder which, without early diagnosis and appropriate multidisciplinary management, can lead to severe and irreversible neurological damage. Timely identification through expanded newborn screening and early implementation of a strict BCAAs diet are essential to improve the patient's prognosis and quality of life. Additionally, parental consanguinity underscores the importance of proper genetic counseling to prevent and anticipate such conditions. Despite neurological and social sequelae, comprehensive follow-up has allowed partial integration of the patient into educational and work life, emphasizing the need for continuous, accessible medical care focused on both clinical and psychosocial aspects. Furthermore, increasing awareness and knowledge of MSUD, a largely underrecognized disease, is crucial to promoting early detection, timely diagnosis, and adequate support for affected families. Finally, this case reinforces the urgency to strengthen newborn screening programs and specialized care to ensure better outcomes in vulnerable populations.

6. Conflict of Interest

The authors declare that there is no conflict of interest financial, personal, or professional that could have influenced the development of this work.

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