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Case Report

MSUD presenting with phenylalanine elevation on neonatal screening

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ABSTRACT

Maple syrup urine disease (MSUD) is an inborn error of metabolism characterized by an increase in branched-chain amino acids (BCAAs), resulting from a deficiency in the branched-chain α-ketoacid dehydrogenase (BCKD) enzyme. A 22-day-old asymptomatic male infant was referred to our center following the detection of elevated phenylalanine (PHE) levels in the newborn screening program and was hospitalized with suspected Phenylketonuria (PKU). Blood amino acid analysis revealed a normal PHE level (48.9 nmol/mL), while BCAA levels were markedly elevated: Leucine 824.4 nmol/mL (normal: 48-175), isoleucine 413.1 nmol/mL (normal: 31-105), and valine 683.1 nmol/mL (normal: 83-300). Results confirmed false positive result for PKU diagnosis however, laboratory findings were consistent with MSUD. Phenylketonuria, a preliminary diagnosis made due to high PHE levels in newborn screening, has masked the underlying MSUD diagnosis, and is presented here as an extremely rare phenomenon. This case is reported to underscore a critical gap in our country's newborn screening program, which does not currently include MSUD. Considering the acute and potentially fatal neonatal presentation of MSUD, our findings underline the need to expand the national newborn screening program to include MSUD.

Keywords: Branched-chain amino acids, leucine, maple syrup urine disease, phenylalanine, phenylketonuria

Introduction

Maple syrup urine disease (MSUD, OMIM #24860) is an inborn error of metabolism caused by a deficiency of the branched-chain α-ketoacid dehydrogenase (BCKD) enzyme, resulting in the accumulation of branched-chain amino acids (BCAA), leucine (LEU), isoleucine (ILE) and valine (VAL). The BCKD enzyme is a multi-enzyme complex consisting of three catalytic components. It consists of the E1 subunit, a decarboxylase composed of subunits 1a and 1b, the E2 subunit, a transacylase, and the E3 subunit, a dehydrogenase, and is regulated by two regulatory enzymes, a kinase and a phosphatase. The catalytic components require five cofactors for optimal enzyme function: thiamine pyrophosphate (TPP), flavin adenine dinucleotide (FAD), nicotinamide adenine dinucleotide (NAD), coenzyme Q10, and a lipoamide prosthetic group (1). It is diagnosed by autosomal recessively inherited mutations in any of the genes encoding the catalytic subunits of the BCKD complex: BCKDHA (E1a), BCKDHB (E1b), DBT (E2) or DLD (E3) (2). The E3 subunit encoded by the DLD gene is also a component of the pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase enzyme complexes; therefore, its deficiency is accompanied by various findings (2). The incidence is extremely rare, approximately one in 150.000 live births (3). Clinical symptoms result from an increase in branched-chain amino acids (BCAAs), which have neurotoxic effects. Leucine is the mainly responsible amino acid for the clinical signs (4). MSUD is classified into classic, intermediate and intermittent subtypes based on clinical manifestations and age of onset. Classic MSUD have clinical signs within the first weeks after birth, including maple syrup odor, feeding problems, seizures, coma and possibly death (5). It can be screened by detecting elevated leucine levels from the neonatal period (6). Phenylketonuria (PKU) is an autosomal recessive disorder of aromatic amino acid metabolism. In

PKU, phenylalanine (PHE) cannot be converted to tyrosine due to a deficiency in the PHE-hydroxylase enzyme, and PHE levels increase (7). Here, we report a patient who had elevated PHE level detected in newborn screening and was initially suspected of having PKU, had elevated blood leucine levels, and was incidentally diagnosed with MSUD in the absence of any clinical findings. We present this case, which is extremely rare in the literature.

Case Report

Blood samples for the newborn screening program were collected on the seventh day of life, which revealed elevated PHE levels. Subsequently, the patient was referred and admitted to our center at 22 days of age for further evaluation. He had no additional clinical complaints. Physical examination revealed normal vital signs appropriate for age and gender, and normal organ system assessment. Laboratory tests mainly included serum glucose, blood gas analysis, liver and kidney function tests and plasma-amino acid analysis. The serum glucose was 99 mg/dL, PH 7.42, base excess -2.9 mmol/L, lactic acid 3.8 mmol/L, white blood cell count 8.70×10^3/uL, neutrophil percentage (N%) 24.4%, hemoglobin 14.5 g/dL, platelet 377×10^9/L, serum total protein 5.4 g/dL, serum albumin 3.9 g/dL, uric acid 3.2 mg/dL. Plasma-amino acid analysis demonstrated PHE 48.9 nmol/mL (28-80), isoleucine 413.1 nmol/mL (31-105), leucine 824.4 nmol/mL (48-175) and valine 683.1 nmol/mL (83-300) (Table I). Whole exome sequencing (WES) analysis, performed to confirm the diagnosis of MSUD, revealed compound heterozygous mutations in the BCKDHA gene (NM_000709.4); c.745 G>A (p.G249S) likely pathogenic (paternal) and c.1312 T>A (p.Y438N) pathogenic (maternal). No mutation was reported in the PAH gene (NM_000277.3).

Laboratory test results were compatible with MSUD. The diagnosis was confirmed by genetic analysis and treatment was started. Protein and leucine restricted diet was introduced. His diet included 3 g/kg/D protein and 25 mg/kg/D leucine. Control BCAA values decreased after the diet began. Thiamine vitamin was added. He benefited significantly from thiamine. During the follow-up, he did not experience a metabolic attack, and neurological and developmental assessments showed a normal course. Plasma leucine levels consistently remained below 400 nmol/mL. Adding thiamine to his treatment made the decrease in leucine levels even more pronounced. During follow-up, the protein-restricted diet was gradually reduced, and the patient benefited from thiamine therapy (Figure 1). Written informed consent was obtained from the patient's parents for the publication of this case report. Patient data confidentiality was strictly maintained throughout the process.

Table I: Laboratory findings across different clinical stages

Metabolic Parameters	Reference Values	22. Days	120. Days	240. Days
Glucose (mg/dL)	51- 99	50	82	79
pH	7.35- 7.45	7.39	7.38	7.40
HCO3 (mEq/L)	22- 26	21.2	21.3	19.5
Lactate (mmol/L)	<2.5	3.8	3.3	4.7
Ammonia (µmol/L)	<90	90.2	48.4	38
AST (U/L)	<40	68	42	59
ALT (U/L)	<40	33	27	32
Leucine (nmol/mL)	48- 175	824.4	57.6	130.2
Isoleucine (nmol/mL)	31- 105	413.1	164.6	126.4
Valine (nmol/mL)	83- 300	683.1	354.2	150.3
Phenylalanine (nmol/mL)	28- 80	48.9	39.9	61.6

Day 22 represents the pre-treatment admission, Day 120 represents the period strictly on a leucine-restricted diet, and Day 240 represents the follow-up period after the addition of thiamine.

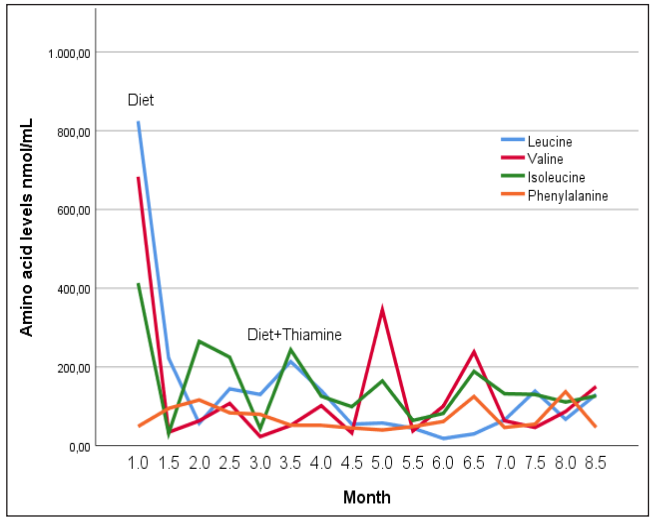

Figure 1: Amino acid levels and response to treatment over time. The graph indicates the initial phase treated only with a restricted diet (Months 1.0 to 3.0) and the subsequent phase where thiamine was added to the diet therapy (Months 3.5 onwards).

Discussion

Classic MSUD is a devastating metabolic disorder that presents in the neonatal period with feeding difficulties, vomiting and restlessness, progressing to lethargy and coma within 48-72 hours after birth. If undetected, a complete neurologic syndrome with seizures, opisthotonus and progressive encephalopathy occurs within the first week and a fatal outcome can occur shortly thereafter due to respiratory failure. In many patients, severe and permanent brain damage can occur even if symptoms are controlled (8). Patients with elevated blood LEU concentrations are presumed to have MSUD until proven otherwise. Protein catabolism, infection, presence of other metabolic disorders, liver disorders, steroid use and parenteral nutrition may cause LEU elevations in newborns. The traditional treatment in the acute phase is hemodialysis. In the chronic phase, strict leucine-restricted diet therapy is required. The treatment plan is to feed a formula that does not contain BCAA. The aim is to maintain plasma BCAA levels within the non-neurotoxic range and to meet adequate nutritional needs. Vitamin B1 and L-carnitine therapies have also been reported to be beneficial in long-term treatment (9). In many countries, MSUD is included in newborn screening programs. In cases of LEU elevation, detailed investigations are performed for the diagnosis of MSUD. Similarly, PKU is also screened in many countries

and PHE levels are measured. In the literature, cases with elevated PHE in newborn screening and subsequently diagnosed as MSUD are very rare. In a study by Capistrano-Estrada et al. (10) 15 patients were diagnosed with MSUD among approximately one million patients with elevated Phe. The biochemical basis for elevated PHE in MSUD patients on neonatal screening involves the complex interplay of neutral amino acids sharing the same transport systems. Elevated BCAAs, particularly leucine, compete for the Large Neutral Amino Acid Transporter (LAT1). While this typically leads to decreased cerebral PHE levels, systemic elevations of PHE in the neonatal period of MSUD patients may be attributed to intense catabolism and protein degradation during metabolic crisis, or interference in the analytical methods used during initial screening (11). Similar to the literature, our patient lacked classic MSUD symptoms such as feeding difficulties or encephalopathy during the neonatal period, and the underlying MSUD diagnosis was incidentally unmasked due to the false-positive PHE elevation. The primary limitation of this case report is that it is based on a single patient's experience. Additionally, long-term neurodevelopmental follow-up data beyond the current observation period are not yet available.

Conclusion

This rare case underscores a critical gap in our country's newborn screening program, which does not currently test for MSUD. Considering the acute and often fatal neonatal presentation of the disease, we recommend the inclusion of MSUD in the screening panel. This report contributes to the literature by providing further evidence of the benefits of early screening.

References

1. Chuang JL, Wynn RM, Moss CC, et al. Structural and biochemical basis for novel mutations in homozygous Israeli maple syrup urine disease patients: a proposed mechanism for the thiamin-responsive phenotype. J Biol Chem. 2004;279(17):17792-800. https://doi.org/10.1074/jbc.M313879200
2. Frazier DM, Allgeier C, Homer C, et al. Nutrition management guideline for maple syrup urine disease: an evidence- and consensus-based approach. Mol Genet Metab. 2014;112(3):210-7. https://doi.org/10.1016/j.ymgme.2014.05.006
3. Strauss KA, Carson VJ, Soltys K, et al. Branched-chain α-ketoacid dehydrogenase deficiency (maple syrup urine disease): Treatment, biomarkers, and outcomes. Mol Genet Metab. 2020;129(3):193-206. https://doi.org/10.1016/j.ymgme.2020.01.006
4. Schadewaldt P, Wendel U. Metabolism of branched-chain amino acids in maple syrup urine disease. Eur J Pediatr. 1997;156 Suppl 1:S62-S66. https://doi.org/10.1007/PL00014274
5. Hassan SA, Gupta V. Maple Syrup Urine Disease. In: StatPearls. Treasure Island (FL): StatPearls Publishing; September 5, 2022.
6. Stroek K, Boelen A, Bouva MJ, et al. Evaluation of 11 years of newborn screening for maple syrup urine disease in the Netherlands and a systematic review of the literature: Strategies for optimization. JIMD Rep. 2020;54(1):68-78. Published 2020 May 13. https://doi.org/10.1002/jmd2.12124
7. van Spronsen FJ, van Wegberg AM, Ahring K, et al. Key European guidelines for the diagnosis and management of patients with phenylketonuria. Lancet Diabetes Endocrinol. 2017;5(9):743-56. https://doi.org/10.1016/S2213-8587(16)30320-5
8. Strauss KA, Puffenberger EG, Carson VJ. Maple Syrup Urine Disease. In: Adam MP, Feldman J, Mirzaa GM, et al., eds. GeneReviews®. Seattle (WA): University of Washington, Seattle; January 30, 2006.
9. Duan Y, Li F, Li Y, et al. The role of leucine and its metabolites in protein and energy metabolism. Amino Acids. 2016;48(1):41-51. https://doi.org/10.1007/s00726-015-2067-1
10. Capistrano-Estrada, Sylvia, and Charity M. Jomento. "Detection of maple syrup urine disease on newborn screening second tier testing for phenylketonuria." Acta Medica Philippina 43.2 (2009). https://doi.org/10.47895/amp.v43i2.2509
11. Manoli I, Venditti CP. Disorders of branched chain amino acid metabolism. Transl Sci Rare Dis. 2016;1(2):91-110. https://doi.org/10.3233/TRD-160009