Discover Medicine

Case Report

A case of concurrent malnutrition in maple syrup urine disease: challenges and solutions in Indonesia

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Received: 14 April 2024 / Accepted: 7 August 2024
Published online: 29 August 2024

Abstract

Background Maple syrup urine disease (MSUD) is a rare autosomal recessive inborn error of metabolism characterised by the impaired breakdown of branched-chain amino acids. Detecting MSUD in newborns is challenging due to the lack of distinctive signs, especially in resource-limited settings like Indonesia.

Case presentation A 2-year-old boy presented to the paediatric metabolic clinic with inactivity, a history of uncontrolled epilepsy, global developmental delay and moderate malnutrition. He was born at 40 weeks of gestation, weighing 3100 g, to consanguineous parents. The patient faced feeding problems and was lethargic after birth, with recurrent episodes of generalised seizure and spasticity. Diagnosed with MSUD at four months, the initial response to thiamine supplementation and MSUD Anamix formula was positive. However, weight loss occurred after switching to unregulated family food, as MSUD-specific infant formula became inaccessible and unsustainable due to high costs for the caregivers. Upon compliance with nutritional advice, the child regained weight and progressed appropriately for his age.

Conclusion Inborn errors of metabolism like MSUD should be considered in atypical disease presentations. In resource-limited settings, management should be tailored to local product availability and accessibility to ensure effective care.

Keywords Maple syrup urine disease · Inborn errors of metabolism · Malnutrition · Children · Case report

1 Introduction

Awareness of inborn errors of metabolism (IEM) has increased in recent years and is considered the differential diagnosis of any child exhibiting an atypical presentation. IEM encompasses a spectrum of disorders characterised by the failure of physiological metabolic pathways. One such disorder is maple syrup urine disease (MSUD), wherein a deficiency of branched-chain α-ketoacid dehydrogenase (BCKD) results in the accumulation of branched-chain amino acids (BCAAs), including valine, leucine, and isoleucine. This rare autosomal recessive condition typically manifests in the first week of life with non-specific symptoms such as feeding difficulties, abnormal movements, and lethargy. Timely diagnosis is imperative, as the neurotoxic accumulation of leucine, for instance, disrupts water homeostasis in the subcortical grey matter, causing brain swelling [1].

Untreated MSUD has severe consequences, with studies indicating that BCAAs accumulation induces neuronal and glial cell apoptosis, leading to neurodegeneration [2]. This study presents a rare case of MSUD in Indonesia, a resource-limited setting with constraints on genetic metabolic testing. Compounding the challenge, the MSUD-specific formula is not covered by national health insurance, contributing to malnutrition in affected patients. Therefore, a comprehensive

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understanding of nutritional management is essential for managing children with MSUD to prevent complications and foster optimal growth and development.

2 Case presentation

A 2-year-old boy admitted to the paediatric metabolic clinic presented with lethargy, uncontrolled epilepsy, global developmental delay, and moderate malnutrition. Born from a P3A0 mother at 40 weeks' gestation, he weighed 3100 g and had no birth asphyxia. His parents were first degree cousins. Although there was no family history of metabolic diseases, there were reports of relatives dying before the first year of life from unknown causes.

At day 4 of life, the child experienced recurrent generalised seizure, spasticity, and episodic bradypnea with desaturation, leading to three weeks of mechanical ventilation and three months of hospitalisation at NICU. Physical exam revealed pallor, microcephaly (head circumference 31 cm), a liver palpable 4 cm below the costal margin, poor swallowing reflex, and spastic tetraparesis. Diagnostic investigations include head CT scans showing ventriculomegaly and periventricular oedema, EEG revealing burst suppression patterns, and echocardiography identifying an atrial septal defect.

At four months old, a diagnosis of MSUD was confirmed through urine and blood spot analysis in Japan using gas chromatography–mass spectrometry and acylcarnitine analysis. Elevated urine levels of specific metabolites indicative of MSUD was detected, including lactate, 2-OH-isovalerate, 2-keto-isovalerate, 2-OH-isocaproate, 2-OH-3-methyl valerate, 2-keto-isocaproate, 2-keto-3-methyl valerate, along with ketosis (elevated 3-OH-butyrate) and tyrosiluria (elevated PHPLA and PHPPA).

The child was prescribed thiamine supplementation and MSUD *Anamix* formula, along with valine (35–90 mg/kg) and isoleucine (30–80 mg/kg), resulting in normal weight increment until 18 months. However, weight declined when the family switched to unregulated family food due to the high cost and inaccessibility of the MSUD formula (Fig. 1). To address this, we worked with a dietitian to recommend a low-protein milk formula available in the local market and educated caregivers on incorporating low-protein foods like sweet potatoes, spinach, and green beans into family meals. The child successfully regained sufficient weight.

3 Discussion

MSUD is an inherited metabolic disorder characterised by a deficiency of BCKD activity, leading to impaired metabolism and accumulation of BCAAs and their metabolites. Excessive levels of these substances can trigger neurotoxicity and hinder neurotransmitter synthesis and myelination in the brain. Thus, nutrition therapy is crucial in managing MSUD, with the primary goal of restricting BCAA intake and minimising toxic metabolites to maintain safe plasma levels.

The prevalence of MSUD is approximately 1 in 150,000 births. The classical type constitutes three-fourth of all MSUD cases [1], as in our case, where symptoms manifest soon after birth. Like earlier case reports, the baby was initially well at birth but developed feeding difficulties and recurrent seizures shortly thereafter [3, 4]. In a case from India, lethargy and poor feeding were noted at day 14 of life, without clinical seizures observed [5]. Moreover, our case did not experience hypoglycemic encephalopathy, as documented in Liu and colleagues' case [4]. Unfortunately, we were unable to conduct an MRI on our patient or measure leucine and valine concentrations, thus preventing us from determining whether differences in clinical presentations between our case and previous reports are attributable to BCAAs level.

In 2014, Frazier and colleagues formulated evidence-based nutrition management guidelines for MSUD, recommending daily dietary BCAA and protein intake based on age groups [6]. Frequent monitoring of BCAA levels, especially during acute illnesses, is advised. High-dose thiamine supplementation, a cofactor of the BCKD enzyme, is commonly administered to enhance dietary BCAA tolerance but is only adjunct to the dietary approach [6, 7]. Various international formula milk producers offer MSUD-specific infant formula available in Indonesia upon request. However, the high cost and lack of national health insurance coverage for these formulas poses challenges for caregivers, necessitating a comprehensive understanding of the disease and available nutritional alternatives. Currently, MSUD-specific infant formulas have been incorporated into the national formulary in Indonesia.

Drawing insights from this case, Fig. 1 illustrates substantial catch-up growth beyond the − 2 standard deviation line by 12 months, affirming the effectiveness of managing the case with MSUD-specific infant formula to support growth. However, transitioning to regular family food without stringent BCAA intake control decelerated growth rate. The diet, primarily composed of carbohydrates to minimise BCAA intake, led to stunted growth and wasting. This

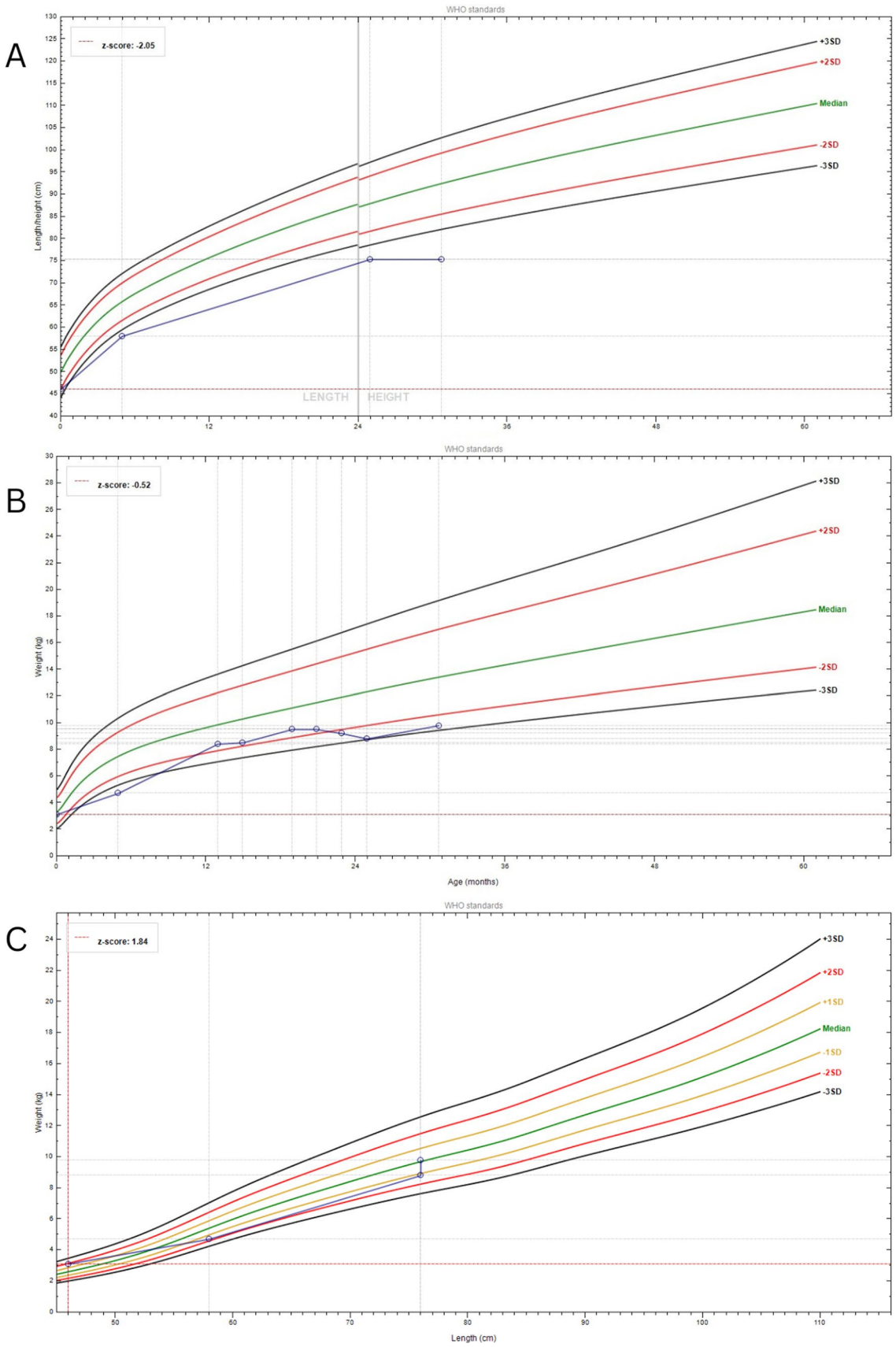

Fig. 1 Serial anthropometric measurements of the second-case boy, **A** length-for-age Z-score, **B** weight-for-age Z-score, and **C** weight-for-length Z-score

underscores the crucial role of nutrition therapy in controlling blood BCAA concentrations, ensuring sufficient quantities to support normal growth and intellectual development. Kong and Rajikan also emphasised that poor metabolic control in MSUD children is associated with stunting, undernutrition, microcephaly, and intellectual disability [8].

Recognising that BCAAs are vital for growth, supplementation of isoleucine and valine is common in MSUD patients to prevent deficiencies and expedite the reduction of leucine plasma levels [9]. This supports the concept of relatively lower plasma levels of valine and isoleucine in MSUD, will return to normal faster than leucine [6, 9]. Infants can be given leucine-free infant formula if available, as proven successful in Iran, where valine and isoleucine supplements are unavailable [10]. Alternatively, 1% solution of valine and isoleucine can be added to food if necessary [6]. Caregivers are advised to avoid high-protein foods like cheese, eggs and meat, opting for controlled amounts of foods such as potatoes and cereals as leucine substitutes. Special low-protein foods from supermarkets, such as pasta or biscuits, can diversify diets and are more feasible in the long term.

Liver transplant emerges as a promising therapy option in many countries, freeing patients from BCAA restrictions post-transplant and eliminating the risk of metabolic decompensation or neurologic insults [6]; however, this option is not currently indicated for MSUD patients in Indonesia.

4 Conclusion

This case report underscores the importance of considering inborn metabolism errors in infants with atypical clinical presentations. Despite resource limitations that may delay timely diagnosis of MSUD, this case demonstrates that normal growth is attainable with appropriate nutrition therapy. It emphasises the critical role of providing MSUD-specific formulas and understanding alternative dietary strategies to support optimal growth and development in MSUD patients.

Acknowledgements We would like to thank Professor Seiji Yamaguchi from Shimane University for their collaboration and support in establishing the diagnosis for this case.

Author contributions NN initiated the investigation. AL wrote the first draft. NN was the physician managing the patient's hospital care. All authors reviewed and approved the final version of the article.

Funding The authors did not receive support from any organization for the submitted work.

Data availability The data that support the findings of this study are not openly available to protect patient's privacy and are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate Informed consent was obtained from both parents of the two patients prior to submission. A sentence confirming that informed consents (consent to participate and consent to publish) were obtained from all participants or, if participants are under 18, from a parent and/or legal guardian.

Competing interests The authors declare no competing interests.

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