Intermittent Maple Syrup Urine Disease: Two Case Reports

abstract

The presenting symptoms and clinical course of 2 cases of intermittent maple syrup urine disease (MSUD) are described. Intermittent MSUD is a potentially life-threatening metabolic disorder caused by a deficiency of branched-chain α-keto acid dehydrogenase, the enzyme complex that decarboxylates the 3 branched-chain amino acids. In contrast to classic MSUD, children with the intermittent form show normal development with normal intelligence and, when asymptomatic, normal levels of branched-chain amino acids. Symptoms usually appear between 5 months and 2 years of age, when a trivial infection such as otitis media or viral gastroenteritis triggers catabolism of muscle protein. Intermittent MSUD should be suspected in cases of common infections with a clinically atypical course, especially in children displaying ataxia or marked drowsiness. Pediatrics 2014;133:e458–e460

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KEY WORDS
maple syrup urine disease, branched-chain ketoacidurias, inborn errors of metabolism

ABBREVIATIONS
BCKD—branched-chain α-keto acid dehydrogenase
MSUD—maple syrup urine disease

Dr Axler identified the cases and wrote the initial draft of the manuscript; Dr Holmquist identified the cases and reviewed and revised the manuscript; and both authors approved the final manuscript as submitted.

www.pediatrics.org/cgi/doi/10.1542/peds.2013-0427
doi:10.1542/peds.2013-0427

Accepted for publication Jul 23, 2013

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.
**CASE 1**

At the age of 18 months, during an episode of fever, a girl was hospitalized showing symptoms of unsteadiness, slurred speech, and confusion. On suspicion of encephalitis, acyclovir was administered, but no conclusive diagnosis was reached. In the years that followed, the patient displayed similar episodes in conjunction with fever; displaying drowsiness, unsteadiness, and incoherent speech. During an episode at the age of 4 years, an MRI was performed with normal results, and EEG under chloral hydrate sedation showed slight generalized slowing.

At the age of 6, during a family episode of common streptococcal pharyngitis, the patient developed high fever and vomiting and became increasingly somnolent. Encephalitis or meningitis was initially suspected, and the patient received acyclovir and cefotaxime. Lumbar puncture was normal, and standard workup showed metabolic acidosis (pH 7.25, base excess −11) and mild hyponatremia (130 mmol/L). Plasma levels of lactate and glucose were normal, as were conventional liver tests and blood count. The patient was rehydrated with 10% intravenous glucose, after which sodium decreased to 124 mmol/L, prompting addition of sodium. A peculiar, fruity urine odor was noted, “reminiscent of decaying pears,” after which the national poison information center was consulted. However, toxicology tests, including salicylates and ethylene glycol, were negative. Ten hours after admission the patient, reacting solely to pain stimuli, was transferred to the ICU. Going over the patient’s recent history, it was noted that during a less severe episode 2 months previously, an analysis of plasma amino acids had been performed, showing elevations of leucine, isoleucine, and valine consistent with maple syrup urine disease (MSUD). A new metabolic workup was ordered, showing similar results. After a treatment of protein restriction and addition of lipids and non–branched-chain amino acids to the glucose infusion, the levels of branched-chain amino acids were normalized over the next 2 days (leucine, 985–586–36 mmol/L; isoleucine, 286–148–16 mmol/L; valine, 598–352–56 mmol/L). Clinical recovery was slower, but the patient could be released from the hospital after a week, with detailed instructions to the family concerning actions to take in case of infection. Apart from 3 episodes with moderately elevated branched-chain amino acids, prompting admission overnight for observation, the patient has had almost a decade of normal development.

**CASE 2**

A 2-year-old girl entered the health care center after her parents noted unsteadiness and “absent behavior” during several episodes of fever. The neurologic examination was normal. Epilepsy was considered, but no EEG was ordered. Three months later, the girl entered the hospital with similar but more severe symptoms after a 3-day history of fever with low food intake. Early in the day, she had seizurelike episodes with vigorous limb movements as well as confusion, during which she was unable to recognize her parents. Later in the afternoon she became increasingly somnolent. During examination the patient made no eye contact and lay in an odd, opisthotonuslike posture on the bed. Because an epileptic seizure could not be ruled out, the patient received diazepam, with no effect. Encephalitis or meningitis was suspected, and the patient received acyclovir and cefotaxime. Throat Streptococcus test was positive, whereas EEG, lumbar puncture, and head computed tomography scan were normal. The patient was transferred to an ICU, where she displayed several seizurelike episodes with extension movements of the limbs. More extensive EEG testing showed intermittent bilateral slowing. Slight parietooccipital hyperintensity on the right side on MRI made encephalitis the most probable diagnosis, although herpes simplex and varicella tests were negative. No clinical improvement was noted, and on the second day after admission the patient reacted only to painful stimuli. However, an analysis of plasma amino acids showed marked elevations of leucine, isoleucine, and valine consistent with MSUD. A treatment consisting of protein restriction and glucose, lipids, and non–branched-chain amino acids led to the normalization of levels (leucine, 1094–869–56 mmol/L; isoleucine, 673–413–60 mmol/L; valine, 1280–921–225 mmol/L). After 2 years of follow-up, the patient shows normal development without new episodes of absence seizures or increased branched-chain amino acid levels.

**DISCUSSION**

The first cases of MSUD were described in 1954, after 4 Massachusetts siblings had died before 3 months of age from a neurodegenerative disorder. The children’s urine had an odor reminiscent of maple syrup. MSUD is caused by a deficiency in branched-chain α-keto acid dehydrogenase (BCKD), the enzyme complex that decarboxylates the 3 branched-chain amino acids leucine, isoleucine, and valine to their corresponding α-keto acids. In the classic variant of the disease described in the original report, the result is an accumulation of both amino and α-keto acids within a week after birth, resulting in dystonia, seizures, and encephalopathy as well as markedly elevated levels of branched-chain amino acids in plasma and urine. The clinical symptoms are caused mainly by leucine, which is rapidly transported across the blood–brain barrier and neurotoxic at high concentrations.2

In the classic variant of MSUD there is little or no detectable BCKD complex activity (<2%). In patients with some
residual BCKD activity (typically 3%–30%), milder variants of the disease are seen. Patients with intermediate MSUD display persistent elevations of branched-chain amino acids, as well as neurologic impairment, whereas children with intermittent MSUD show normal development with normal intelligence and, when asymptomatic, normal levels of branched-chain amino acids.

BCKD has 4 subunit components (E1a, E1b, E2, and E3). Surprisingly, DNA sequence analysis of the 2 cases presented here displayed compound heterozygosity for identical mutations in the \textit{DBT} gene, which encodes the E2 subunit: c.75_76delAT and c.901C>T. The first mutation causes a frame shift and no functional protein, whereas the second mutation has been described in conjunction with nonsense and missense mutations in several cases of intermittent MSUD, with an average residual BCKD activity of 14\%.\cite{4}

Clinically, the 2 cases are typical of intermittent MSUD. Symptoms usually first appear between 5 months and 2 years of age. A trivial infection such as otitis media or viral gastroenteritis triggers catabolism of muscle protein, approximately a third of which consists of branched chain amino acids. The capacity of BCKD is exceeded, and branched-chain amino acids and \(\alpha\)-keto acids accumulate, with clinical progression from ataxia and drowsiness to, if untreated, lethargy and coma. Deaths have been reported in inadequately diagnosed cases. The treatment consists of restricting protein catabolism through glucose infusion and withholding dietary branched-chain amino acids until normal plasma levels return. In special cases, levels can be corrected through hemodialysis. Upon leaving the hospital, patients with intermittent MSUD should receive written instructions concerning dietary adjustments and other actions to take in case of infection or poor food intake.

**CONCLUSIONS**

Intermittent MSUD is a potentially life-threatening metabolic disorder that should be suspected in cases of common infections with a clinically atypical course, especially in children displaying ataxia or marked drowsiness. It is important to remember that affected people are asymptomatic between episodes and laboratory tests normal. It should also be noted that although MSUD is often included in metabolic screening of newborns, it is uncertain with regard to the non-classic forms of MSUD.\cite{5} Cases like the 2 described here will therefore probably continue to present in clinical practice.

**REFERENCES**


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Pediatrics 2014;133:e458; originally published online January 6, 2014;
DOI: 10.1542/peds.2013-0427

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*Pediatrics* 2014;133;e458; originally published online January 6, 2014;
DOI: 10.1542/peds.2013-0427

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