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Case Report

Late-onset maple syrup urine disease triggered by human herpesvirus-6 mediated encephalopathy in a toddler

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ABSTRACT

Metabolic crisis should always be on the differential diagnosis of a toddler presenting with focal neurologic signs and refractory ketoacidosis. Maple syrup urine disease (MSUD) is an autosomal recessive metabolic disorder caused by an enzyme deficiency in the branched-chain α-ketoacid dehydrogenase (BCKDH) complex that leads to toxic buildup of the branched-chain amino acids (BCAA) leucine, isoleucine, and valine. Classically diagnosed in the neonatal period (especially with the advent of newborn screening), our patient is a rare case of a previously healthy toddler with late-onset or intermittent MSUD triggered by human herpesvirus-6 and a fasting state. Though MSUD as a diagnosis is incredibly rare beyond the neonatal period, prompt recognition and treatment can be life-saving and lead to good outcomes.

Keywords: Maple syrup urine disease, Metabolic crisis, Human herpesvirus-6

INTRODUCTION

Maple syrup urine disease (MSUD) is an autosomal recessive genetic disorder caused by an enzyme deficiency that leads to toxic buildup of the branched-chain amino acids leucine, isoleucine, and valine.[1] Classically diagnosed in the neonatal period, babies present with symptoms of lethargy, poor feeding, and progressive neurologic findings. Here we present a rare case of a previously healthy toddler with seizures and encephalopathy ultimately diagnosed with late-onset or intermittent MSUD triggered by encephalopathy.

CASE REPORT

A 16-month-old girl with a history of mild gross motor delay (episodes of lower extremity instability/weakness while standing and wobbliness while sitting) presented to the emergency department (ED) with one day of increased sleepiness, decreased oral intake, and decreased urine output. The parents endorsed that approximately ten days prior, she experienced an episode of unsteady gait which led to a fall and prompted medical attention; she was eventually cleared to go home after some observation in an ED. Otherwise, up until this presentation, she was in her usual state of health. They reported no fevers, recent illnesses, ingestions, travel, or sick contacts. Her immunizations were up to date.

In the ED, she was found to be unresponsive with right gaze deviation and right upper extremity stiffening that lasted several minutes. Intravenous lorazepam was administered, and a computerized tomography (CT) scan of the brain showed no acute intracranial pathology. Initial pertinent laboratory tests revealed hypoglycemia (serum glucose level of 52 mg/dl), metabolic acidosis (serum bicarbonate level of 16 mmol/l) with a normal serum lactate (1.2 mmol/l), an elevated anion gap (24 meq/l), and urinalysis with 2+ ketonuria. Erythrocyte sedimentation

rate (ESR) was markedly elevated at >130 mm/hour but a C-reactive protein (CRP) was normal at 2.7 mg/l (reference range <5 mg/l). Lumbar puncture was performed and yielded a normal white blood cell (WBC) count (1/µl), decreased cerebrospinal fluid (CSF) glucose level of 32 mg/dl, and a positive qualitative CSF polymerase chain reaction (PCR) for human herpesvirus-6 (HHV-6).

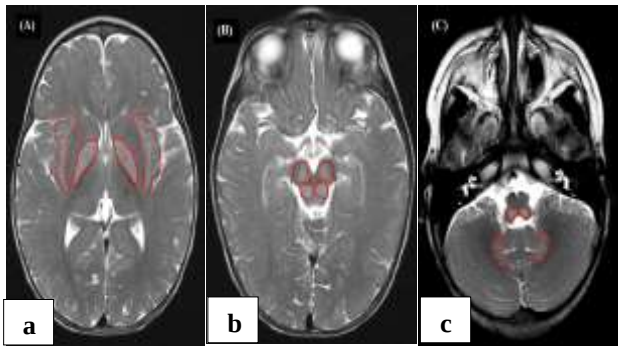

Figure 1: MRI Axial T2-weighted TSE (turbo spin echo) sequences of the brain showing multifocal enhancement outlined in red: (a) symmetric T2 hyperintensity of the bilateral globi pallidi, external capsules, and claustra; (b) symmetric T2 hyperintensity throughout the midbrain; and (c) symmetric T2 hyperintensity of the dorsal medulla and dentate nuclei.

Intravenous fluid resuscitation and dextrose was given. Broad-spectrum anti-infectives were initiated after culture specimens from the serum, urine, and CSF were obtained. Magnetic resonance imaging (MRI) of the brain showed symmetrically elevated T2 signal in the globi pallidi, the central midbrain, dorsal brainstem, and deep nuclei of the cerebellum (Figure 1). She was managed with anti-epileptic drugs to control seizure-like posturing with no ictal correlate on electroencephalogram (EEG). She continued to deteriorate requiring intubation.

Initially, multiple confounding factors led the clinical team to a provisional diagnosis of infectious encephalopathy and status epilepticus secondary to HHV-6. However, with the MRI showing extensive enhancement of deep brain structures in the setting of persistent anion gap ketoacidosis (Table 1), inborn error of metabolism (IEM) became a top differential prompting an urgent metabolic genetics consultation. This led to a magnetic resonance (MR) spectroscopy that showed characteristic branched chain peaks in both gray and white matter areas (Figure 2) and a serum amino acid assay that yielded a plasma leucine level of 2499 umol/l (range <180). MSUD was the unifying diagnosis.

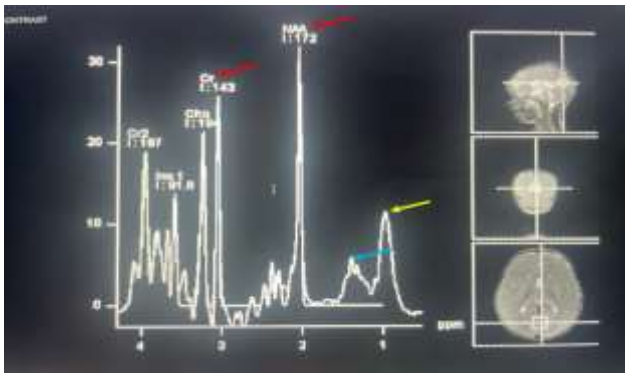

Figure 2: Magnetic resonance spectroscopy (MRS) of the bilateral paramedian occipital gray matter with metabolite peaks showing a decreased NAA/Cr ratio (=1.2 at 2.0 ppm, red arrows), subtle elevation of lactate (1.3 ppm; blue arrow) and branched-chain amino acid peaks (0.9 ppm, yellow arrow) in both gray matter and white matter areas suggestive of MSUD.

Table 1: MUDPILES - a mnemonic for the most common pediatric etiologies of high anion gap metabolic acidosis.[8]

M	U	D	P	I	L	E	S
Methanol	Uremia	Diabetic ketoacidosis	Paracetamol, propylene glycol	Iron, isoniazid, inborn errors of metabolism	Lactic acidosis	Ethylene glycol	Salicylates

Patient outcome

Our patient underwent dialysis for leucine-mediated CNS toxicity after MSUD was confirmed. Leucine levels were monitored and eventually normalized after 24 hours of dialysis. She was concurrently started on enteral valine and isoleucine supplementation, and an amino acid-modified nutrition plan free of any BCAAs. After a 2-week hospitalization, she was back to her neurologic baseline and was discharged home on her special diet as well as enteral thiamine, valine, and isoleucine. Nearly 8 months after diagnosis, she was meeting all developmental milestones. Genetic analysis eventually showed two pathogenic variants in the DBT gene which is associated with autosomal recessive MSUD. Of special note, the patient's younger sister was diagnosed with neonatal MSUD one year after this hospitalization.

DISCUSSION

Acute encephalopathy in the pediatric setting has a very broad differential that includes infection such as bacterial/viral meningitis or encephalitis; central nervous system (CNS) diseases such as acute disseminated encephalomyelitis (ADEM), obstructive hydrocephalus, or status epilepticus; metabolic derangements such as hyponatremia or hypoglycemia; toxic ingestions; and inborn errors of metabolism.[1] These states may all lead to

a rapid progression of an altered mental state.[2] Typically, infection presents with fevers, a prodrome of generalized symptoms such as fussiness or fatigue, and an elevated serum WBC, with radiographic evidence of symmetric involvement of the bilateral basal ganglia.[3] CNS diseases present with symptoms that may be gradual or subtle but often include headache and vomiting.[4] Metabolic derangements are usually preceded by fluid losses from the gastrointestinal tract or dehydration that is elicited in the history, and if sudden may impact the deep gray nuclei on imaging.[5] Toxic ingestions, if not witnessed, can vary symptomatically depending on the ingested substance and may include alterations in pupil size and sweat dysregulation, with stereotyped patterns on imaging including bilateral globus pallidus involvement.[6] And inborn errors of metabolism if not diagnosed in the neonatal period, may be triggered and subsequently discovered by an acute infection or fasting state.[7] Developmental delay may also be a non-specific sign of IEM, particularly if associated with truncal ataxia, as with our patient.[8,9]

There are five main subtypes of MSUD classified based on age at presentation and percentage of enzymatic activity: neonatal or classic, intermediate, intermittent, thiamine-responsive, and E3-deficient.[10] Symptoms common to each subtype include neurological and developmental abnormalities, encephalopathy, poor feeding, and a maple syrup odor to the urine. Diagnosis is highly dependent on newborn screenings (for which our patient's was normal), clinical findings, and biochemical values. Additionally, to determine the subtype and individualize treatment, genetic testing is indicated.

The neonatal, or classic, subtype of MSUD is classified as <2% enzyme activity and presents in the neonatal period as the most severe subtype. Symptoms develop within four to seven days of life, beginning with lethargy and poor feeding, followed by neurological abnormalities, such as opisthotonus (backward, arching spasm of the head, neck, and spine), and bicycling movements.[11] Finally, patients develop the characteristic maple syrup odor in their urine. Further clinical symptoms can vary based on the degree of metabolic decompensation and level of treatment. If left untreated, eventual development of cerebral edema may be fatal. With classic MSUD, characteristic laboratory findings include increased levels of plasma alloisoleucine and BCAA, urine branched-chain keto acids (BCKA), and ketonuria.

The intermediate form of MSUD presents with 3-30% enzymatic activity. Generally, patients with this subtype are asymptomatic in the neonatal period and are diagnosed primarily between the ages of 5 months and 7 years. They also have gradual neurologic and subsequent developmental delay. Similar to other subtypes of MSUD, these patients present with increased plasma BCAAs and urine BCKAs.

Intermittent MSUD is classified as enzymatic activity between 5 and 20%. Patients with this subtype present at variable ages and undergo metabolic crisis primarily in stressful situations, such as infection or in the post-operative state. As such, a diagnosis of intermittent MSUD is generally caught between 5 months and 2 years of age, with an initial presentation of infection. Importantly, laboratory findings may be normal between symptomatic periods.

Thiamine-responsive MSUD constitutes enzymatic activity ranging between 2 and 40%. Clinically, this subtype is similar to intermediate MSUD. However, this form responds well to thiamine supplementation, with improvement in leucine tolerance and BCAA levels when undergoing this therapy.

The final subtype, pyruvate dehydrogenase E3-deficient MSUD, is the rarest form. It presents similarly to intermediate MSUD, but an important difference is the presence of severe lactic acidosis between 8 weeks and 6 months of age. With progression, patients present with neurologic deterioration, developmental delays, and movement disorders. Laboratory testing shows the typical increase in BCAAs, accompanied by increases in lactate, pyruvate, α-ketoglutarate, α-hydroxyisovalerate, and α-hydroxyglutarate.

Though MRI of the brain may be helpful in diagnosing metabolic disease, our patient's MRI had features that would be atypical for MSUD including a lack of both supratentorial white matter involvement and cerebellar white matter involvement. The symmetry and clean/non-edematous margins though were suggestive of a possible metabolic etiology, which aided in the clinical decision making of serum and urine amino acid analysis allowing for definitive diagnosis of MSUD.

Dietary modification is a crucial part of MSUD management and includes a protein restricted diet with isoleucine and valine amino acid supplementation as compensation. Parental guidance for sick days, intercurrent infection, or metabolic crisis (typically manifesting as altered sensorium and vomiting) is also paramount and includes increasing carbohydrate rich foods (high caloric intake) to prevent protein catabolism as well as decreasing protein sources to minimize BCAA toxicity.[12]

In neonatal/classic MSUD, there may be benefit to orthotopic liver transplantation in patients unresponsive to dietary interventions. Liver transplantation has also been shown to prevent further brain injury but does not reverse pre-existing neurological abnormalities.

CONCLUSION

Acute encephalopathy of the child is an emergency that warrants a robust and expedited workup to narrow the differential and prevent irreversible harm. Metabolic crisis

should be on the differential diagnosis of a toddler presenting with encephalopathy, focal neurologic signs, and refractory ketoacidosis especially in the setting of dehydration or infection. MRI of the brain may be helpful in this context, but quantitative serum amino acid analysis is diagnostic. Though MSUD as a diagnosis is rare beyond the neonatal period, prompt recognition and treatment to normalize the buildup of toxic amino acid byproducts can be lifesaving and lead to good outcomes. Regression of developmental milestones, particularly signs of truncal ataxia, should raise suspicion for IEM.

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