

Recurrent Encephalopathy During Febrile Illnesses in a 6-Year-Old Boy

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Abstract

Acute onset of encephalopathy is often due to infections or intoxications, but a high index of suspicion should exist for metabolic or autoimmune causes particularly in recurrent cases. A 6-year-old previously healthy Caucasian male presented with confusion and somnolence. He had several days of fever, myalgia, headaches, and rhinorrhea and was influenza-A positive. He was noted to have new urinary incontinence, inability to follow commands, and was responsive only to noxious stimuli. His neurological examination revealed bilateral ankle clonus. Laboratory results were significant for hypoglycemia and high anion gap metabolic acidosis. Cerebrospinal fluid was unremarkable and cultures remained negative. A magnetic resonance imaging (MRI) of the brain showed diffuse gray matter restricted diffusion. His presentation was attributed to acute influenza-A encephalitis. Four months later, he presented with emesis, abdominal pain, dehydration, and hypoglycemia. He subsequently developed dysarthria and confusion. A brain MRI was similar to his previous presentation. A repeat lumbar puncture was normal. A urine organic acid profile showed elevations of ketones and branched chain ketoacids, with mild elevations of N-acetyl leucine and N-acetyl isoleucine. This pattern is consistent with maple syrup urine disease (MSUD). Genetic testing revealed that he is a heterozygote for 2 pathogenic variants in the BCKDHB gene (P200X and G278S), confirming MSUD. This case highlights the importance of broadening workup to include inborn errors of metabolism in cases of unexplained encephalopathy. Providers should be aware that diseases such as MSUD can occur in intermittent forms that may not be detected until early childhood.

Keywords

general pediatrics, radiology, neurology

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Case Report

A 6-year-old previously healthy Caucasian male presented with sudden onset of confusion and somnolence. He had several preceding days of fever, myalgia, headaches, and rhinorrhea and was influenza-A positive by rapid antigen testing via nasal swab. On arrival, he was noted to have new urinary incontinence, inability to follow commands, and was responsive only to noxious stimuli. His neurological examination revealed intact cranial nerves, equal and reactive pupils, normal tone and deep tendon reflexes, bilateral ankle clonus, and flexor plantar reflexes. Laboratory results were significant for hypoglycemia (57 mg/dL), metabolic acidosis (bicarbonate 12 mmol/L) with elevated anion gap of 31 mEq/L. Cerebrospinal fluid (CSF) obtained by lumbar puncture was unremarkable with one white blood cell, no red blood cells, and normal glucose and protein. Blood, urine, and CSF cultures remained negative. Magnetic

resonance imaging (MRI) of the brain showed diffuse gray matter restricted diffusion with sparing of white matter, findings favored to reflect sequelae of diffuse encephalitis. He was treated with 5 days of oseltamivir. He received intensive physical, occupational, and speech therapy and was discharged to a neurological rehabilitation program. Subsequently, he fully recovered over the course of several weeks. His presentation was attributed to acute influenza-A encephalitis.

Four months later, he presented with 2 days of periumbilical abdominal pain, poor appetite, and recurrent nonbilious emesis. His temperature was 97.5°F, heart

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rate was 135 beats per minute, blood pressure was 104/67 mm Hg, and respiratory rate was 22 breaths per minute. He appeared uncomfortable but non-toxic. His examination was significant for mild periumbilical pain without guarding. Notably, his mental status and neurological examination were unremarkable. Urine studies were notable for elevated urine specific gravity of 1.030 and large urine ketones. Bloodwork was notable for hypoglycemia (65 mg/dL), anion gap metabolic acidosis (bicarbonate 13 mmol/L, anion gap 25 mEq/L), and acute kidney injury (blood urea nitrogen 30 mg/dL, creatinine of twice his baseline at 0.6 mg/dL). He was fluid resuscitated and his heart rate normalized.

Hospital Course

He was admitted for rehydration due to persistent emesis. His acute kidney injury resolved with intravenous fluids. However, shortly after admission he developed dysarthria, which progressed to confusion and difficulty following 2-step commands. A brain MRI showed decreased but persistent abnormal diffuse restricted diffusion and abnormal increased T2/FLAIR signal throughout the cortical gray matter, basal ganglia, brainstem, cerebellar peduncles, and cerebellar dentate nuclei, favored to reflect resolving diffuse encephalitis, or possibly a new diffuse toxic or metabolic insult. A lumbar puncture was performed with normal opening pressure, cell count, and protein/glucose.

As this was this patient's second event of encephalopathy, elevated anion gap metabolic acidosis, and hypoglycemia in the setting of acute illness with accompanying diffuse gray matter changes on neuroimaging, clinical concern grew for an autoimmune or metabolic process as opposed to infection alone.

CSF was sent for an autoimmune encephalitis panel. Plasma amino acids, acylcarnitine/carnitine ratio, lactate, pyruvate, ammonia, and urine organic acids were obtained to complete the workup. These were pending at discharge.

After 3 days, the patient's condition had dramatically improved, with clear speech, resolution of confusion, and a normal neurologic examination. His appetite returned to normal and emesis resolved. He was told to avoid fasting due to concern for potential metabolic etiologies of his symptoms, and to seek immediate medical care for persistent emesis. He was discharged with close neurology follow-up without a clear etiology to the cause.

Final Diagnosis

Ultimately, his urine organic acid profile showed marked elevations of ketones and branched chain

ketoacids, with mild elevations of N-acetyl leucine and N-acetyl isoleucine. This pattern is consistent with maple syrup urine disease (MSUD) during an acute metabolic decompensation. Plasma amino acid profile showed elevations of allo-isoleucine, leucine, isoleucine, and valine, also consistent with MSUD. Alanine and glutamine were low suggestive of metabolic decompensation. Genetic testing revealed that he is a heterozygote for 2 pathogenic variants in the BCKDHB gene (P200X and G278S), confirming MSUD.

Discussion

MSUD is well described in the literature. Pediatricians are familiar with its inclusion in the newborn screen and its classic clinical presentation. Less commonly characterized is an intermittent variant of MSUD, which can be asymptomatic until an otherwise healthy child experiences a metabolic stressor, and has been shown to pass undetected by newborn screening techniques.¹ This case report adds data to an evolving picture of school-aged patients presenting with intermittent MSUD. It also underscores the importance of a physician's high index of suspicion for underlying metabolic disease in patients who present with recurring encephalopathy or who demonstrate significantly atypical courses of common infections.

The patient described in the report above had an uncomplicated birth and perinatal history, a benign neonatal course, and passed his newborn screen. He had mild language delays that responded well to speech therapy but had no learning disabilities or other developmental delays. Notes from this patient's follow-up appointment with a geneticist echoed this observation, which detailed that his genetic findings, consistent with intermittent type MSUD, involve normal growth and development throughout infancy and early childhood. Patients do well in between crises and their prognosis is favorable after initiation of leucine restriction.² Notably, metabolic laboratory results will be normal when asymptomatic and thus are often missed on newborn screening.

In intermittent MSUD, biochemical abnormalities are absent when the patient is not in acute crisis. Despite this observation, increased evidence suggests that patients with MSUD do not perfectly fit into a specific subtype due to overlapping symptoms that represent a spectrum of disease severity. It is routine to refer to a child's newborn screens when he or she is admitted with acute neurologic changes or metabolic disturbances. The newborn screen for MSUD is a sophisticated but imperfect test. In some cases of variant forms of MSUD

diagnosed in late infancy or early childhood, patients were found to have branched chain amino acid levels below the institution's cutoff. Different institutions use different cutoffs, use different methods of testing, and also time spot collection differently.¹ These nonstandard variables may contribute to the few missed positive screens, and more generally, any misleading data confounds the clinical picture when an older child presents in crisis for the first time.

Intermittent MSUD symptoms usually first appear between 5 months and 2 years of age. In patients who are out of a typical age window for classic and even non-classic diagnoses, atypical presentations and courses of common infections should ignite suspicion for a metabolic etiology.^{3,4}

Another factor that deserves mention is the patient's neuroimaging findings; diffusion restriction on diffusion-weighted MRI has been found in patients with neurometabolic conditions.⁵ Such findings correlate strongly with the patient's MRI, which showed decreased but persistent abnormal diffuse restricted diffusion during his second admission. More studies are needed to better standardize neuroimaging findings seen in this patient population, but serve as a useful supplement to laboratory data.

Conclusion

The key element to this case and others is the repetitive nature of presenting symptoms in otherwise healthy children to the hospital. A clinician should have a high index of suspicion for an underlying metabolic condition when a child has a history of multiple hospital admissions for similar or identical presenting neurologic symptoms that are otherwise unexplained. A reported history of passing the newborn screen can offer false assurances to a diagnosing clinician in cases of intermittent MSUD. Diffusion-weighted MRI showing diffuse areas of diffusion restriction may be helpful in narrowing a differential.

Author Contributions

ES: Contributed to conception and design; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

JA: Contributed to conception and design; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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