

MRI Findings of Adult Maple Syrup Urine Disease Exacerbation

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Maple syrup urine disease (MSUD) is an inherited disorder of branched-chain amino acid (BCAA) metabolism that manifests in early infancy. While there is ample description of imaging features of neonates in the medical literature, the neuroimaging findings in adults have not been as well described; the disorder only rarely presents in adulthood, and children that survive beyond infancy are usually maintained on strict dietary control to prevent metabolic decompensation. We present a case of an adult with MSUD exacerbation to highlight the apparent discrepancy between imaging findings in adults with this disorder and the typical imaging appearance in younger patients.

CASE

A 36-year-old male patient presented to our emergency department with a five day history of decreased oral intake, memory disturbance, impaired balance, nausea and urinary retention. The symptoms were likely triggered by a one-week history of the patient inadvertently drinking an incorrect metabolic formula, providing him with an excess of dietary leucine. The patient had a past medical history of classical MSUD diagnosed in infancy, with multiple hospitalizations in childhood for disease control. Additionally, he suffered from osteoporosis, with a prior hip fracture in 2006. On neurological examination, he was confused, with moderate worsening of his baseline symptoms of cerebellar dysfunction including bilateral dysdiadochokinesis, mild right sided dysmetria, difficulty with tandem gait, and abnormal gait with circumduction. Laboratory studies revealed significantly elevated BCAA levels; specifically - leucine: 2766 $\mu\text{mol/L}$ (reference range (RR): 71-175 $\mu\text{mol/L}$); isoleucine: 875 $\mu\text{mol/L}$ (RR: 35-97 $\mu\text{mol/L}$); and valine: 2134 $\mu\text{mol/L}$ (RR: 116-315 $\mu\text{mol/L}$). Baseline BCAA levels over the last three years had been within the ranges of: leucine: 381-638 $\mu\text{mol/L}$; isoleucine: 43-146 $\mu\text{mol/L}$; valine: 96-309 $\mu\text{mol/L}$.

A magnetic resonance imaging (MRI) study was subsequently performed on a 3 Tesla Siemens scanner, including a sagittal spin-echo T1 sequence (echo train (ET): 1, echo time (TE): 8.40 milliseconds (ms), repetition time (TR): 700.00 ms, display field-of-view (DFOV): 22.0 x 22.0 centimeters (cm), matrix: 256 x 218, slice thickness (ST): 4.0 millimeters (mm)), axial fast recovery fast spin echo T2 sequence (ET: 18, TE: 92.00 ms, TR: 5180.00 ms, DFOV: 22.0 x 22.0 cm, matrix: 320 x 320, ST: 4.0 mm), axial fluid-attenuated inversion recovery (FLAIR) sequence (ET: 16, TE: 94.00 ms, TR: 9000.00 ms, TI: 2500.00ms, DFOV: 19.9 x 22.0 cm, matrix: 256 x 232, ST: 4.0 mm), axial diffusion weighted imaging (DWI) sequence (ET: 1, TE: 94.00 ms, TR: 6900.00 ms, DFOV: 22.0 x 22.0 cm, matrix: 160 x 160, ST: 5.0 mm, b values: 0 and 1000 s/mm²), and axial

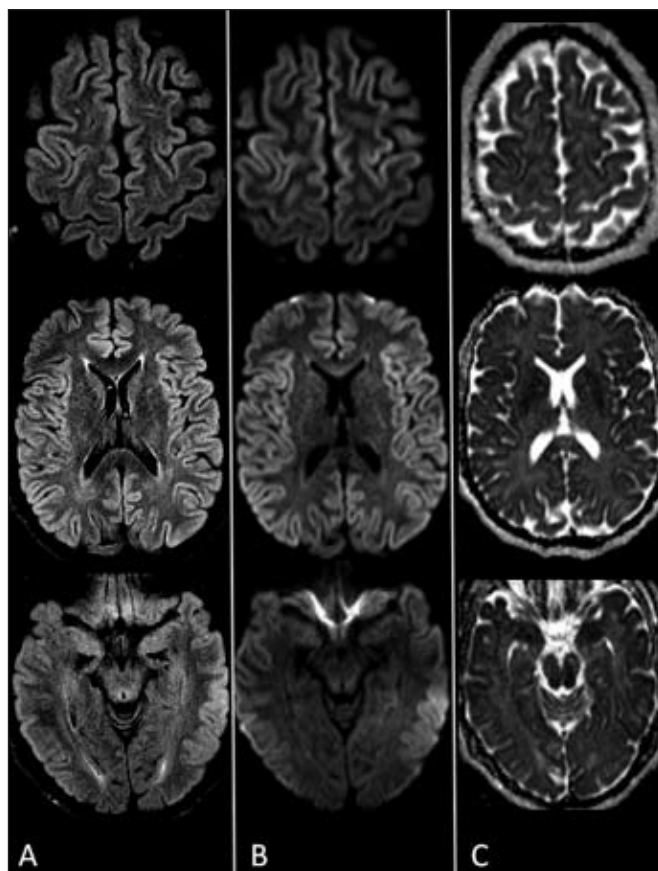


Figure 1: Selected images from MRI study including FLAIR (A), DWI (B) and ADC (C) images at corresponding levels demonstrating increased FLAIR signal, increased DWI signal, and low ADC signal involving the cortex diffusely, compatible with restricted diffusion (cytotoxic edema). Note that the increased FLAIR signal adjacent to the occipital horns of the lateral ventricles is artifactual in nature.

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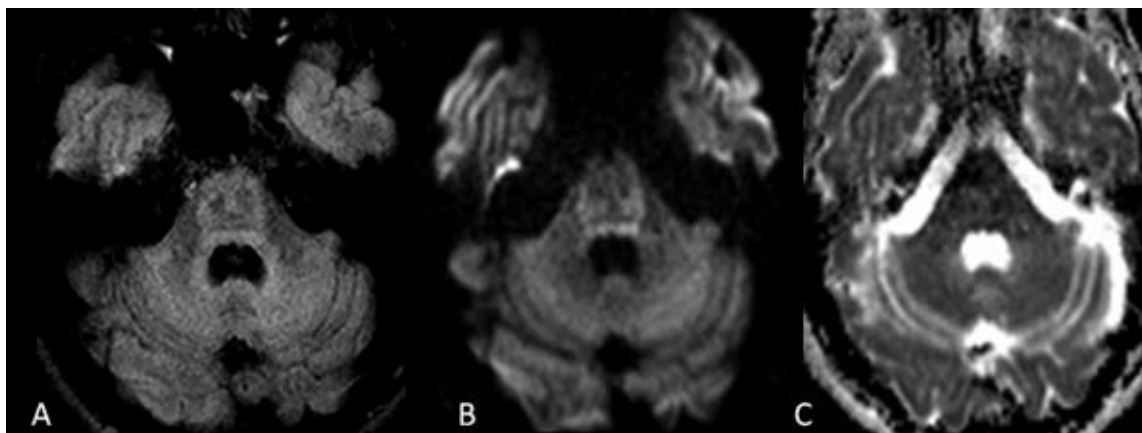


Figure 2: FLAIR (A), DWI (B) and ADC (C) images obtained at the level of the posterior fossa demonstrate increased FLAIR/DWI signal involving the dorsal brainstem, middle cerebellar peduncles, and deep cerebellar white matter, in the absence of low ADC signal, suggestive of chronic sequelae from remote MSUD exacerbations

susceptibility weighted imaging (SWI) sequence (ET: 1, TE: 20.00 ms, TR: 28.00 ms, DFOV: 16.5 x 22.0 cm, matrix: 320 x 221, ST: 2.0 mm).

The MRI findings are summarized in Figures 1 and 2. Cortical thickening with subtle increased FLAIR signal was identified involving the gray matter diffusely; this was most prominent at the superior frontal cortical regions bilaterally. Comparison with selected FLAIR images in a healthy adult patient is demonstrated in Figure 3, in order to highlight the abnormalities identified in our patient. The regions of cortical FLAIR hyperintensity in our patient demonstrated associated restricted diffusion (decreased apparent diffusion coefficient (ADC) values), consistent with cytotoxic edema. Conversely, increased FLAIR signal was identified involving the pons and white matter tracts of the brachium pontis extending into the cerebellar white matter, in the absence of restricted diffusion (normal ADC values), suggestive of sequelae of prior exacerbations of maple syrup urine disease. There was no FLAIR signal abnormality identified involving the subcortical white matter, nor the basal ganglia.

Upon admission, the patient was assessed by the Clinical and Metabolic Genetics team, and diagnosed with an acute MSUD exacerbation on the basis of clinical presentation and laboratory workup. He was managed with a high carbohydrate infusion, maintenance of a leucine-free formula and strict dietary protein control. He was discharged five days later, when neurological symptoms and plasma leucine levels improved to near baseline.

DISCUSSION

Maple syrup urine disease is an autosomal recessive disorder of amino acid metabolism. Reports of incidence vary, with estimates ranging from 1:185 000 to 1:86 800, depending on geographic location. Additionally, certain populations demonstrate a higher incidence of the disease, thought to be on the basis of founder effects, with the highest reported rates within the Pennsylvanian Mennonite population (approximately 1:150 live births)¹⁻⁴. The deficiency of branched-chain ketoacid dehydrogenase (BCKD) leads to the accumulation of branched-

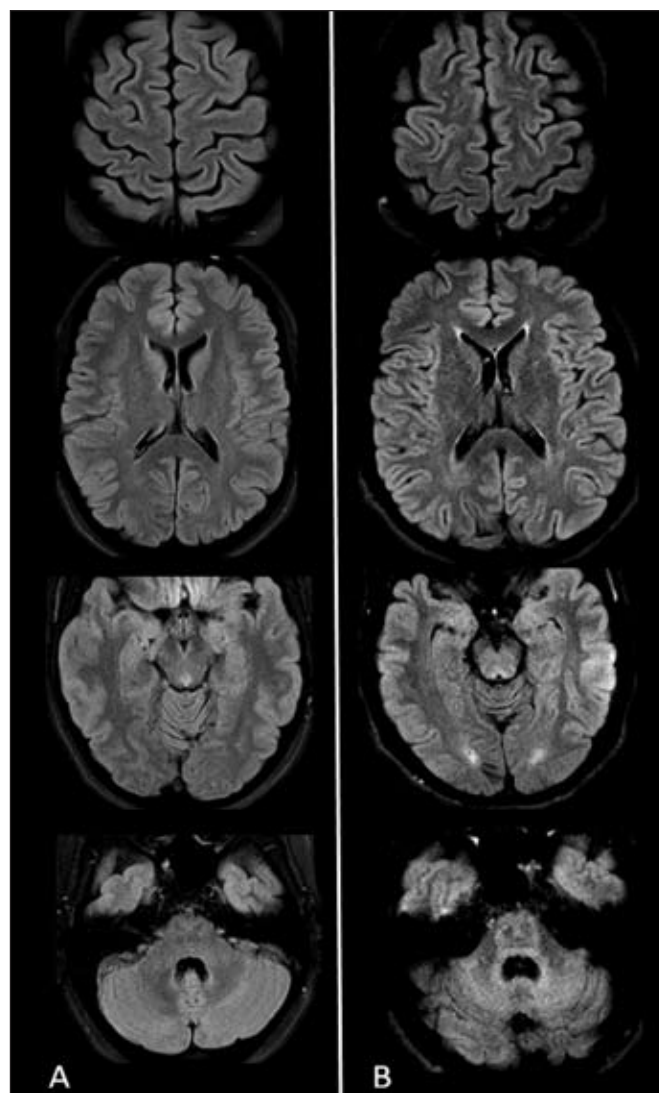


Figure 3: Selected FLAIR images from a normal, healthy adult patient (A) obtained under identical MRI parameters are compared with those of our patient (B), in order to highlight the subtle cortical FLAIR abnormalities identified.

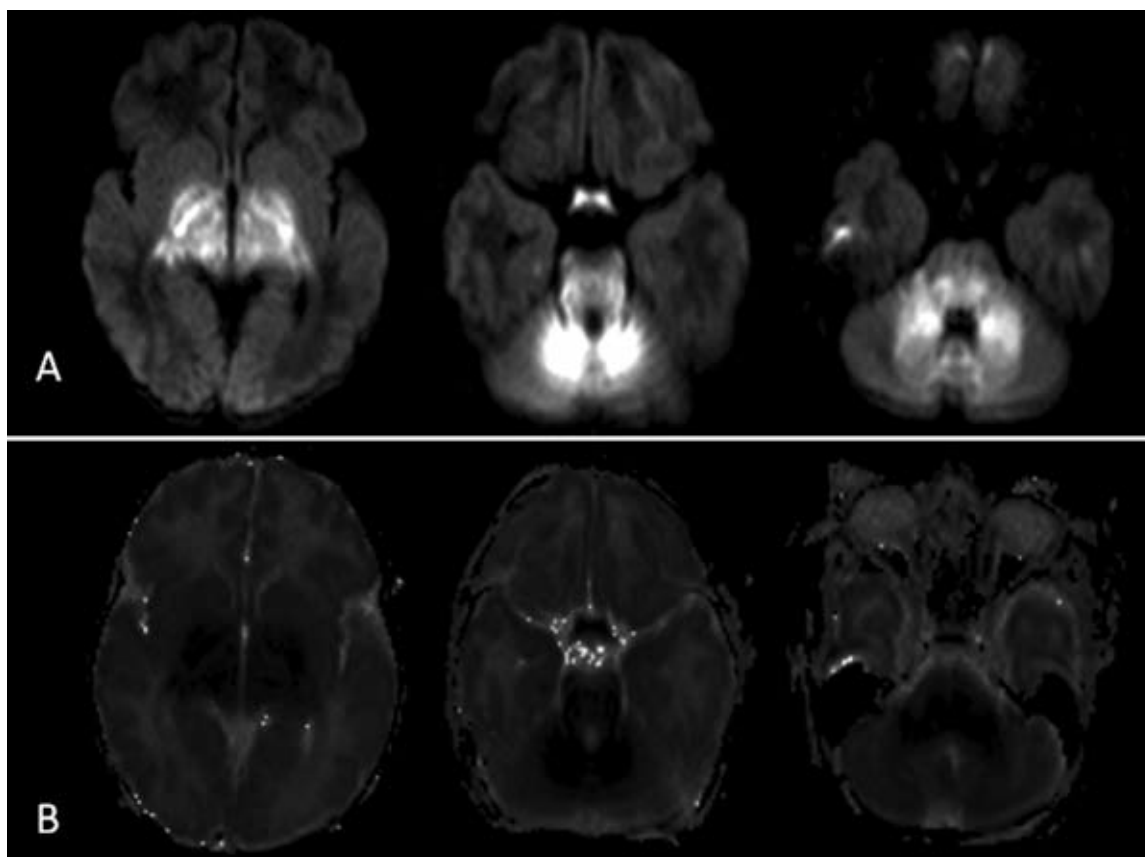


Figure 4: Selected MRI images from a child presenting with MSUD exacerbation, including DWI (A) and ADC (B) images at corresponding levels, demonstrating the classic pattern of childhood MSUD edema with restricted diffusion involving the dorsal brainstem, middle cerebellar peduncles, deep cerebellar white matter, thalami, and posterior limbs of internal capsule (images courtesy of Dr. Juan Pablo Cruz, University of Toronto)

chain amino acids, with the specific build-up of the amino acid leucine contributing to significant neurotoxicity. The classic form of the disease affects 80% of patients, and manifests in infancy, where untreated neonates may demonstrate irritability, poor feeding, and stereotyped movements as early as a few days of life, rapidly progressing to encephalopathy, intermittent apneic episodes, coma and ultimately death by age seven to ten days¹.

Prior literature has concentrated on the MRI findings of neonates and children affected by MSUD. In acute neonatal exacerbations, the classic form demonstrates T2 hyperintensity with diffusion restriction predominantly involving the cerebellar white matter, the dorsal brainstem, the posterior limb of the internal capsule, the globus pallidus, and thalamus (Figure 4) - areas which are thought to correspond to early myelinated regions within the infant brain⁵. This classic pattern of predominantly reversible cytotoxic edema, thought to represent intramyelinic edema, is referred to as the “MSUD edema” pattern. The imaging findings in MSUD may be understood as a direct consequence of the pathophysiologic mechanisms by which MSUD produces metabolic encephalopathy. Impaired leucine degradation results in brain accumulation of breakdown products, specifically α -ketoisocaproate (KIC), which inhibits the normal progress of the Krebs cycle. As a result of diminished

adenosine triphosphate (ATP) synthesis, the function of the Na/K pump is compromised, causing cytotoxic edema⁶.

Little discussion exists on the MRI appearance of acute metabolic decompensation in adult patients. A single case report by Sutter et al. describes an episode of acute exacerbation related to dietary noncompliance in a 23-year-old patient with classical MSUD presenting with visual symptoms; specifically, decreased visual acuity, horizontal diplopia and bilateral papilledema⁷. The corresponding MRI findings were that of bilateral protrusion of the optic nerve heads and regional edema involving the brainstem, basal ganglia and thalami; there is, however, no discussion of the DWI findings in this case. However, within the literature, evidence exists to support alteration in MRI findings in older patients with MSUD exacerbation versus those in younger patients. A series by Jan et al described the MRI findings in six patients with acute decompensation of MSUD, with age ranges from 8 days to 14 years⁸. In all patients, restricted diffusion was demonstrated in the typical areas of neonatal “MSUD edema” - namely, the medulla, pons, midbrain and globus pallidus - with the majority of cases also demonstrating restricted diffusion within the cerebellar white matter and thalamus. Interestingly, however, only in the two older patients (ages 6 and 14 years) was restricted diffusion identified involving the cerebral cortex. The hypothesis for

cortical involvement provided by the authors relates to the known neurotoxic effects of leucine and its metabolites (KIC) on disruption of normal energy metabolism with resulting cytotoxic edema; however, the presence of this finding in older patients alone remains unexplained. The MRI findings in our patient support a hypothesis of shifting neurotoxic effects, such that the pathologic mechanisms that preferentially affect myelinated regions in younger patients, may, with age, progressively involve the cortical grey matter. In contrast, myelinated regions may perhaps develop a relative tolerance to further neurotoxicity.

It is therefore important to note that the radiologic differential diagnosis for the adult MSUD exacerbation is considerably different from that in childhood. Given the salient finding of cortical cytotoxic edema, the differential diagnosis that must be considered would include ischemic processes, such as acute cortical infarction, or hypoxic-ischemic encephalopathy; infectious processes, including cerebritis, or Creutzfeld-Jakob disease; or other metabolic encephalopathies, such as hyperammonemic encephalopathy, hypoglycemia, or mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). Status epilepticus with excitotoxic cortical injury could also give this imaging appearance.

In conclusion, neuroimaging findings in MSUD have been extensively described in neonates and children; however, a paucity of reported literature exists as to the adult findings in acute exacerbation of this disease. Nevertheless, there is adequate evidence to suggest a discrepancy between the MRI manifestations of acute disease decompensation in adults versus those in younger patients. The pathophysiologic mechanisms that underlie this difference remain uncertain; however, an awareness of the expected MRI findings in adults is essential to support the diagnosis and prompt treatment of an acute exacerbation in these patients.

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