Case Report

Late onset arginase deficiency presenting with encephalopathy and midbrain hyperintensity

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Abstract

Urea cycle disorders (UCD) are very rare metabolic disorders that present with encephalopathy and hyperammonemia. Of the UCDs, Arginase deficiency (ARD) is the rarest and presents in childhood with a progressive spastic diplegia or seizures. Acute presentation in adulthood is extremely unusual.[1] We present the first case of adult onset ARD presenting with encephalopathy and diffusion weighted MRI findings that resembled a moustache in the midbrain.

Key Words

Arginase deficiency, midbrain hyperintensity, moustache sign, urea cycle disorder

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Introduction

Urea cycle disorders (UCD) are very rare metabolic disorders with an estimated incidence of 1 in 25-30,000. Arginase deficiency (ARD) is the least common of the UCDs with an estimated incidence of 1:350,000-1,000,000. ARD usually presents with a spastic paraplegia or seizures in childhood and hyperammonemic crises are rare. Presentation in adulthood is uncommon and only one previous case has been reported.[1] We present a rare case of late onset ARD presenting in an elderly male with coma and midbrain hyperintensities on magnetic resonance imaging (MRI) and discuss the management of urea cycle disorders.

Case Report

A 60-year-old man developed fever and chest discomfort and was admitted to a nearby facility. He was detected to have a non-ST elevation myocardial infarction (NSTEMI) and left ventricular (LV) failure and started on noninvasive ventilation. Over the course of a day, he became progressively drowsy and hypotensive and had to be mechanically ventilated. He had a past history of diabetes mellitus and hypertension without any other comorbidities. His routine blood investigations were normal and mild LV dysfunction was noted on Echo. On day 4, he had a bout of melena. Ultrasound abdomen and computed tomography (CT) brain were normal. As serum ammonia was mildly elevated to 80 were he was started on a low protein diet and rifaximin. However, he continued to be comatose and was shifted to our facility. On arrival, he was intubated, comatose, with sluggish pupillary reaction, and had scattered crepitations in both lung fields. Serum sodium was 150 mEq/l and serum ammonia was 134 red c (normal lab values 27-90 al la). Blood glucose levels and anion gap were normal. Arterial blood gases revealed a mild respiratory alkalosis on volume control ventilation.

A repeat ultrasound abdomen was normal. Electroencephalogram (EEG) showed mild, diffused, slow waves. MRI brain revealed bilateral symmetrical areas of diffusion restriction in the medial cerebral peduncles, periaqueductal grey matter, tectal plate, dorsal midbrain, and superior cerebellar peduncles resembling

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a rical areas of diffusion restrictiointensities were seen in the bilateral precentral gyri, temporal cortices, and amygdala [Figure 1]. The possibilities of Wernickeslateral preing a rical pontine myelinolysis, or mycoplasma encephalitis were considered and he was started on thiamine, azithromycin, and free water replacement. Cerebrospinal fluid (CSF) study showed 10 cells (100% lymphocytes), CSF glucose of 133, proteins of 80 mg/dl, and was negative for a pan-central nervous system (CNS) panel (XCyton Syndrome Evaluation System (SES) panel). Mycoplasma antibodies were negative and serum sodium was slowly corrected over the next few days. Intravenous (IV) methylprednisolone was given at a dose of 1 g/day over 5 days. However, serum (S.) NH3 levels were 158 levels were 158 everiven at on day 9 despite lactulose and rifaximin and he continued to remain comatose. At this point, the possibility of an alternative cause of hyperammonemia was considered and work up for a urea cycle disorder was initiated. He was started on sodium benzoate 3 g 4-hourly and arginine 3 g 4-hourly empirically through nasogastric tube. Protein feeds were restricted. He started developing frequent diarrhea necessitating only rice water feeding. By day 16, a repeat MRI was completely normal. By day 18, he had started opening eyes and inconsistently obeying commands. After a tracheostomy, he was briefly transitioned off to BIPAP and spontaneous breathing before requiring mechanical ventilatory support again. Critical illness polyneuropathy was suspected due to his flaccid quadriparesis and confirmed with nerve conduction studies. S. NH_3 hovered around 78 und 78 y, hehemodialysis was being considered, sepsis set in and his condition rapidly worsened. He expired on day 23. On day 25, his blood arginase levels (683.99 level) and urinary orotic acid levels (1.72 urinal) were elevated. These results were suggestive of ARD [Table 1]. Red blood cell (RBC) arginase enzyme activity or targeted molecular genetic studies could not be performed. The patient had nine siblings and there was no family history of unexpected deaths.

Discussion

The urea cycle is the primary pathway responsible for the disposal of nitrogen waste (predominantly NH3) after protein metabolism by incorporating it into urea [Figure 2]. In the process, the amino acids citrulline, arginine, and ornithine are also produced.

Urea cycle defects (UCD) result from genetic defects affecting components of the urea cycle. Severe defects in enzymes in the pathway usually result in symptoms during the neonatal period of life. However, partial defects in these enzymes or a defect in the sixth enzyme Arginase (ARG1) might delay the symptomatology till late adulthood.[1] These are then unmasked during periods of crises such as intercurrent illness, sepsis, protein loads, and medications (such as valproic acid or salicylates). UCDs present with sensorial alteration, nausea and vomiting, encephalopathy, or unexplained respiratory alkalosis (due to the effect of NH_3 on the brainstem respiratory centers). Any unexplained hyperammonemia (>80 μ0/dl) in the absence of hepatorenal dysfunction should prompt a plasma amino acid and urinary organic acid profiling to identify a UCD [Table 2 and Figure 3]. Defects of a single metabolic enzyme disrupt the normal functioning of metabolic pathways and leads to aberrant accumulation of "upstream" metabolites or reduced levels of yme disrupt metabolites or other critical cellular components. Diagnosis requires estimation of plasma ammonia, quantitative amino acid analysis, and urinary orotic

Table 1: Urea cycle disorder panel results (LC-MS/MS, GC/MS)

Amino acid	Result (μmol/l)	Normative range (μmol/l)	
Glutamine	90.49	205-756	
Ornithine	2.89	48-195	
Citrulline	0.92	12-55	
Arginine	683.99	15-128	
Arginosuccinic acid	1.16	0-1	
Orotic acid urine results (GC-MS)			
Compound	Result	Reference range in %	Elevation factor
Uracil	3	2.8	1.07
Orotic acid	1.72	0.3	5.73

LC = Liquid chromatography, MS = mass spectrometry, GC = gas chromatography

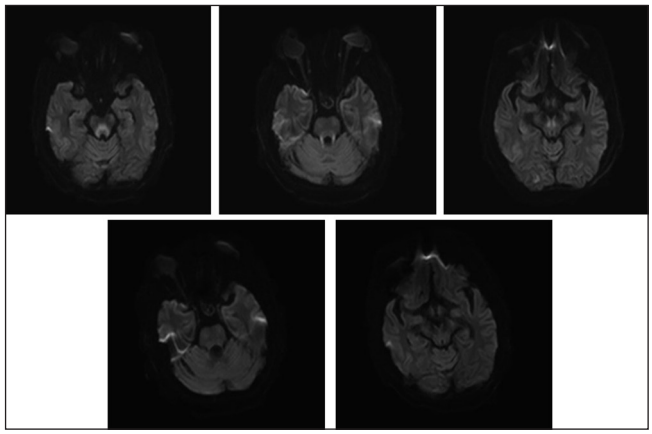

Figure 1: MRI brain; diffusion-weighted sequences. Top panels showing bilateral symmetrical areas of diffusion restriction in the, periaqueductal grey matter, tectal plate, dorsal midbrain, and superior cerebellar peduncles. MRI = Magnetic resonance imaging

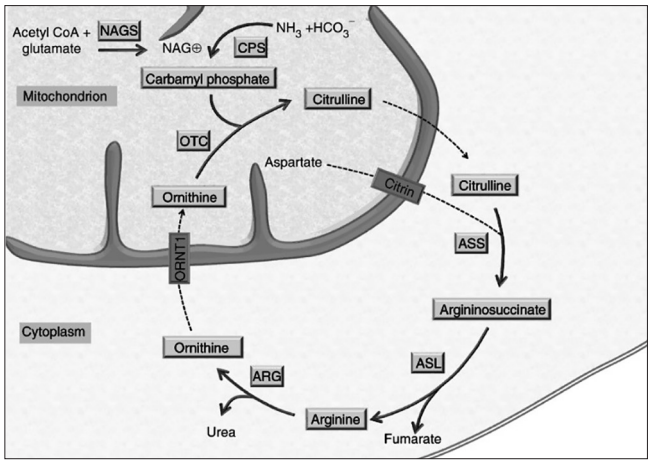

Figure 2: Urea cycle. CPSI = Carbamoyl phosphate synthetase I, NAGS = N-acetylglutamate synthase, OTC = ornithine transcarbamylase, ASS = arginosuccinic acid synthase, ASL = argininosuccinic acid lyase, ARG = arginase

Table 2: Analysis of plasma amino acids and urinary orotic acid in the differentiation of UCD

Amino acid	CPS1D	OTCD	ASSD	ASLD	ARD
Citrulline	Absent	Reduced	Reduced	Very high	Mildly elevated
Arginine	Reduced	Reduced	Reduced	Reduced	High
Orotic acid	Low	Elevated	Elevated	Elevated	Elevated

CPSID = Carbamoyl phosphate synthetase I deficiency, OTCD = ornithine transcarbamylase deficiency, ASSD = arginosuccinic acid synthase deficiency, ASLD = argininosuccinic acid lyase deficiency, ARD = arginase deficiency, UCD = urea cycle disorders

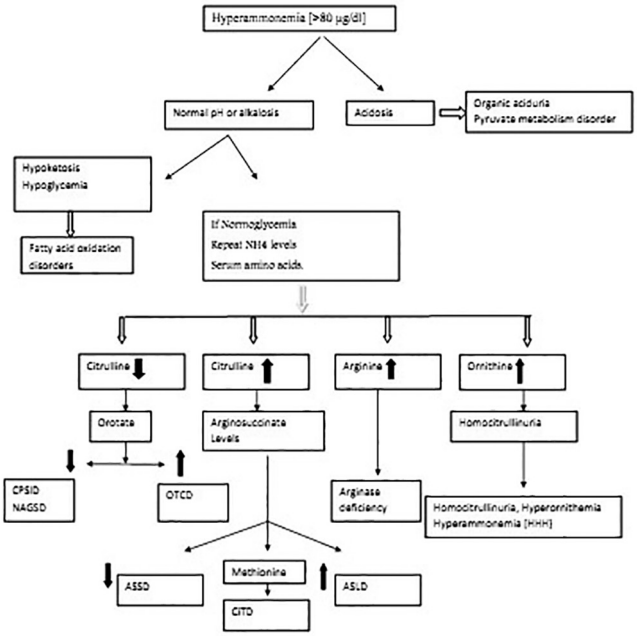

Figure 3: Suggested work up of hyperammonemia. CPSID = CPS I deficiency, NAGSD = NAGS deficiency, OTCD = OTC deficiency, ASSD = ASS deficiency, CitD = citrin deficiency, ASLD = ASL deficiency

acid levels. Definitive testing requires testing RBC arginase enzyme activity or targeted molecular genetic studies of ARG1. The principles of management in UCDs include reversal of the catabolic state through glucose supplementation and reduction of protein intake, and expediting the removal of ammonia by administering nitrogen scavengers such as sodium benzoate, sodium phenyl acetate, or sodium phenyl butyrate which utilizes glutamine and glycine and excrete them in urine as hippurate and phenylacetylglutamine. L-arginine and/or L-citrulline may be required in specific UCDs. The fastest way to ameliorate hyperammonemia is by hemodialysis or hemofiltration while liver transplantation is awaited.

Hyperargenemia is an autosomal recessive disorder that can mimic spastic cerebral palsy with progressive spastic diplegia and occasional seizures. The manifestations are thought to arise from hyperarginenemia itself rather than hyperammonemia. Guanidino compounds that arise due to increased arginine levels are thought to act as neurotoxins by inhibiting transketolase activity causing demyelination and pyramidal signs as well as affecting GABAergic transmission resulting in epileptogenesis.[2] MRI only shows nonspecific findings of cerebral atrophy in hyperarginemia,[2] although patients with hyperammonemic encephalopathy can show symmetric involvement of the cingulate gyrus and insular cortex on MRI as well as asymmetric cortical involvement.[3] Only one previous late onset case of hyperaginemia presenting as an acute paraparesis has been reported to our knowledge.

Our patient had a very severe elevation of arginine (prior to administration of oral arginine) along with an elevation of urinary orotic acid. Going by the dictum that the defective enzyme leads to maximal accumulation of the nearest the nearest ofe lead't elevated arginine levels are highly suggestive of an ARD. Our patient was unusual in having an encephalopathy due to ARD with peculiar MRI findings.

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Conflicts of interest
There are no conflicts of interest.

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