Carbonic Anhydrase-VA Deficiency: A Close Mimicker of Urea Cycle Disorders

Inborn errors of metabolism (IEM) are a heterogenous group of disorders in which the body cannot metabolize the food components normally. They occur due to single-gene defects which cause a clinically significant block in the metabolic pathway resulting either in accumulation of substrate behind the block or deficiency of the product.[1] Early suspicion and management can be life-saving in these disorders. We here, report a baby who had an acute life-threatening event in early infancy followed by persistent hyperammonemic encephalopathy combined with hyperlactatemia and increased urinary ketones.

A one and a half year old boy, first born to non-consangionously married couple, was symptomatic since day 3 of life. He was born term and had a smooth perinatal transition. At 68 hours of life, he was found to be cyanosed and in cardiac arrest, but was revived after giving cardio-pulmonary resuscitation for 2 minutes. Considering an acute life-threatening event, differentials considered were sepsis, seizures, gastro-esophageal reflex disease, metabolic disorders, electrolyte disturbances, and cardiac dysrhythmias. His electroencephalography, sepsis screen, electrocardiogram, and serum electrolytes were normal. He was noted to have metabolic acidosis along with hyperlactatemia (pH-7.1, HCO3-12, lactate-17 mmol/l). Metabolic acidosis resolved within next 12 hours, but hyperlactatemia persisted Serum ammonia was (102 μmol/l). After introduction of feeds the serum ammonia rapidly elevated to 245 μmol/l and hence feeds were withheld. He was started on sodium benzoate along with carnitine, zinc, biotin, riboflavin, and folic acid supplements. He was extubated on day 8 of life. Initial possibilities suspected were hypoxia due to cardiac arrest/cardiogenic shock, urea cycle defects, organic academia and mitochondrial respiratory chain disorders. Hypoxia induced by cardiac arrest was unlikely because of persistent hyperammonemia, hyperlactatemia despite correction of metabolic acidosis. We excluded meningitis and initial cranial magnetic resonance image was normal. Urinary ketones were increased, tandem mass spectrometry, urine gas chromatography-mass spectrometry, and serum glucose were normal. The infant was followed up every month to monitor ammonia levels with maximum up to 340 μmol/l and the dose of sodium benzoate was adjusted accordingly. His developmental milestones were also assessed at the same visits and were appropriate for age. Neurological examination was normal with no neurocutaneous markers. Clinical exome sequencing revealed autosomal recessive compound heterozygous variants in exon 1 (c.123G > T) and exon 6 (c.690C > T) of *CA5A* gene, which was confirmed by sanger sequencing. Hence carbonic anhydrase VA (CA-VA) deficiency was confirmed. On follow-up at 1.5 years, the anthropometric measurements were weight 12 kg (0.37 Z score) height 80 cm (−0.89 Z score), and head circumference 47 cm (−1.27 Z score). He can walk independently, speak two to four words, and can eat by spoon. His biochemical parameters were normal except he continued to have high normal serum ammonia (90 μmol/l) and serum lactate (10 mmol/l) and was on sodium benzoate along with carnitine and riboflavin supplements.

CA-VA belongs to a family of zinc metalloproteases, that provides bicarbonate as a substrate to various enzymes in mitochondria including carbomyl phosphate synthetase I, pyruvate carboxylase, propionyl CoA carboxylase and 3-methylcrotonyl-CoA carboxylase. Deficiency of this isoenzyme results in the dysfunction of all the above four enzymes and affects urea cycle, tricarboxylic acid cycle and gluconeogenesis.[2,3] The main symptoms include excessive lethargy, poor feeding, tachypnoea, seizures, and coma. Obligatory laboratory parameters include hyperammonemia, elevated blood lactate, and elevated ketones. Ancillary parameters include metabolic acidosis and hypoglycaemia.[4] The common differentials to be considered in such a scenario are summarized in Table 1. Management includes care during acute crisis and chronic long-term strategies. In acute crisis, intravenous fluids at 1.5 times maintenance should be started along with extra calories via intravenous lipids, restriction of protein initially for at least 48 hours and slow addition of essential aminoacids, broad spectrum antibiotics for suspected

Table 1: Common differentials to be considered in a child with hyperammonemia and hyperlactatemia[5]

Lab parameters	CA-VA deficiency	Hypoxia due to Cardiac arrest	Urea cycle defects (CPS/NAG1 def)	Pyruvate carboxylase deficiency
Serum Ammonia	Increased	Normal to increased	Increased	Increased
Serum lactate	Increased	Increased	Normal	Increased
Serum glucose	Normal to decreased	Normal to decreased	Normal	Decreased
HCO3	Decreased	Decreased to normal	Normal	Normal to decreased
Urine ketones	Increased	Normal	Normal	Increased
Plasma Glutamine	Increased	Normal	Increased	Decreased
Plasma Citrulline	Normal to decreased	Normal	Decreased	Increased

CA-VA: Carbonic anhydrase-VA; CPS: Carbomyl phosphate synthetase; NAG1: N-acetyl-glutamate-1

sepsis, and avoidance of certain drugs like acetazolamide, topiramate, zonisamide, valproate, glucocorticosteroids, mannitol and cautious use of 3% saline.[3,4] Long-term strategies include supplementation with zinc, carnitine, biotin, and coenzyme Q, trial of ammonia scavenging agents such as carglumic acid (250 mg/kg/day), sodium benzoate (250 mg/kg/day) and arginine (200 mg/kg/day) to lower serum ammonia levels.[5] The good prognosis is due to the overlapping function of CA-VB which can compensate for the deficiency of CA-VA and non-enzymatic production of some amounts of bicarbonate.[5] Till now 15 patients had been reported with CA-VA deficiency, of which 11 had normal development, 3 had learning disabilities and motor delay and 1 patient died due to complications.[2,4,6] In the absence of genetic testing, the disorder may remain underdiagnosed as transient hyperammonemia of newborn.[5]

Our case highlights that whenever a newborn presents with persistent hyperammonemia, hyperlactatemia, and encephalopathy, CA-VA deficiency must be considered Genetic testing confirms the diagnosis and helps in prenatal counseling.

Consent

Written informed consent obtained from parents.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Bhanudeep Singanamalla, Arushi Gahlot Saini, Savita Verma Attri[1], Renu Suthar, Kanya Mukhopadhyay[2]

Pediatric Neurology Unit, [1]Pediatric Biochemistry, [2]Neonatology Unit, Department of Pediatrics, Advanced Pediatrics Centre, Post Graduate Institute of Medical Education & Research (PGIMER), Chandigarh, India

Address for correspondence: Dr. Arushi Gahlot Saini, Assistant Professor, Pediatric Neurology Unit, Department of Pediatrics, Advanced Pediatric Centre, Post Graduate Institute of Medical Education and Research, Chandigarh - 160 012, India.
E-mail: doc.arushi@gmail.com

References

1. Agana M, Frueh J, Kamboj M, Patel DR, Kanungo S. Common metabolic disorder (inborn errors of metabolism) concerns in primary care practice. Ann Transl Med 2018;6:469.
2. Van Karnebeek CD, Sly WS, Ross CJ, Salvarinova R, Yaplito-Lee J, Santra S, *et al*. Mitochondrial carbonic anhydrase VA deficiency resulting from CA5A alterations presents with hyperammonemia in early childhood. Am J Hum Genet 2014;94:453-61.
3. Shah GN, Rubbelke TS, Hendin J, Nguyen H, Waheed A, Shoemaker JD, *et al*. Targeted mutagenesis of mitochondrial carbonic anhydrases VA and VB implicates both enzymes in ammonia detoxification and glucose metabolism. Proc Natl Acad Sci U S A 2013;110:7423-8.
4. Diez-Fernandez C, Rüfenacht V, Santra S, Lund AM, Santer R, Lindner M, *et al*. Defective hepatic bicarbonate production due to carbonic anhydrase VA deficiency leads to early-onset life-threatening metabolic crisis. Genet Med Off J Am Coll Med Genet 2016;18:991-1000.
5. Van Karnebeek C, Häberle J. Carbonic anhydrase VA deficiency. 2015 Apr 2. In: Adam MP, Ardinger HH, Pagon RA, *et al*., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020.
6. Baertling F, Wagner M, Brunet T, Sabir H, Wieczorek D, Meitinger T, *et al*. Fatal metabolic decompensation in carbonic anhydrase VA deficiency despite early treatment and control of hyperammonemia. Genet Med 2020;22:654-5.

Submitted: 06-Jun-2020 **Revised:** 24-Jun-2020 **Accepted:** 16-Jul-2020
Published: 18-Mar-2021

DOI: 10.4103/aian.AIAN_563_20