Majety M, Nagalla LC, Ravipati S, Venkataramana K.P.K.N, Suryanarayana. Atypical/Mysterious Presentation of Hypoammonemia in CAVA-Deficient Neonate: A Case Report. J Pediatrics & Pediatr Med. 2025; 5(4): 1-4

Journal of Pediatrics and Pediatric Medicine

Journal of Pediatrics and Pediatric Medicine

Case Report Open Access

Atypical/Mysterious Presentation of Hypoammonemia in CAVA-Deficient Neonate: A Case Report

Madhavi Majety[1], Laasya Chowdary Nagalla[2*], Shivani Ravipati[2], K.P.K.N. Venkataramana[3], Suryanarayana[3]

[1]Hospital for Children, Vijayawada, India.
[2*]Dr.Pinnamaneni Siddhartha Institute of Medical Sciences and Research Foundation, Vijayawada, India.
[3]Nori Multi-speciality Hospital, Vijayawada, India.

Article Info

Article Notes
Received: December 30, 2024
Accepted: January 25, 2025

***Correspondence:**
*Dr. Laasya Chowdary Nagalla, Dr. Pinnamaneni Siddhartha Institute of Medical Sciences and Research Foundation, Vijayawada, India. Email; laasyachowdary0714@gmail.com.

Keywords
Carbonic Anhydrase VA deficiency
Hypoammonemia
Neonate
Metabolic Acidosis
Shock
Exome Sequencing

Abstract

Background: This case report presents a rare manifestation of carbonic anhydrase (CAVA) deficiency in a neonate, challenging the typical metabolic profile associated with this condition.

Case presentation: A single female preterm born to 3rd-degree consanguineous parents exhibited severe metabolic acidosis, hypoxemia, and shock but notably lacked hyperammonemia, which is an apparently obligatory sign of CAVA deficiency. The baby's clinical course was complicated by respiratory distress, sepsis, neutropenia, and pulmonary haemorrhage, leading to a fatal outcome at 47 hours of life. Investigations including blood sugars, serum ammonia, and liver function tests provided atypical findings. The case has been managed symptomatically. Clinical exome sequencing revealed a homozygous missense mutation in the CA5A gene.

Conclusions: The case underscores the need for a deeper understanding of CAVA deficiency pathogenesis and suggests the possibility of variant presentations, even in severe cases. This report aims to broaden the clinical spectrum associated with CAVA deficiency and encourage further research into its varied presentations.

Background

Carbonic anhydrases are a group of zinc metalloenzymes that catalyse the reversible hydration of CO2 ($CO2+H2O \leftrightarrow HCO3+H+$). Around 14 isoenzymes of carbonic anhydrase are described in humans; they can be located in the cytoplasm, the mitochondria, some of which are secreted, and others that are membrane-bound[1,2]. Carbonic anhydrase VA (CAVA) is most highly expressed in the liver, skeletal muscle, and kidneys, while Carbonic anhydrase VB (CAVB) is readily detected in most tissues[3].

The CA5A gene mutation causes amino acid substitution from lysine to glutamic acid at codon 241, which leads to mitochondrial carbonic anhydrase VA (CAVA) deficiency[4,5]. It is a rare autosomal recessive inborn error of metabolism and can be presented with hyperammonemia, ketonuria, lactic acidosis, lethargy, and hypoglycemia, commonly in birth-to-school age groups, as observed to date. It usually responds to treatment. However, in some cases, it can cause neuromorbidity in later life, which might be due to hyperammonemia encephalopathy (feeding intolerance, lethargy, tachypnea, seizures, and coma)[6,7].

We present a case of congenital CAVA deficiency due to a mutation in exon 6 of the CA5A gene, manifesting as fatal neonatal elevated lactate, metabolic acidosis, ketonuria, and shock. The absence of

hyperammonemia is remarkable and raises intriguing questions about the possible mechanisms of pathogenesis. This is the first report of such a metabolic profile of CAVA deficiency.

Case presentation

A single female preterm was delivered at 32+2 weeks gestational age by a lower segment cesarean section, the indication being pregnancy-induced hypertension (PIH) with severe preeclampsia in a tertiary care paediatric and neonatal referral centre. She was an appropriate for gestational age (AGA) baby with a birth weight of 1.38 kg.

The infant was born to third-degree consanguineous parents. There was no history of neonatal deaths or neuromorbidities in the family. Obstetric history was notable for one miscarriage previously (Figure 1). The present pregnancy was an assisted conception by in-vitro fertilisation, indication being poor ovarian reserve (parents' gametes were used). Antenatal history was unremarkable except for PIH.

The baby cried immediately after birth but required free-flow oxygen to maintain targeted oxygen saturation. As soon as the baby developed respiratory distress and grunts, the Silverman Anderson Score (SAS) was calculated to be 4, and the baby was immediately shifted to the Neonatal Intensive Care Unit (NICU) with Continuous Positive Airway Pressure (CPAP) support for further management. On admission to the NICU, the baby was started on CPAP with 25% FiO2 and 5 cm of positive end-expiratory pressure (PEEP) and was started on full enteral orogastric feeds. X-rays of the chest were suggestive of mild respiratory distress syndrome (RDS) changes.

At 2 hours of life (HoL), the baby's Fio2 requirement was increased by more than 30%, and a loading dose of surfactant (100 mg/1 kg) was given by the Intubation Surfactant and Extubation (InSurE) technique.

At 12 HoL, as the sepsis screen was positive with a CRP value of 28 mg/L (normal value <6 mg/L), she was started on empirical IV antibiotics after sending blood for culture sensitivity. Given neutropenia of 1100 cells/cumm (normal >1500 cells/cumm), the baby was started on granulocyte colony-stimulating factor (GCSF) injections according to our unit protocol.

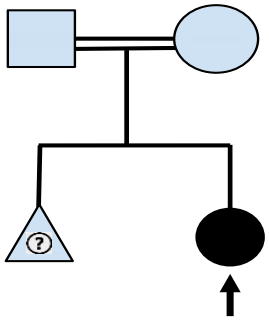

Figure 1: Pedigree flowchart of the affected child

At 16 HoL, the baby had desaturation while on CPAP support, was intubated, and was switched to the Synchronised Intermittent Positive Pressure Ventilation + Volume Guarantee (SIPPV+VG) mode of ventilation. This was later changed to High-Frequency Oscillation + Volume Guarantee (HFO+VG) mode because of persistent hypoxemia. Blood gas analysis showed severe mixed acidosis with high lactate levels initially. A repeat arterial blood gas (ABG) test showed severe persistent metabolic acidosis with high lactate levels (as high as 14 mmol/L), requiring repeated bicarbonate corrections.

At 23 HoL, the baby developed hypotension and required treatment with fluid boluses, multiple inotropes, and a stress dose of hydrocortisone.

At 40 HoL, the baby had pulmonary haemorrhage and desaturation and hence was retubed and started on high-frequency oscillation (HFO) with inhaled nitric oxide (INO) given persistent hypoxemia.

At 47 HoL, the baby had a repeat pulmonary bleed with desaturation and could not be revived.

The Baby's investigation reports are as follows:

Random blood sugars were monitored throughout the NICU stay, and the baby remained euglycemic. Serum ammonia was 19 ug/dl (normal 50–100 ug/dl). Prothrombin time: 19.8 sec, INR: 1.4, APTT: 39.4 sec.

Liver function tests were unremarkable except for a total protein value of 4.4 g/dl and serum albumin levels of 2.8 g/dl with an A:G ratio of 1.75. Serum ferritin levels were normal at 104 ug/ml (25–200 ug/ml).

The neurosonogram was normal. 2D echocardiography showed tricuspid regurgitation with severe pulmonary artery hypertension (PAH) and a large patent ductus arteriosus (PAD) (3 mm in size) with a bidirectional shunt.

The blood culture report came as sterile.

Tandem mass spectrometry (TMS): The carnitine-acylcarnitine profile revealed normal total carnitine, low free carnitine levels, normal acylcarnitine levels, and a relatively high acyl/free carnitine ratio (Low-free carnitine can be seen in any sick child.) Elevated levels of alanine were found. (Alanine is a surrogate marker for lactate and helps to rule out spurious elevations of lactate.)

Elevated levels of tyrosine, methionine, and phenylalanine were found, which may be suggestive of hepatic mitochondriopathy. Serum fibroblast growth factor (FGF 21) was found elevated to 653.71 pg/ml as against a normal range of 30-225 pg/ml (FGF 21 is elevated in mitochondrial diseases and was done to rule out the same).

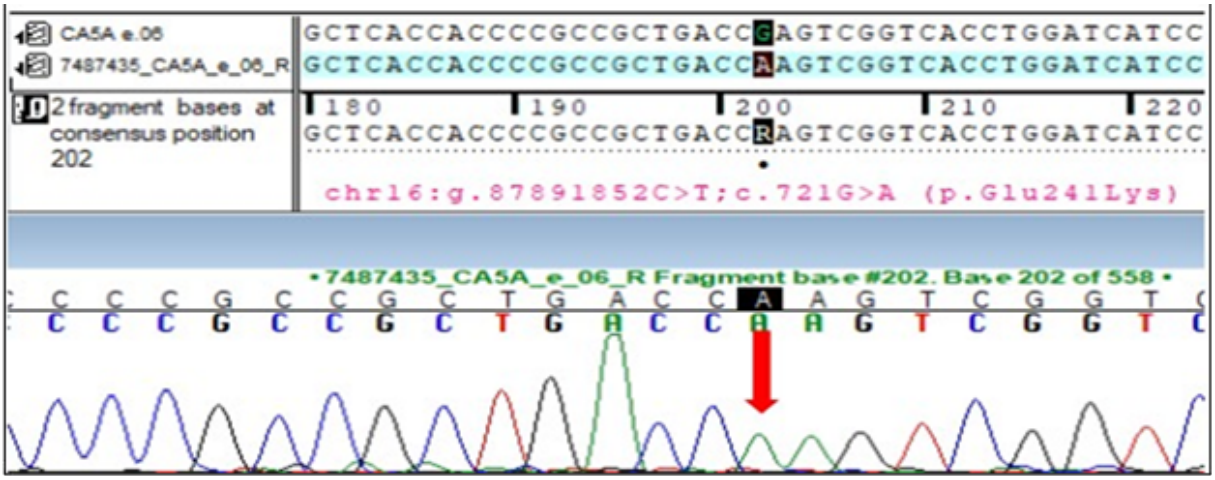

Figure 2: Sequence chromatogram and alignment to the reference sequence showing the variant in exon 6 of the CA5A gene (chr16: g.87891952C>T; c.721G>A; p. Glu241Lys) detected in a homozygous condition in the baby.

GC-MS of urine samples showed elevated levels of lactic acid, pyruvic acid, and ketones (2-hydroxy butyric acid, 3-hydroxy butyric acid, and 4-hydroxy phenylacetic acid), which can be due to liver disease.

According to whole exome sequencing (WES), a homozygous missense variation causing the amino acid lysine to replace glutamic acid at codon 241 was identified in exon 6 of the CA5A gene (Chr 16: g.87891852 C>T, Depth 100X). It is a nuclear gene mutation that is pathogenic, and the diagnosis appeared correct on reverse phenotyping. Sanger sequencing was employed to validate the variant, given that the CA5A gene is classified as a pseudogene in the human genome.

The results indicated that the variant was present in exon 6 of the CA5A gene in a homozygous state (chr 16: g.87891852 C>T:c.721G>A:p.Glu241Lys) (Figure 2). The parents were counselled to undergo genetic testing themselves. The same pathogenic variant was detected in heterozygous conditions in both the asymptomatic parents of the index patient, thus confirming the initial diagnosis.

Discussion

CAVA deficiency is an autosomal recessive genetic disorder affecting liver metabolism that results in defective hepatic bicarbonate production. CAVA supplies bicarbonate to four hepatic mitochondrial enzymes, namely carbamoyl phosphate synthetase (CPS1: the first step of the urea cycle), pyruvate carboxylase (PC: glucose metabolism), propionyl COA carboxylase (PCC), and 3-methylcrotonyl CoA carboxylase (3MCC: branched-chain amino acid metabolism)[4] (Figure 3).

There are 22 cases of CAVA deficiency reported worldwide. Of these, 17 children were of South Asian origin, 1 Turkish child, 2 of Belgian-Scottish descent, 1 was a Russian child, and 1 was of unreported origin. In 2014, van Karnebeek et al.[9] first identified the disease in

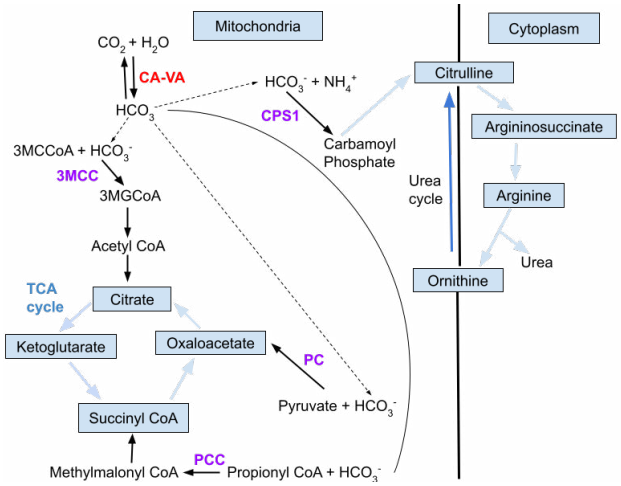

Figure 3: Biochemical pathways using bicarbonate produced by carbonic anhydrase VA.

Figure shows three metabolic enzymes: carbamoyl phosphate synthetase (CPS1), used in the first step of the urea cycle; pyruvate carboxylase (PC), an important enzyme in glucose metabolism; propionyl co-A (PCC), an enzyme that converts propionyl CoA to methylmalonyl CoA; and 3-methylcrotonyl CoA carboxylase (3MCC), an enzyme required for branched-chain amino acid metabolism. All these enzymes require bicarbonate, which is supplied by the carbonic anhydrase VA (CAVA).

Reproduced the image using Google Docs from ref[8].

four patients from three unrelated families. High levels of ammonia in newborns or infants, metabolic acidosis, low blood sugar, excretion of carboxylase substrates and related metabolites in the urine, and high levels of lactate and ketone bodies in the blood are all common symptoms of this disorder[3,4,8]. Other abnormalities include increased serum alanine and impaired bicarbonate. Aside from sporadic acute episodes during early childhood, the course of the disorder is generally benign[3].

A case study by N Mani Urmila et al. reported the initial

association of CAVA deficiency resulting from a novel gene variant with infantile spasms[10]. The child experienced refractory seizures on the third day of life and subsequently presented with infantile spasms and developmental delay at eight months of age. High-dose oral steroids and anti-seizure medications (including levetiracetam, sodium valproate, clobazam, and lacosamide) were optimized.

One possible approach to treating metabolic decompensation is to lower ammonia levels with agents like sodium benzoate and induce anabolism by administering glucose and lipids. Anecdotal evidence suggests an additional positive effect of N-carbamylglutamate (NCG) on hyperammonemia. Our patient, who was born prematurely, received initial treatment with surfactant. Subsequently, the patient's septic shock was managed through the administration of intravenous antibiotics, and positive pressure ventilation was utilised for ongoing respiratory support.

A homozygous mutation in the CA5A gene causes CAVA deficiency. The majority of instances of CAVA deficiency arise due to missense mutations or deletions, both of which can be readily identified through the use of exome sequencing. In our index case, clinical exome sequencing detected a pathogenic variant caused by a homozygous missense variation in exon 6 of the CA5A gene. The gene CA5A has an OMIM phenotype number of 615751, and the gene locus is 114761. The genetic location for the condition is 16q24.2.

The homozygous CA5A mutation c.721G>A (p. Glu241Lys) identified in our patient was initially reported in three patients, with two cases documented by Diez Fernandez et al. and one case by Olgac et al. The patients reported by Diez Fernandez et al.[4] exhibited elevated levels of ammonia and glutamine during the neonatal period. Furthermore, elevated lactate levels, severe ketonuria, lactic aciduria, and dicarboxylic aciduria were observed in the patients. Interestingly, neither of these patients had hypoglycemia, although a case by Olgac et al[6]. had a brief period of refractory hypoglycemia. Nevertheless, the individuals who possessed the CA5A genotype displayed notable resemblances in terms of biochemical markers and the progression of the disease. All three individuals exhibited normal developmental patterns in their later years.

Our case study with the same CA5A mutation is unique because it did not have any hyperammonemia or hypoglycemia. Instead, it had hypoammonemia, severe hypoxemia, and refractory shock, which ended in death. The exact cause of this is still not well understood. Whether the relative sparing of CPS1 and PC enzyme functions or the overlapping function of CAVB, the other isoenzyme, can explain the pathogenesis or not needs further exploration, and we are sure that our case report will prompt further research in this area.

Conclusion

This report shows the unique presentation of CAVA deficiency, which has to be considered in the differential diagnosis of early-onset, life-threatening metabolic acidosis, hyperlactatemia with or without hyperammonemia, and hypoglycemia. This case, while focusing on symptomatic treatment, necessitates an exploration of pathophysiology and symptomatology to formulate specific treatment plans. Furthermore, targeted preconceptional genetic testing can be a recommended approach for the early diagnosis.

Acknowledgement

We thank the patient and their parents for their participation and consent in the study. This research was conducted independently and did not receive any financial support from external sources.

Conflict of interest

We have no conflicts of interest to disclose.

References

1. Supuran CT. Structure and function of carbonic anhydrases. Biochemical Journal. 2016 Jul 15; 473(14): 2023-32.
2. Zamanova S, Shabana AM, Mondal UK, et al. Carbonic anhydrases as disease markers. Expert opinion on therapeutic patents. 2019 Jul 3; 29(7): 509-33.
3. Shah GN, Hewett-Emmett D, Grubb JH, et al. Mitochondrial carbonic anhydrase CA VB:differences in tissue distribution and pattern of evolution from those of CA VA suggest distinct physiological roles. Proceedings of the National Academy of Sciences. 2000 Feb 15; 97(4): 1677-82.
4. Diez-Fernandez C, Rüfenacht V, Santra S, et al. Defective hepatic bicarbonate production due to carbonic anhydrase VA deficiency leads to early-onset life-threatening metabolic crisis. Genetics in Medicine. 2016 Oct; 18(10): 991-1000.
5. Semenova N, Marakhonov A, Ampleeva M, et al. Hyperammonemia in Russia Due to Carbonic Anhydrase VA Deficiency Caused by Homozygous Mutation p. Lys185Lys (c. 555G> A) of the CA5A Gene. International Journal of Molecular Sciences. 2022 Nov 30; 23(23): 15026.
6. Olgac A, Kasapkara CS, Kilic M, et al. Carbonic anhydrase VA deficiency: a very rare case of hyperammonemic encephalopathy. Journal of Pediatric Endocrinology and Metabolism. 2020 Aug 18; 33(10): 1349-52.
7. Konanki R, Akella RR, Panigrahy N, et al. Mitochondrial carbonic anhydrase VA deficiency in three Indian infants manifesting early metabolic crisis. Brain and Development. 2020 Aug 1; 42(7): 534-8.
8. Marwaha A, Ibrahim J, Rice T, et al. Two cases of carbonic anhydrase VA deficiency—An ultrarare metabolic decompensation syndrome presenting with hyperammonemia, lactic acidosis, ketonuria, and good clinical outcome. JIMD Reports. 2021; 57: 9-14.
9. Van Karnebeek C. D, Sly W. S, Ross C. J, et al. Mitochondrial carbonic anhydrase VA deficiency resulting from CA5A alterations presents with hyperammonemia in early childhood. Am. J. Hum. Genet. 94: 453-461, 2014.
10. N Mani Urmila, D Kewalramani, U Balakrishnan, et al. A case of carbonic anhydrase type VA deficiency presenting as West syndrome in an infant with a novel mutation in the CA-VA gene. Epilepsy & Behavior Reports 20 (2022) 100573.