Case Report

Rare Yet Reversible: CA5A Deficiency Presenting as Neonatal Metabolic Crisis

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ABSTRACT

Carbonic anhydrase 5A (CA5A) deficiency (OMIM 615751) is a rare autosomal recessive metabolic disorder caused by mutations in the *CA5A* gene on chromosome 16q24.2. Deficiency of this mitochondrial enzyme disrupts bicarbonate production, impairing ureagenesis and energy metabolism, and typically presents in neonates with hyperammonemic encephalopathy, lactic acidosis, and hypoglycemia. We report a term neonate who developed severe hyperammonemia with encephalopathy on day 4 of life, requiring peritoneal dialysis, nitrogen scavengers, and ventilatory support. Tandem mass spectrometry and urinary GCMS were non-diagnostic, but singleton exome sequencing identified a homozygous *CA5A* variant, c.721G>A (p.Glu241Lys), classified as likely pathogenic. With early intervention, the infant recovered fully and remains metabolically stable with normal growth and neurodevelopment at 5 years of age. This case underscores the diagnostic challenge of *CA5A* deficiency, highlights the role of exome sequencing, and demonstrates the potential for excellent long-term outcomes with timely recognition and management.

Key words: Carbonic anhydrase 5A, hyperammonemia, peritoneal dialysis

Carbonic anhydrase 5A (CA5A) deficiency (OMIM 615751) is an exceptionally rare autosomal recessive disorder caused by pathogenic variants in the CA5A gene on chromosome 16q24.2.[1] The enzyme is critical for mitochondrial bicarbonate production, a substrate for carbamoyl phosphate synthetase 1 (CPS1), pyruvate carboxylase, propionyl-CoA carboxylase, and 3-methylcrotonyl-CoA carboxylase. Dysfunction results in impaired ureagenesis and energy metabolism, often manifesting in the neonatal period with hyperammonemic encephalopathy, lactic acidosis, and hypoglycemia.[2]

Unlike many other urea cycle disorders, most patients experience a single life-threatening metabolic crisis followed by long-term stability, likely due to compensatory activity of CA5B.[3] Recent reports emphasize the importance of rapid recognition and genetic confirmation for optimal outcomes. Given the rarity and diagnostic overlap with other metabolic crises, CA5A deficiency presents unique challenges in neonatal intensive care. We discuss the case of a term neonate who developed severe hyperammonemia with encephalopathy on day 4 of life diagnosed with this rare disorder.

CASE SUMMARY

A term female neonate, birthweight 3000 g, was delivered by cesarean section for fetal distress with meconium-stained liquor. She required 24 hours of NICU care for transient respiratory distress, resolving by 48 hours. At 72 hours, she became lethargic with poor feeding and hypoglycemia. On day 4, she deteriorated further with stupor, tachypnea, and absent reflexes. Laboratory evaluation revealed severe hyperammonemia (1369 µmol/L), metabolic acidosis, and elevated lactate. Tandem mass spectrometry and urinary GCMS were non-diagnostic.

Empirical treatment for urea cycle disorder was initiated: intravenous dextrose, nitrogen scavenger (sodium benzoate), L-arginine, and peritoneal dialysis (chosen over hemodialysis due to neonatal feasibility). Ammonia levels fell to 278 µmol/L, with clinical improvement. She was discharged on day 12 with nitrogen scavengers and special formula.

Genetic testing (singleton exome sequencing) identified a homozygous variant in exon 6 of the CA5A gene, c.721G>A (p.Glu241Lys), classified as likely pathogenic. Both parents were carriers. At 5 years of follow-up, the child remains metabolically stable with normal growth and neurodevelopment, managed on a low-protein diet with periodic monitoring.

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Table 1: Timeline of Key Events

Day of Life	Clinical Events / Interventions
0-1	Cesarean delivery, transient respiratory distress, NICU admission
3	Lethargy, hypoglycemia, poor feeding
4	Severe encephalopathy, hyperammonemia (1369 µmol/L), peritoneal dialysis, sodium benzoate, L-arginine
6	Extubated, ammonia improved to 278 µmol/L
12	Discharged on scavenger therapy and special formula
1 year	Exome sequencing confirmed CA5A deficiency (c.721G>A, p.Glu241Lys, homozygous)
5 years	Normal growth and development, metabolically stable

DISCUSSION

Human CA5A is a mitochondrial enzyme present in the liver, kidney and skeletal muscle.[4] CA5A supplies bicarbonate as a substrate of four mitochondrial enzymes: carbamoyl phosphate synthetase 1 (CPS1), 3-methylcrotonyl-CoA carboxylase (3MCC), propionyl-CoA carboxylase (PCC), and pyruvate carboxylase (PC).[3] CA5A deficiency disrupts mitochondrial bicarbonate supply, impairing ureagenesis and multiple metabolic pathways. Clinically, neonates present with hyperammonemia, metabolic acidosis, lactic acidosis, and hypoglycemia. Negative tandem mass spectrometry and GCMS can mislead clinicians, making exome sequencing essential for diagnosis. Our case illustrates this diagnostic challenge.

Management relies on rapid ammonia reduction. Carglumic acid has shown benefit in some reports, but in resource-limited settings, nitrogen scavengers such as sodium benzoate and peritoneal dialysis remain effective.[4, 5, 6] Hemodialysis is preferred when available, but peritoneal dialysis was lifesaving in our patient.[7] Supportive therapies including L-arginine and dietary modifications further aided recovery.[8]

In most patients reported so far, a single metabolic decompensation attack has been reported, and they have remained stable thereafter with no further crisis.[2] This is because CA 5B gene which is usually less contributing to ureagenesis shows compensatory action in CA5A deficiency.[4, 9] Long-term follow-up usually shows normal growth and neurodevelopment, as seen in our patient. However, fatal cases have been reported, underscoring the importance of vigilance during intercurrent illnesses.[9]

Comparison with literature shows that most cases present before day 5 of life with hyperammonemia, lactic acidosis, and hypoglycemia.[6] Our case reinforces these findings but also demonstrates complete long-term recovery with timely intervention. Reports by Marwaha et al. and Baertling et al. highlight similar clinical patterns, confirming that early recognition and intervention are crucial.[2, 10]

Genetic Confirmation

Exome sequencing revealed a homozygous missense variant c.721G>A (p.Glu241Lys) in exon 6 of the CA5A gene, classified as likely pathogenic. Both parents were carriers, confirming autosomal recessive inheritance and recurrence risk. The identification of this variant was pivotal in establishing the diagnosis, guiding genetic counseling, and informing future reproductive planning. Detailed laboratory methods were excluded here for conciseness. A similar variant was previously reported in a 3-day-old infant by Abdulwahhab SB et al.[11]

An ethnic association has also been recognized in CA-VA deficiency, with a higher frequency observed among individuals of South Asian descent, especially those of Indian origin. This pattern is thought to be related to a founder mutation in the CA5A gene. Such findings emphasize the importance of community-based genetic screening and targeted counselling in at-risk populations.[11]

CONCLUSION

This case highlights the rarity and diagnostic complexity of CA5A deficiency, a potentially reversible but life-threatening neonatal metabolic crisis. When standard metabolic screens are negative, CA5A deficiency should be considered in neonates with hyperammonemia and lactic acidosis. Exome sequencing plays a critical role in confirming the diagnosis. Early recognition and timely interventions including nitrogen scavengers and dialysis can ensure survival and excellent neurodevelopmental outcomes. Greater clinician awareness is needed to avoid missed diagnoses and to optimize care. Genetic counseling remains essential for affected families.

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