A case of carbonic anhydrase type VA deficiency presenting as West syndrome in an infant with a novel mutation in the CA-VA gene

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ABSTRACT
Carbonic anhydrase VA (CA-VA) deficiency is a rare autosomal-recessive inborn error of metabolism. It is imperative to consider CA-VA deficiency as a differential diagnosis in neonates with hyperammonemia not attributed to defects in urea cycle enzymes, organic acid disorders, hypoglycemia, and primary hyperlactatemia.

The case described in this report had a metabolic crisis on day three of life with biochemical abnormalities demonstrating hypoglycemia, elevated ammonia, and lactate. At eight months, he presented with developmental delay and infantile spasms. Considering the history of consanguinity and infantile spasms, clinical exome sequencing was done, which revealed a pathogenic novel mutation suggestive of CA-VA deficiency.

On review of the literature, we found that about 21 affected individuals have been reported to date. Unprovoked seizures or epilepsy have not yet been described in CA-VA deficiency. This report expands the phenotypic spectrum of neurological manifestations of CA-VA deficiency and adds to the existing number of cases in the reported literature.

Introduction
Carbonic anhydrase VA (CA5A) deficiency is a rare autosomal-recessive inborn error of metabolism (IEM). Carbonic anhydrase VA (CA5A) is an isofrom of enzyme carbonic anhydrase. The most common ethnicity reported so far belongs to South Asian origin. Though epilepsy is known to be associated with IEMs [1], it has not been described in CA5A deficiency. None of the previous cases were reported to be presenting with seizures or infantile spasms, unlike our case. To our best knowledge, CA5A presenting as West syndrome has not yet been reported. The disease course is rarely fatal and fulminant. We report a rare case with a novel gene variant of the CA5A presenting with infantile spasms.

Case summary
The index case is an 8-month-old boy born out of a second-degree consanguineous parentage with two developmentally normal elder siblings. The child’s previous history until his presentation to our hospital has been described as the following. The antenatal period was uneventful. He was born full-term via normal vaginal delivery. The baby cried at birth, was on-demand breastfeeding, and tolerated it well. On the third day of life, the baby developed an irritable cry and refusal to feed. He had hypoglycemia and he was loaded with dextrose-containing fluids. On examination, he had respiratory distress, and decreased tone in all four limbs. Head circumference at birth was not available. He was admitted to a neonatal intensive care unit suspecting aspiration pneumonia. The child had refractory seizures in the form of tonic and multi-focal clonic seizures. He was intubated and was put on pressure mode ventilation for ten days. He required multiple anti-seizure medications (Phenobarbitone, phenytoin, levetiracetam, clonazepam, lacosamide, midazolam infusion, pyridoxine, and pyridoxal phosphate). Continuous electroencephalogram (CEEG) was not done.

In view of poor perfusion, he was started on adrenaline and dobutamine inotropes, which were tapered and stopped. Lumbar puncture was done, and cerebrospinal fluid (CSF) analysis was normal, ruling out infective etiology. Serum ammonia (379 umol/L, normal range: 17.0–34.2) and serum arterial lactate (25.3 mg/dL,
normal range: 4.5 to 19.8) were elevated. Suspecting metabolic disorder, blood acylcarnitine profile with tandem mass spectrometry (TMS) and urine organic acid analysis with gas chromatography-mass spectrometry (GCMS) were done and the parameters were within normal limits. He was weaned off to oxygen via hood and eventually to room air. A definitive diagnosis was not reached. He was discharged on day 30 of life with anti-seizure medications (Levetiracetam, lacosamide, and clonazepam), which were tapered and stopped over the period of next six months as he remained seizure-free. Further details of follow-up or any electroencephalogram (EEG) findings in this period were not available.

At seven months, the child was taken to pediatrician for head lag and abnormal jerky movements. EEG done at that time was suggestive of bilateral generalized epileptiform activity and he was started on valproate and levetiracetam.

At eight months, the child presented to our unit with infantile spasms and developmental delay. Examination revealed microcephaly [38 CM, <-3 Z Score according to World Health Organization (WHO) growth chart], subtle dysmorphic features (depressed nasal bridge, low set ears), bilateral cortical thumb, and hypotonias of bilateral lower limbs. Magnetic resonance imaging of the brain showed mild cortical atrophy, otherwise, there was no signal abnormality noticed. The interictal scalp EEG was done and had modified hypsarrhythmia during sleep (Fig. 1A & B). High-dose oral steroids were started and anti-seizure medications (levetiracetam, sodium valproate, clozapam, and lacosamide) were optimized.

Strong clinical suspicion of metabolic etiology was considered, and clinical exome sequencing was done which revealed a novel homozygous nonsense variant in exon 1 of CA5A gene (chr16: g.87936392C > T) that results in a stop codon and premature truncation of the protein at codon 20 (p. Trp20Ter) suggestive of CA5A deficiency (c.59G > A; (p. Trp20Ter)). Infantile spasms did not respond to four week trial of oral corticosteroids. Subsequently, anti-seizure medications were titrated and topiramate was added. With the addition of topiramate and gradual dose escalation, his spasms resolved.

At nine months of age, serum ammonia and lactate were within normal limits. The child had developmental delay and no further episodes of the metabolic crisis were noted. A sick day regimen (Intravenous dextrose-containing fluids, protein-free diet, avoiding fasting, and immediate hospitalization in case of warning signs) was counselled to the parents. Supportive treatments with physiotherapy and developmental stimulation were initiated. Now the child is 14 months old, and spasms are under remission for six months. With these measures, he is slowly gaining developmental milestones. At present, the development status of the child is as follows, partial neck holding is present, cries for different needs, and recognizes his mother.

Discussion

Epilepsy is known to be associated with IEMs. IEM should be suspected especially if there is a positive family history, parental consanguinity, developmental delay, developmental regression, failure to thrive, dysmorphic features, neurological abnormalities, severe metabolic acidosis, and abnormal urine odor [1]. Around 3–22 % of IEM have been found in infants presenting with West syndrome [2].

In a Chinese cohort of 60 patients with West syndrome, 22 % had IEM [3]. In a retrospective Saudi Arabian study of 80 patients, 12.5 % were diagnosed with neurometabolic disorders. High association of West syndrome with IEM was among phenylketonuria, non-ketotic hyperglycinemia, Menkes disease, pyridoxine responsive or dependent seizures, methylmalonic aciduria, and mitochondrial disorders [4].

IEM disorders are associated with multiple types of seizures. Seizures may be the presenting symptom or triggered due to intercurrent illness and metabolic complications such as hypoglycemia. However, unprovoked seizures or epilepsy have not been described in CA5A deficiency. EEG findings are usually age-dependent, with burst suppression patterns in the neonatal period, and hypsarrhythmia in infancy evolving to generalized spike-wave patterns in childhood [1]. There is a paucity of reports of CA5A deficiency presenting as West Syndrome in the existing literature (Table.1).

CA5A deficiency is an extremely rare autosomal-recessive IEM. CA5A is a mitochondrial enzyme expressed in liver, kidney, and skeletal muscle. It is involved in essential metabolic pathways and deficiency leads to increased levels of enzymes carbamoyl phosphate synthetase-I, pyruvate carboxylase, propionyl-CoA carboxylase, and 3-methylcrotonyl-CoA carboxylase, thereby resulting in hyperammonemia, elevated lactate, and hypoglycemic episodes. The encoding gene CA5A (OMIM 114761) spans ~50 kb, contains 7 exons and 6 introns, and maps to 16q24.2 3 [5–7].

CA5A deficiency is characterized by acute onset of encephalopathy usually in the neonatal period to early infancy. The age spectrum is between day two of life and early childhood (up to 20 months). It usually presents as acute hyperammonemic encephalopathy including lethargy, poor feeding, seizures, respiratory distress, weight loss, hypoglycemia episodes, and coma. Biochemical abnormalities include metabolic acidosis, and respiratory alkalosis with elevated alanine, glutamine, and lactate. Blood TMS and urine GCMS detect elevations of carboxylase substrates [5–7].

An acute metabolic crisis should be treated as an emergency as the prognosis depends on the duration and severity of the hyperammonemia. Central nervous system insult can be prevented by early and appropriate management. They are usually managed as in other IEM disorders with intravenous glucose infusion, no protein, high lipid diet, and ammonia-reducing drugs such as sodium benzoate. Ammonia-lowering medications like carglumate are still under research, however, it has been used in the cases reported so far [5,6,8]. In case of high levels of ammonia (>500 ummol/L) extracorporeal detoxification can be considered [5].

N-carbamyl-γ-glutamate is a deacylase-resistant N-acetyl-d-glucosamine (NAG) analog, given enterally can enter liver mitochondria where it can replace NAG in activation of carbamoyl phosphate synthetase I (CPS1). It acts as a specific substitutive therapy for N-acetyl glutamate synthase (NAGS) deficiency, enhances CPS1 activity, and thus partially compensates for reduced HCO3– resulting from CA5A deficiency. In most reported individuals who were given carglumic acid during the acute phase, hyperammonemia and clinical symptoms resolved earlier (within 12 hours). Without carglumic acid, hyperammonemia persisted longer (i.e., an additional 1–2 days) [9].

We performed a literature review and collated the reported cases of CA5A deficiency published so far and their details have been summarized in (Table. 1). There are only 21 cases of CA5A deficiency reported worldwide. Of these, 16 (76 %) cases were of South Asian origin. None of the previous cases were reported to be presenting with seizures or infantile spasms, unlike our case. In those 21 cases, 2(9 %) children died during the crisis, 17 (89 %) children were developmentally normal and 3 (16 %) of them had developmental delays. Only 6 (31 %) of them had multiple episodes of metabolic crisis and others (13 [68 %]) were limited to single metabolic decompensation. The disease course was fulminant and fatal in two of those cases reported despite rapid initiation of treatment [10].
Our index case did not have any additional episodes of metabolic crisis, despite which he has a significant developmental delay. He also has a background of South Asian origin like majority of the cases reported (Table 1). In our case, subtle dysmorphic features were seen, which have not been described in previous cases. We speculate that these dysmorphic features are non-specific. The possibility of development of west syndrome in the index case could be because of the sequelae of the early metabolic crisis, although MRI did not show evidence of it. It could have been avoided if the case had been diagnosed and early therapy initiated. There was no response to steroids in our patient. We believe that the optimization of anti-seizure medications and the addition of topiramate led to resolution of the spasms.

Prompt initiation of supportive treatment during the metabolic crisis has led to a good neurodevelopmental outcome, consistent with previously reported cases (Table 1). It is essential to consider CASA deficiency as a differential diagnosis in neonatal hyperammonemia not attributable to urea cycle disorders. So far, the prognosis of the disease has been reported to be good. Most of the available newborn screening profiles do not pick up this deficiency possibly due to low biochemical profiles [5]. Routine investigations for IEM including blood TMS and urine GCMS could be inconclusive. The diagnosis can be confirmed by molecular gene testing only.

Conclusion

In this case report, we have described the first association of CASA deficiency due to a novel gene variant with infantile spasms. Children who had initial metabolic insult as in our case should be actively followed up for seizures or infantile spasms. This report expands the phenotypic spectrum of neurological manifestations of CASA deficiency and adds to the existing number of cases in the reported literature. It should be considered as one of the differential diagnosis of children presenting with infantile spasms and
| S.No | Mutation CA5A | Ethnic background | Onset | Response to carbamyl glutamate | Extracorporeal detoxification | Additional crisis | Neurological outcome (long-term) | Reference |
|------|---------------|------------------|-------|--------------------------------|-----------------------------|-------------------|--------------------------------|-----------|
| 1    | Exon 1 c.123G > A | Turkish Consanguineous | 4 Days | Yes | None | None | Normal at age 12 months | Carmen Diez-Fernandez et al. [5] |
| 2    | Exon 3 c.458_459 + 22del24bp | Indian Consanguineous (Not first cousins) | 5 Months | Not used | None | 2 Years | Normal at age 10 years | Carmen Diez-Fernandez et al. [5] |
| 3    | Exon 4 c.555G > A | Russian Non-consanguineous | 4 Days | Yes | None | Not reported | Normal at age 6 months | Van Karnebeek et al. [6] |
| 4    | Intron 4 C.555 + 4_555 + 183del180bp | Pakistani Consanguineous (First cousins) | 4 Years | Not used | None | 4 Years 1 month | Normal at age 10 years | Carmen Diez-Fernandez et al. [5] |
| 5    | Exon 6 c.697 T > C | Belgian-Scottish Non-consanguineous | First Day | Yes (Single dose in crisis) | None | 2.5 and 3.5 years | Normal development and behavior at age 4.5 years, below-average motor coordination | Van Karnebeek et al. [6] |
| 6    | Exon 6 c.697 T > C | Belgian-Scottish Non-consanguineous | First Day | Yes | None | Not reported | Bayley Scales of infant and toddler development below average | Van Karnebeek et al. [6] |
| 7    | Exon 6 c.721G > A | Bangladesh Consanguineous | 5 Days | Yes | None | None | Normal | Carmen Diez-Fernandez et al. [5] |
| 8    | Exon 6 c.721G > A | Pakistani Consanguineous | 4 Days | Yes | Hemodialysis | None | Normal at age 3 years | Carmen Diez-Fernandez et al. [5] |
| 9    | Exon 6c.619-3420_c.774 + 502del4078bp | Pakistani Consanguineous (First cousins) | 13 Months | Not used | None | 16 Months | Normal at 11 years | Van Karnebeek et al. [6] |
| 10   | Exon 6c.619-3420_c.774 + 502del4078bp | Pakistani Consanguineous (First cousins) | 2 Days | Not used | Hemodialysis (6 h) | 23 Months | Normal at age 6 years | Van Karnebeek et al. [6] |
| 11   | Exon 6c.619-3420_c.774 + 502del4078bp | Indian Consanguineous (Not first cousins) | 20 Months | Not used | None | None | Normal at age 4 years | Van Karnebeek et al. [6] |
| 12   | Exon 6c.619-3420_c.774 + 502del4078bp | Pakistani Consanguineous (Not first cousins) | 3 Days | Not used | Not reported | None | Normal at age 4 years | Van Karnebeek et al. [6] |
| 13   | Exon 6c.619-3420_c.774 + 502del4078bp | Pakistani Consanguineous (First cousins) | 3 Days | Not used | Hemofiltration | None | Learning difficulties and speech delay at 5 years | Van Karnebeek et al. [6] |
| S.No | Mutation CASA | Ethnic background | Onset | Response to carbamyl glutamate | Extracorporeal detoxification | Additional crisis | Neurological outcome (long-term) | Reference |
|------|---------------|------------------|-------|-------------------------------|-------------------------------|------------------|----------------------------------|-----------|
| 14   | Exon 6 c.619-3420.c.774 + 502del4708bp | Pakistani Non-consanguineous | 2 Days | Yes | Hemodialysis | None | Normal at age 9 months | Van Karnebeek et al. [6] |
| 15   | exon 6c.721G > A (p. E241K) | Indian Non-consanguineous | 3 Days | Not used | None | None | Normal at age 18 months | Ramesh Konanki et al. [7] |
| 16   | Exon 7 compound heterozygous for c.788G > A and c.868C > T | Indian Non-consanguineous | 8 Months | Not used | None | 22 months | 22 months, died during the crisis | Ramesh Konanki et al. [7] |
| 17   | c.-56_143-1.143 + 1 del in exon 1 of the CASA gene | Indian Non-consanguineous | 2 Days | Not used | Peritoneal dialysis | None | Normal at age 4 months | Ramesh Konanki et al. [7] |
| 18   | homozygous, c.721G > A (p. Glu241Lys) | Second degree consanguineous | 2 Days | Yes, along with Sodium benzoate | None | None | Normal at age 1.5 years | Asburce Olgaç, et al. [8] |
| 19   | first two exons of the CASA gene | Indian Non-consanguineous | 18 Months | Yes, along with sodium benzoate, sodium phenylacetate, L-arginine | None | Died during the crisis | Died during the crisis | Fabian Baertling, et al. [10] |
| 20   | heterozygous variants: c.721G > A, p.(Glu241Lys), and c.619-7.774 +del | Indian Non-consanguineous | First Day | Yes, along with sodium benzoate, L-arginine | Hemodialysis | None | Normal at age 19 months | Marwaha A, et al. [11] |
| 21   | homozygous variant c.721G > A, p.(Glu241Lys) | Sri Lankan Second degree consanguineous | 3 Days | Yes, along with sodium benzoate, sodium phenylacetate, L-carnitine, L-arginine | None | None | Normal at age 9 years | Marwaha A, et al. [11] |

Table adapted with permission from 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. 2016;18(10):991–1000.
hyperammonemia. There is a need to do multicentric studies to further characterize the clinical presentation and natural history of CA5A deficiency.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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