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SUCCINIC SEMIALDEHYDE DEHYDROGENASE DEFICIENCY – A RARE CAUSE OF METABOLIC STROKE

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ABSTRACT
Succinic semialdehyde dehydrogenase (SSADH) deficiency is a rare neurometabolic disorder characterized by defective degradation of gamma-aminobutyric acid (GABA), a major inhibitory neurotransmitter of the brain. Children with SSADH deficiency present with motor and mental delay, intractable seizures, infantile onset hypotonia, speech disturbances, extrapyramidal symptoms and ataxia. This wide spectrum results from increased accumulation of 4hydroxy butyric acid (4HBA) leading to down regulation of GABA receptors, which likely explain epileptogenesis but the pathophysiology of stroke in SSADH deficiency is not much elucidated. Here, we report an infant aged 11 months, product of consanguineous marriage with significant family history of motor delay and intellectual disability, who presented with sudden onset focal neurological deficit preceded by diarrheal illness. Examination revealed an infant with age-appropriate milestones having left uncrossed hemiplegia along with neuroradiological evidence of right globus pallidus ischemic infarct. Urinary organic acid profile by chromatography was suggestive of 4-hydroxybutyricaciduria.

Key Words: Succinic semialdehyde dehydrogenase(SSADH), stroke, urinary organic acids, 4-Hydroxybutyricaciduria.

INTRODUCTION
Succinic semialdehyde dehydrogenase (SSADH) deficiency, a rare neurometabolic disorder, has autosomal recessive pattern of inheritance. This biochemical disorder affects metabolism of inhibitory neurotransmitter gamma-aminobutyric acid (GABA), leading to abnormal accumulation of succinic semialdehyde (Figure 1). Clinical manifestations of SSADH deficiency range from infantile hypotonia, developmental delay, cognitive impairment, speech issues, intractable seizures, choreoathetosis and ataxia. This variable presentation results from accumulation of 4-hydroxybutyric acid (4-HBA) which is the end product of succinic semialdehyde (SSA).[1] Elevation of 4-HBA owing to its neurotoxic effects likely explain the pathophysiology of seizures; a hallmark of SSADH deficiency.[2] Mitochondrial dysfunction occurs due to decrease in activities of respiratory chain complexes I-IV by defective coupling of GABA in Kreb's cycle resulting in increased incidence of oxidative stress.[3]

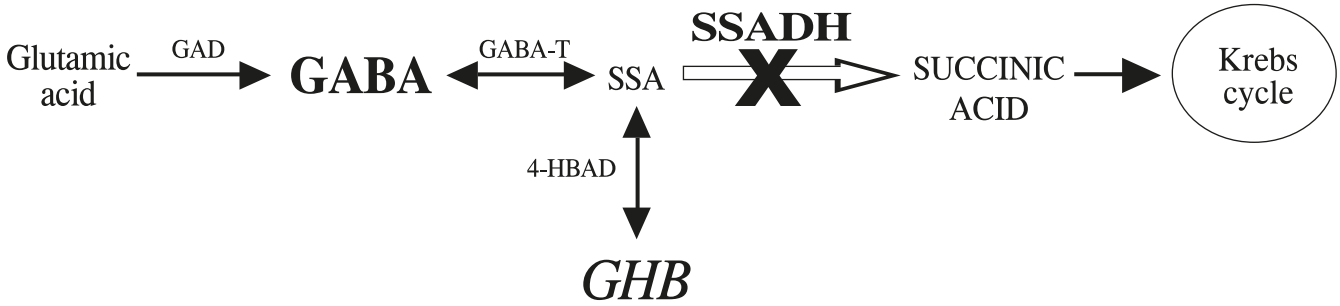

Figure 1: Metabolic Pathways of gamma amino butyric acid (GABA)
Abbreviations: GABA (gamma amino butyric acid), GAD (glutamic dehydrogenase), GABA-T (GABA transaminase), GHB (gamma hydroxybutyrate), SSA (succinic semialdehyde)

SSADH deficiency shows both intrafamilial and interfamilial phenotypic heterogeneity;commonest presentation being seizures and developmental delay. To the best of our knowledge there is a single case of SSADH deficiency reported with stroke without any clinical or sub-clinical seizures.[4] Diagnosis of SSADH deficiency is established by an abnormal urine organic acid pattern, including increased excretion of 4-hydroxybutyric acid and confirmation by identification of biallelic pathogenic variants in aldehyde dehydrogenase 5 family, member A1 (ALDH5A1) gene.[5]

CASE PRESENTATION

An 11 months old boy, 5th issue of consanguineous parents with significant family history of two mid-trimester miscarriages, motor and cognitive delay in two siblings, one having recurrent seizures; born at term to healthy mother with no apparent antenatal and neonatal risk factors. He had first presentation to The Children's Hospital and Institute of Child Health, Lahore at age of 11 months with acute paucity of movement on left half of body, following recovery from a diarrheal illness.There were no associated seizures, persistent vomiting, unconsciousness, feeding difficulty, voice change or facial deviation. Past history was suggestive of two admissions at age of 20 days and six months with respiratory illness. His motor milestones were age appropriate with acquisition of neck holding at 3 months, independent sitting at 8.5 months, started cooing but no reciprocal babbling.

On examination, he had acidotic breathing, left sided uncrossed hemiplegia and dystonic posture of left hand. Power of left side was 2/5 in upper limb and 3/5 in lower limb with 3+ deep tendon reflexes and bilaterally upgoing plantar response. Cranial nerves were intact and no visceromegaly was found. There was no independent sitting during the illness. His workup showed normoglycemia, no ketosis, raised anion gap (24) acidosis with pH:6.94 and HCO3: 9, normal values of plasma lactate (10.5 mg/dl) , ammonia (80 micromol/L) and normal EEG. CT brain plain showed hypodense right globus pallidus, MRI head revealed T2W hyperintensity in right globus pallidus and right crus of mid-brain with restricted diffusion on DW/ADC map (Figure 2).

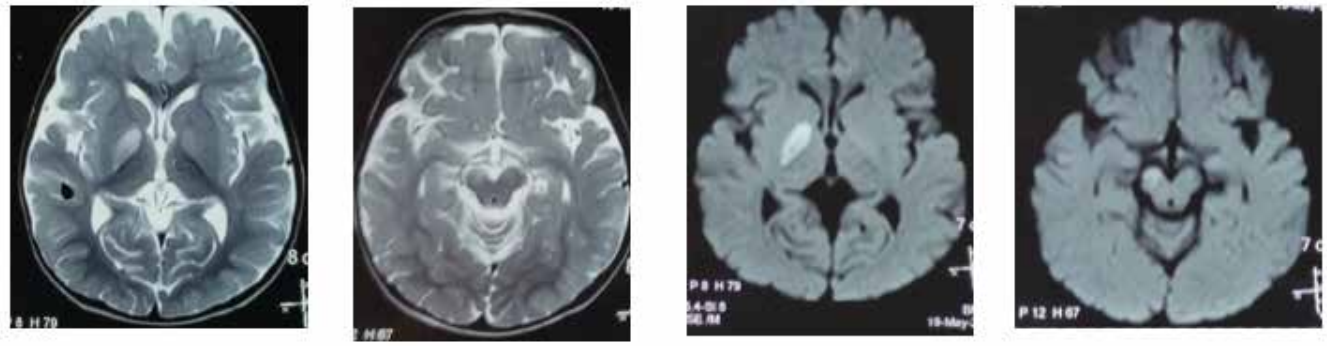

Figure 2: T2W & DWI Hyperintense Signals in Globus Pallidus and crus of Mid-Brain

Considering significant family history of two siblings of motor and mental delay & two miscarriages, past history of breathing difficulty, onset of acute stroke preceded by diarrheal illness, raised anion gap acidosis, globus pallidus and midbrain infarct, we extended the workup to find the likely possibility of underlying metabolic disorder. Plasma amino acid quantification showed raised glutamate, glycine, alanine and proline. Urinary organic acid by gas chromatography mass spectrometry (GCMS) showed marked excretion of 4-hydroxybutyric acid along with small peak of 2, 4- hydroxybutyric acid & 4, 5-dihydroxyhexanoic lactone suggestive of 4-hydroxybutyric aciduria (4-HBA). His whole exome sequencing revealed homozygous class 1 (pathogenic variant) in ALDH5A1 gene consistent with diagnosis of succinic acid semialdehyde dehydrogenase (SSADH) deficiency (OMIM ID#271980), as shown in Table 1. His parents were heterozygous for the same variant. Afterwards patient had two more admissions with raised anion gap metabolic acidosis triggered by febrile illness managed conservatively. At present patient is 23 months old, regained independent sitting and standing with support and started calling parents with improvement in power to 4/5.

Table 1: Results of Genetic Testing

GENE	VARIANT COORDINATES	ZYGOSITY	TYPE & CLASSIFICATION
ALDH5A1	NM_170740.1:c.909+1G>T	Homozygous	Splicing Pathogenic (Class 1)

DISCUSSION

Pediatric stroke warrants a detailed diagnostic work up including arteriopathies, cardiac, hematological and metabolic etiologies. Consanguinity, significant family history of motor and cognitive impairment, unexplained sudden death, multisystem involvement and fluctuating course of illness give a clue to underlying neurometabolic problem.[6] Metabolic stroke has been commonly reported in patients with homocystinuria, methylmalonic aciduria, glutaric aciduria, isovaleric aciduria, propionic aciduria, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), and Fabry disease.[7]

The end product of SSADH deficiency, 4-hydroxybutyric acid, is neurotoxic and causes escalation of various parameters of oxidative stress.[8] Acute infective illness as seen in our case might have worsened the underlying oxidative stress, followed by recovery with the cessation of the catabolic process. Common clinical presentation of SSADH deficiency is clinical and electrographic seizures owing to down-regulation of GABA receptors by 4-HBA. However, our patient never had clinical or electrographic seizures. Other manifestations of this defect are motor delay, movement disorders, ocular abnormalities and behavioral issues.[9] Patients with seizures benefit from vigabatrin and magnesium valproate by causing irreversible inhibition of GABA transaminase, and variable clinical responses have been reported in patients with SSADH deficiency while on treatment with vigabatrin.[10, 11]

CONCLUSION

Metabolic strokes once considered to be unusual are not uncommon entity now. Acute onset encephalopathy, involuntary movements, focal seizures on a background of motor mental delay, similar family history and multisystem involvement are a sufficient clue to think about underlying metabolic defect. Acute management should focus on elimination of catabolic stress inducing factor, meticulous neuroprotective care, correction of acidosis, electrolyte imbalance and hypoglycemia. Diagnostic clues can be obtained from aforementioned metabolic derangements, plasma ammonia, lactate, involvement of highly metabolic active sites in brain imaging, plasma amino acid and urinary organic acid profile.[12] Genetic diagnosis is gold standard in diagnosis as well as for genetic counseling.

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Areeba Wasim; data collection, data analysis, manuscript writing, manuscript review
Javeria Raza Alvi; data collection, manuscript writing, manuscript review
Tipu Sultan; data analysis, manuscript review