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Short Communication

A rare cause for seizures in an adult male – First report of a rare mutation in HMBS gene (c.730_731del) from India

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Acute intermittent porphyria is an autosomal dominant disorder with incomplete penetrance caused by deficiency of Porphobilinogen deaminase (PBGD) (a.k.a hydroxymethylbilane synthase (HMBS) and is more common in females.[1] The triad of seizures, abdominal pain and hyponatremia in a young woman is highly suggestive of acute porphyria.[2]The HMBS gene which comprises 15 exons, spans approximately 10 kilobase on 11q23.3. It encodes 361 amino acids. More than 500 HMBS gene variants have been reported. Here we report a rare mutation in HMBS gene (c.730_731del) in a male from Kerala. This variant is so far not reported from India.

A 27-year-old boy presented to emergency department with one episode of generalised tonic clonic seizure followed by post ictal confusion. There was no history of fever or headache. He has a history of generalised, almost continuous abdominal pain for the past 3 days. There were few episodes of vomiting. On examination he was afebrile, conscious, alert, oriented and there were no focal neurological deficits or meningeal signs. His blood pressure varied between 120/80 mm of Hg and 160/90 mm of Hg and heart rate varied between 74/minute to 124/minute. His motor and sensory systems were normal with normal reflexes. Abdomen was soft with normal bowel sounds. Ultrasound abdomen and CT abdomen were normal. He had a history of Covid 19 infection 2 years back while in Dubai and was on ventilator for few days. At that time, he had hyponatremia and one episode of seizure. Significant past history includes recurrent abdominal pain and was evaluated at multiple hospitals without any specific diagnosis. His previous upper gastrointestinal endoscopy was normal. His episodes of abdominal pain were often precipitated by alcohol intake. Prior to the present episode he had an alcoholic binge. There was no illicit drug use prior to present episode. There was no family history of similar illness or epilepsy.

His CT head and EEG were normal. His routine investigations showed severe hyponatremia (116.6mEq/L), markedly elevated creatine phosphokinase (60000U/L) and transient hyperthyroidism. In view of abdominal pain, seizure, hyponatremia urine was sent for Porphobilinogen assay and was repeatedly positive. He was treated with intravenous levetiracetam, 25% dextrose and 3% saline. He was advised 24-hour urine porphobilinogen and amino levulinic acid (ALA) assay. Due to financial restraints, we could only do 24-hour urine ALA and was elevated. We did not give haem infusion or Givosiran due to unavailability in India.

Abdominal pain, neurological dysfunction, and psychiatric disturbances form the classic triad of acute hepatic porphyria. Severe, diffuse abdominal pain is the most common symptom, although severe pain can occur in

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Table 1:

Investigations	Results	Normal Values
Sodium	116.4mEq/L	136-145 mEq/L
Potassium	3.6mEq/L	3.5-5.5 mEq/L
S. Osmolality	258mOsm/Kg	275-295mOsm/Kg
Creatinine	1.44 mg%	0.8-1.2 mg%
Uric acid	15.48mg%	3.5-7.2mg%
Amylase	93U/L	22-80U/L
SGPT	149U/L	<50 U/L

lumbar region or lower limbs. Other signs and symptoms are nausea, vomiting, weakness, tachycardia, hyponatremia, constipation, neuropathy, mental status changes, systemic arterial hypertension, and change in urine colour.[3]

Proposed mechanism to explain the symptomatology of an acute attack are 1) depletion of heme in the cells of the central nervous system 2) neurotoxicity of accumulated intermediates, especially aminolevulinic acid and 3) neurotransmitter disturbance secondary to the deficiency of heme and tryptophan pyrrolase (a heme dependent enzyme) in the liver. There are structural similarities between ALA and gamma-amino butyric acid (GABA), resulting in ALA interfering and interacting with GABA receptors. This may be responsible for occurrence of seizures during acute porphyric attacks. 5-Hydroxytryptophan and serotonin in the nervous system are produced in excess secondary to heme deficiency. It might contribute to some of psychiatric symptoms as well as peripheral neuropathy.

Next generation sequencing showed heterozygous mutation in exon 11 of HMBS gene c.730_731del (pLeu244AlafsTer6). It's a 2 base pair deletion in exon 11 of HMBS gene in Chromosome 11 that results in a frameshift and premature truncation of the protein, 6 amino acids downstream to codon 244. To date, 504 mutations have been identified, of which 203 are point mutations, 107 are deletions mutations, 102 are splicing mutations, 48 are insertion mutations, and 44 are other types of mutations.[4] Patients with frame shift variants have moderate phenotype. This variant has not been reported previously from India. A study from China revealed that c.673C> T was the most common mutation and that the c.517C> T mutation was the next most common mutation.[5] Small deletions at c.730_731 is also reported from UK, Italy and Japan.[6,7]

Prompt diagnosis in cases presenting as seizures is important as anti-seizure medications like phenytoin and phenobarbitone can induce ALA synthase and can precipitate quadriparesis and respiratory weakness. Seizures are reported to occur in 3%–20% of patients of AIP. Anti-epileptic medications documented to be safe during porphyric attacks are benzodiazepines, gabapentin, and levetiracetam. For uncontrolled status epilepticus, propofol infusion has been reported to be safe.

Our patient presented with generalised tonic-clonic seizures and abdominal pain. Evaluation showed severe hyponatremia and rhabdomyolysis. A triad of seizures, abdominal pain and hyponatremia should raise suspicion of porphyria and should be confirmed by biochemical testing. Confirmation by genetic testing may help to prognosticate the illness. A study of large group of patients with c.730_731 deletion may help to elucidate this unique combination abdominal pain, seizures, hyponatremia, rhabdomyolysis, transient hyperthyroidism and mild elevation of serum pancreatic enzymes.

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Conflict of Interest

None.

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