Case Report

Recurrent Seizures in an Adolescent Female-A Daunting Puzzle

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Abstract

Acute porphyrias are metabolic disorders resulting from deficiency of a specific enzyme involved in heme biosynthetic pathway. These deficiencies also affect normal renal physiology, as kidneys are also involved in heme synthesis. Sometimes, this could even lead to end stage renal disease. Acute Intermittent Porphyria, an autosomal dominant disorder arising from half-normal activity of hydroxymethylbilane synthase, is characterized by occurrence of vague neurovisceral attacks (abdominal pain, nausea, vomiting, constipation and neuropsychiatric symptoms), with urinary excretion of porphyrin precursors, such as 5-Amino-levulinic acid (ALA) and Porphobilinogen (PBG). Acute attacks are triggered by dehydration, diarrhea, steroids, low calorie diets. Treatment includes avoidance of precipitating factors, adequate hydration, high carbohydrate diet and heme replacement. Here, we present an adolescent female who had presented with recurrent abdominal pain, dyselectrolyemia with associated seizures, was diagnosed with Acute Intermittent Porphyria and recovered well with symptomatic management.

Keywords: *Acute intermittent Porphyria, hyponatremia, hydroxymethylbilane synthase*

Introduction

Acute intermittent porphyria (AIP) is presented with vague abdominal and neuropsychiatric manifestations. Although these symptoms can be easily recognized in retrospect, the diagnosis continues to be a great challenge, requiring a strong index of suspicion.[1] We describe a patient who presented with recurrent abdominal pain and seizures, in association with hyponatremia and hypokalemia, eventually diagnosed to have AIP secondary to hydroxymethylbilane synthase deficiency.

Case Description

A 15-year-old female presented to our emergency department with four episodes of generalized tonic-clonic seizures over the past 24 h. On examination, she was pale and drowsy, but devoid of any focal motor deficit. Her blood pressure was 130/80 mm Hg, pulse rate was 108/min, temperature was 36.8 degree Celsius, and random blood sugar level was 112 mg/dL. Two months prior to presenting to us, she started experiencing recurrent episodes of vague abdominal pain, which would last for several minutes to hours and resolve spontaneously. Two weeks earlier, she had a similar episode associated with acute urinary retention, for which she was treated with injection furosemide, injection amikacin, injection pantoprazole, and laxative elsewhere.

Evaluation in our hospital revealed anemia with hemoglobin of 9.2 g%, total white blood count of 10,300 cells/cu.mm, differential count showing 85% polymorphs, 13% lymphocytes, 2% eosinophils, and platelet count of 3.12 lakh cells/cu.mm. Peripheral smear study revealed normochromic normocytic anemia. Urinalysis was unremarkable. Her blood urea was 17 mg/dL and serum creatinine-1.1 mg/dL. Serum electrolytes showed presence of hyponatremia (Sodium = 103 mEq/dL) and hypokalemia (Potassium = 3.0 mEq/dL). Her magnesium was 3.9 mg/dL and phosphorus was 4.1 mg/dL. Initial computed tomography imaging of the brain was unremarkable.

She was euvolemic, and in view of acute severe symptomatic hyponatremia and hypokalemia, she was treated with intravenous 3% saline and potassium infusion. She was also initiated on intravenous phenytoin at a loading dose of 15 mg/kg followed by maintenance dose of 100 mg thrice a day for seizures. After 3 days of treatment, she recovered without

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any neurological deficit and her sodium and potassium levels gradually became normal.

Two days later, she developed status epilepticus again. Her electrolytes revealed sodium of 111 mEq/dL and potassium of 2.3 mEq/dL. She was again initiated on intravenous 3% saline and potassium supplements. She recovered without any neurological deficit. Her repeat urinalysis was normal.

Magnetic resonance imaging of the brain showed T2 fluid attenuated inversion recovery (FLAIR) hyperintensity in the right frontal lobe and subcortical U-fibers, in which case, the differentials thought of were posterior reversible encephalopathy, extra pontine myelinolysis, and post-ictal changes. However, in the absence of an acute rise in blood pressure and renal failure, posterior reversible encephalopathy was unlikely.

She was clinically euvolemic. Hyponatremia evaluation revealed serum sodium of 111 mEq/dL, serum osmolality of 244 mOsm/kg, urine osmolality of 440 mOsm/kg, urine sodium of 88 mEq/dL, serum uric acid of 2.8 mg/dL, serum creatinine of 0.9 mg/dL, serum cortisol of 15 mg/dL, and thyroid-stimulating hormone of 3.5 mIU/L. She was not on any diuretics. Hence, a diagnosis of syndrome of inappropriate anti-diuretic hormone (ADH) secretion was entertained. On evaluation, there was no evidence of any infection, organic neurological disorders, or malignancy. She was not on any antipsychotic therapy.

During the hospital stay, she continued to have muscle cramps with severe spasmodic episodes of abdominal pain, which now subsided on treatment with opioids. Ultrasonogram of the abdomen revealed sludge in the gall bladder, normal-sized kidneys, normal pelvicalyceal system, and a normal urinary bladder. Computed tomography of the abdomen revealed multiple tiny gall stones. Serum Amylase (275.9 U/L) and lipase (486.4 U/L) were elevated. During this episode of acute abdomen, her urine was noticed to have a reddish hue, which did not further change color on standing. Repeat urinalysis did not show any active sediments.

For the management of symptomatic gallstones, laparoscopic cholecystectomy was contemplated. Meanwhile, she again presented with acute abdominal pain and was treated with opioids. During this episode, her urine was noticed to be of port-wine color, which aroused a strong suspicion of porphyria. Hence we proceeded with the screening test for porphyria, i.e, the Watson Schwartz method which turned out to be positive [Figures 1 and 2] Also examination under ultraviolet lamp showed pink fluorescence at 410 nm. A 24-h urinary assay for porphobilinogen (PBG) and aminolevulinic acid (ALA) was done and they turned out to be normal, probably because it was done after the acute episode had subsided. However, with a strong suspicion of porphyria, analysis of the hydroxymethybilane synthase (*HMBS)* gene

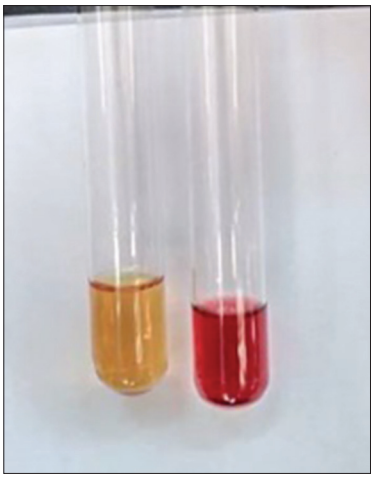

Figure 1: On addition of 1 ml of Ehrlich reagent (4-dimethylaminobenzaldehyde) to 1 ml of urine produces port wine color in patient's urine containing PBG

encoding HMBS was done using targeted next-generation sequencing. It revealed a heterozygous missense variant in exon 13 of the *HMBS* gene on chromosome 11 that resulted in the amino acid substitution of arginine for glycine at codon 280 (chr11:g. 118963657G>A; Depth of coverage: 60×) (p.Gly280Arg; ENST00000278715.3). The observed variant lies in the porphobilinogen deaminase and C-terminal domain of the HMBS protein and has previously been reported in a patient affected with acute intermittent porphyria, thus confirming the diagnosis in our patient.[2] She was started on intravenous glucose following which she became better. Anticonvulsants were stopped. She was advised high carbohydrate diet with added salt, lifelong. She is currently doing well and is on an OPD basis follow-ups.

Discussion

AIP is an autosomal dominant disorder occurring due to partial deficiency of PBG deaminase activity (also, called hydroxymethyl bilane synthase). The first case of porphyria probably sulphonal induced was described by Stokvis in the year 1889.[3] The prevalence of *HMBS gene variants* in the general population is 1/1675, which might be an underestimation in view of non-specific clinical symptoms and the diagnosis requires a strong index of suspicion by the clinicians.[4] HMBS deficiency leads to accumulation of porphyrin precursors, such as 5-ALA and PBG, which tends to increase greatly in conditions where heme synthesis in liver is upregulated, such as calorie restriction, infection, menstrual cycle, and also due to cytochrome P450 enzyme inducers. The acute episode of AIP is characterized by the neurovisceral attack, which is characterized by intermittent severe abdominal pain, nausea, vomiting, constipation or diarrhea, urinary retention or Incontinence, hypertension, tachycardia, and complicated by neuropsychiatric manifestations such as agitation, confusion, peripheral neuropathy, and coma. Typically, AIP crises occur frequently in post-pubertal females.[5] Hence, under normal

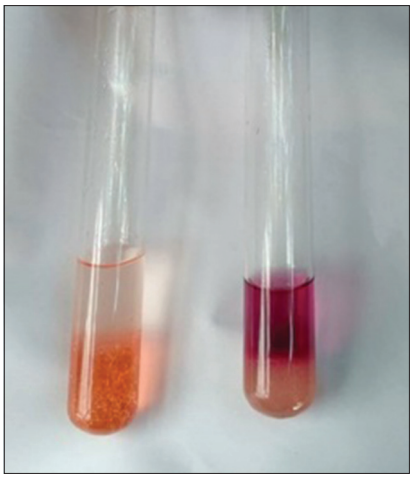

Figure 2: Chloroform is added to the test tubes, mixed well and allowed to settle. Two immiscible layers are formed; with chloroform being heavier, sinks to the bottom and urine being aqueous, stays on top with red color

circumstances, the enzyme deficiency does not result in crises. Acute diffuse abdominal pain, which does not respond to typical analgesics, but in turn, which may worsen, is the earliest and one of the most characteristic symptom. Notably, hyponatremia is the most common electrolyte disturbance that occurs secondary to gastrointestinal loss, less intake, renal loss, and inappropriate secretion of ADH.[6] Patients may present with symptoms of peripheral neuropathy, whereas the most severe CNS impairment may lead to seizures, respiratory failure, and death. Psychiatric findings include delirium, psychosis, hysteria, anxiety, apathy or depression, and sometimes coma.[7]

Acute intermittent porphyria and kidney

ALA is a highly hydrophilic molecule that is freely excreted in the urine. ALA is taken up through the di- and tri-peptide transporters: PEPT1 and PEPT2, which are present in the apical surface of proximal tubules.[8] ALA, which is taken up by this process, acts as a cytotoxic molecule that promotes oxidative stress in kidneys and causes potent vasoconstriction that can promote injury in target organs. Thus, AIP promotes arteriolar injury owing to vasoconstriction caused by porphyrin precursors, leading to hypertension, which on longterm, can cause chronic kidney disease. In addition, porphyrin precursors also cause tubular injury by means of epithelial and mesenchymal transition, which culminates in chronic interstitial nephritis. Finally, the syndrome of inappropriate ADH secretion is also attributable to AIP attacks, which might result from high levels of ALA causing vascular injury, resulting in focal edema in susceptible regions such as the hypothalamus, which is not protected by the blood-brain barrier. Experimental models of AIP have revealed the vacuolization of neurons in the supra-optic nucleus, leading to leakage of ADH into the circulation.[9]

Management of AIP involves avoidance or treatment of precipitating factors, by adequate hydration, nutrition, opioids for pain management, and administration of heme arginate that inhibits ALA synthase, thereby reducing ALA and PBG synthesis. Resolution of neurovisceral attacks occurs within days. However, the long-term complications include hepatocellular carcinoma without cirrhosis[10-12] and chronic kidney disease. Early diagnosis of AIP may be possible if there is a positive family history or if there is a high level of suspicion. The first step for diagnosis of AIP is measurement of ALA and PBG in 24 h urine, during an acute attack, which would increase to many-fold.[13] Measurement of the PBG deaminase enzyme activity or HMB synthase in RBCs confirms the diagnosis of AIP in 95% of cases. However, definitive diagnosis is performed by a molecular genetic test for the mutant gene, with a detection capacity of over 98%.

Treatment includes daily intake of minimum 300–500 g of carbohydrate, during attacks. If oral intake is inadequate, intravenous dextrose has been shown to decrease the urinary excretion of porphyrin precursors in patients with AIP.[14] Early administration of intravenous heme therapy is also effective in treating acute attacks.[15] Heme is taken up by hepatocytes, where it causes negative feedback on the synthesis of ALA synthase, the rate-limiting enzyme. Alternatively, intravenous hematin (heme albumin and heme arginate) in dosages of 3 to 4 mg/kg body weight per day for as long as 4 days can be tried while monitoring for complications such as coagulopathy, thrombophlebitis, and hemolysis.

Conclusion

AIP should be considered in the differential diagnosis in patients presenting with non-specific abdominal and neuropsychiatric symptoms. Prevention of triggering factors plays a key role in the management of AIP, along with measures to prevent the accumulation of porphyrin precursors.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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