Adult-onset seizures as the initial presentation of acute intermittent porphyria

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Abstract

Acute intermittent porphyria (AIP) is a rare metabolic disorder caused by the deficiency of enzyme porphobilinogen deaminase used in haeme biosynthesis. Nonspecific abdominal pain is the classical presentation of AIP. Patients rarely present with rapid-onset neurological manifestations such as acute peripheral neuropathy or seizures. The knowledge on the management of seizures in AIP is important as some antiepileptic drugs may exacerbate acute attack. Hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion is a recognised cause of seizures in AIP. We report a case of a 20-year-old woman presenting to a tertiary care hospital in Sri Lanka with seizures due to hyponatremia who was eventually diagnosed with AIP. Although AIP is not frequently reported in Sri Lanka, it’s important to have a strong clinical suspicion as an early diagnosis will reduce mortality and morbidity.

Key words: acute intermittent porphyria, seizures, hyponatremia, porphobilinogen deaminase

Introduction

Acute intermittent porphyria is a metabolic disorder due to the deficiency of the enzyme porphobilinogen deaminase caused by a mutation in the hydroxymethylbilane synthase (HMBS) gene.¹ It should be suspected in patients presenting with recurrent abdominal pain with neuropsychiatric manifestations.² We are presenting a case of a 20-year-old woman who was successfully diagnosed and treated after the presentation with seizures due to an acute attack of AIP.

Case presentation

A 20-year-old previously healthy woman presented with an episode of generalized tonic-clonic seizures followed by a persistently reduced level of consciousness. She had a history of severe abdominal pain, constipation, vomiting, low mood and irritability for one week prior to the onset of seizures. There was no history suggestive of a central nervous system infection, autoimmune disease, hypocalcaemia, raised intracranial pressure or malignancies. Her urine was dark purple immediately after catheterisation. On examination her Glasgow coma scale was 7/15 with equal pupils, reduced tone of limbs with global areflexia. Her pulse rate was 120 bpm and blood pressure was 190/110 mmHg. Respiratory and abdominal examination was unremarkable.

Investigations revealed a white cell count of 16 x10⁹/L, a haemoglobin of 11.4 g/dL, and a platelet count of 327 x10⁹/L. Serum creatinine was 0.5mg/dL (0.5-1.1). Serum sodium was 103 mmol/L (135-148) serum potassium was 4.3 mmol/L (3.5-5.1), ionized calcium was 8.4 mg/dL (8.4-10.2), and magnesium was 1.8 mg/dL (1.6-2.6). Osmolality studies revealed a serum osmolality of 244mOsm/KgH₂O (285-295), a urine osmolality of 525mOsm/KgH₂O (500-800) and a urine sodium of 128mmol/L. Total serum bilirubin was 0.7 mg/dL (0.1-1.2), aspartate transaminase (AST) was 276 U/L (8-33), and alanine aminotransferase was 104 U/L (4-36). Erythrocyte sedimentation rate, C-reactive protein and serum amylase were within normal limits. Creatine phosphokinase (CPK) was 14,000 U/L (20-120). Thyroid stimulating hormone and random cortisol were normal. Non-contrast computed tomography (NCCT) of the brain revealed mild cerebral

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oedema and electroencephalogram showed features suggestive of metabolic encephalopathy. Cerebrospinal fluid analysis, cerebrospinal fluid culture and nerve conduction studies were normal. Hoesch test for urine porphobilinogen was positive. Spectrophotometry for urine porphyrins showed a peak at 405 nm called the “Soret peak” which was highly suggestive of porphyria (Figure 1). Genetic testing revealed a heterozygous missense variant HMBS, c.346C>Tp. (Arg116Trp) supporting the clinical and biochemical diagnosis of AIP.

**Discussion**

Acute intermittent porphyria (AIP) is an autosomal dominant disorder with low penetrance caused by defects in the porphobilinogen deaminase enzyme causing accumulation of porphyrin precursors, porphobilinogen (PBG), and aminolevulinic acid (ALA). These will get deposited in the central, peripheral, autonomic, and enteric nervous systems causing symptoms. Antiepileptic drugs, alcohol, a low carbohydrate diet, emotional stress, and physical stress are known precipitating factors.

Most patients present with nonspecific recurrent abdominal pain. Only 5% to 15% of patients present with seizures. Hyponatremia and posterior reversible encephalopathy syndrome (PRES) are two recognized causes of seizures in AIP. The presenting symptoms of AIP due to hyponatremia can vary from vomiting and fatigue to seizures and status epilepticus. In our patient the seizures are likely to be to hyponatremia as the brain imaging was not suggestive of PRES. The basis for hyponatremia in AIP is the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Elevated antidiuretic hormone (ADH) levels had been found in acute attacks. It is thought to be due to stimulation by vascular spasms caused by high PBG and ALA and activation of angiotensin II by sequestered water and electrolytes in the gut during acute attacks. Recurrent vomiting and poor oral intake in an acute episode could further worsen hyponatremia. Our patient had both gastrointestinal loss and poor oral intake with osmolality studies suggestive of SIADH, which eventually caused severe hyponatremia. Therefore, it is important to consider the rare possibility of AIP in a patient presenting with seizures due to hyponatremia along with psychosomatic symptoms as it can be easily overlooked due its rarity.

Hoesch test is a rapid screening test for urine porphobilinogen which detects PBG levels over 10mg/L. It is a highly sensitive qualitative test for urine PBG and it is better than the Watson-Schwartz test which has false positive reactions. Positive Hoesch test was supported by a urine porphyrin analysis by spectro-photometry and genetic analysis. Our patient had heterozygous pathogenic variant HMBS, c.346C>T p. (Arg116Trp) which has been previously described to cause AIP. A patient presenting with peripheral neuropathy due to AIP who was found to have a missense mutation, c.517C>T encoding p.R173W in the HMBS gene has been previously reported in Sri Lanka.

The objective of treating an acute attack is to suppress hepatic ALA synthase-1 (ALAS1) activity. The treatment for acute attacks includes haeme...
replacement and carbohydrate loading. Intravenous haeme is the most effective form of therapy as it provides exogenous haeme which down-regulates ALAS1 enzyme production. This downregulation reduces the ALA and PBG levels which precipitate acute attacks of AIP. Carbohydrate loading used to be the standard treatment for acute attacks, but the effects take a long time to appear. It also downregulates ALAS1 enzyme production and provides energy to the patient who has a poor oral intake. Due to the unavailability of haeme this patient had to be managed with intravenous 10% dextrose for which she showed a remarkable improvement.

Antiepileptic drugs namely valproate, carbamazepine, and phenytoin can precipitate an acute attack of AIP. Therefore seizures in AIP should be treated with drugs like gabapentin, vigabatrin, and levetiracetam, which are shown to be safe. She also had hypertension and tachycardia on admission which are known to be associated with acute attacks of AIP. Interference of norepinephrine reuptake by ALA and PBG in acute attacks and impaired catecholamine metabolism had been suggested to be the pathophysiology behind this. Beta blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers are used for the management of tachycardia and hypertension. We managed our patient's tachycardia with oral bisoprolol 2.5 mg daily and her hypertension gradually resolved in a few hours following sedation and general anesthesia. Stress due to pain can trigger neuroendocrine reactions which activate ALAS1 and worsen symptoms and hypertension. Therefore, pain management in AIP has to be addressed properly. Opioids are a safe and effective option in managing severe pain in addition to the use of acetaminophen and non-steroidal anti-inflammatory drugs. This patient was treated with all three classes of drugs as well as patient-controlled analgesia during the intensive care unit stay.

Conclusion

Better awareness of the presenting symptoms of AIP will increase the vigilance and early detection of this rare disease in Sri Lanka. Early diagnosis even with basic biochemical investigations will result in a favourable outcome. It will also prompt genetic testing and genetic counseling of patients.

Author declarations

Consent for publication

Informed written consent for publishing the patient's details was obtained by the corresponding author.

Conflicts of interests

All the authors declare that they have no competing interests.

Author contributions

AS collected information, followed up the patient, did the literature review and drafted the manuscript. AF, RK, JE, UE were involved in the diagnosis and management of the patient and preparing the manuscript. All authors have read and approved the manuscript.

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