Seizures with abdominal pain—a case of porphyrias complicated with status epilepticus

Izza Rehan[1], Fatima Aslam[2], Iqra Manzoor[3]

Abstract

Acute intermittent porphyria (AIP) is the most common type of porphyria, caused due to the deficiency of HMBS enzyme in the heme synthesis pathway. One of its infrequent and clinically challenging complications is status epilepticus.

We present the case of a 14-year-old boy, who was previously misdiagnosed as having appendicitis and later presented with persistent abdominal pain and seizures that progressed to status epilepticus. Diagnostic workup for organic causes of seizures was unremarkable and a porphobilinogen spot test confirmed the diagnosis. He was treated with dextrose and electrolyte correction along with magnesium sulfate and Levetiracetam for seizure control. The patient had recovered fully on his fortnightly follow-up visit.

Limited local literature and the disease's rarity underscores the significance of this case. Future studies should concentrate on developing new treatment approaches for this multifaceted disease, as well as increasing the diagnostic precision for AIP in individuals who present with seizures. Timely intervention can alleviate suffering and minimise hospitalisations.

Keywords: Acute Intermittent Porphyria, Status epilepticus, Case report, Treatment, Levetiracetam, Seizures.

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Introduction

Porphyrias are a group of rare genetic disorders characterised by an enzyme deficiency in the heme synthesis pathway leading to the build-up of toxic heme precursors. They can be acute or chronic.[1] Classification on the basis of the organ from which porphyrins arise, such as hepatic and erythropoietic porphyria, adds to the complexity of this disease group. Known as the little imitator, it can cause neurovisceral as well as dermatological symptoms making diagnosis a perplexing affair.

Acute intermittent porphyria (AIP) is the most common acute hepatic porphyria worldwide with higher prevalence in women of reproductive age and an autosomal dominant inheritance pattern.

The prevalence of porphyrias is understudied in Pakistan due to misdiagnosis and inadequate case reporting. Porphyrias impact less than 200,000 Americans, while European studies report one in 20,000 AIP cases.[2]

Clinical presentation of AIP includes a myriad of manifestations all owing to the toxic metabolites from the liver. Autonomic and peripheral neuropathy form the pathophysiological basis of abdominal pain, hypertension, arrhythmias, and tachycardia. AIP patients with hypothalamic involvement and syndrome of inappropriate antidiuretic hormone secretion (SIADH) can have seizures due to neurotoxicity or hyponatraemia.[3]

The episodic nature and presentation of heterogeneous symptoms over time make AIP harder to pin down causing frequent misdiagnosis. Early identification and care can lead to positive outcomes.

We present the case of a teenage boy who was misdiagnosed and treated for appendicitis, and suffered a porphyria attack with life-threatening refractory status epilepticus. This case highlights the occurrence and management of status epilepticus in patients with AIP, the differential diagnosis of seizures, increased frequency of misdiagnosis, and the different treatment modalities for acute and chronic management of such patients.

Case Report

A 14-year-old male presented to the Emergency Department of CMH Multan on January 24, 2024, with complaints of abdominal pain and fits. The patient was in his usual state of health five days back when he

[1,2] Final year MBBS Student, CMH Institute of Medical Sciences, Multan, Pakistan. [3]Department of Medicine, CMH Institute of Medical Sciences, Multan, Pakistan.

Correspondence: Iqra Manzoor. **Email:** imanzoor691@gmail.com

ORCID ID: 0009-0007-2557-0367

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developed a dull aching generalised abdominal pain along with vomiting and fever. He went to a local hospital in Layyah where he was diagnosed as a case of appendicitis and underwent an appendectomy. The patient's abdominal pain persisted even after the appendectomy and two days prior to presentation in CMH Multan he developed new onset seizures that were initially focal and later progressed to generalised fits lasting two minutes with a postictal phase, up rolling of eyes, and frothing at the mouth at intervals of two to three hours.

On presentation, he was drowsy. His vital signs were: temperature 37.4oC, pulse 97 beats/min, blood pressure 140/99 mmHg, respiratory rate 18 breaths/min, and SpO2 of 96%.

On physical examination, the abdomen was soft and non-tender with a visible scar of previous appendectomy; cardiac and pulmonary examination was normal. Motor strength was decreased and sensations were intact. Birth and post-natal history were unremarkable. The patient's elder sister and paternal uncle were diagnosed cases of acute intermittent porphyria.

Lab investigation performed during his admission showed deranged electrolytes with mild hyponatraemia (130mmol/l; 135-145 mmol/l), hypokalaemia (2.9mmol/l; 3.5-5.0 mmol/L) and hypocalcaemia (7.69mg/dl; 8.5-10.5 mg/dl). Haemoglobin was 10g/dl (12.0-16.0 g/dL) on admission with a microcytic hypochromic picture on CBC. Total Leukocyte Count was 16.6 x109 (4.5-11.0 x109). Liver function test showed slight rise in ALT (96 U/L; 7-56 U/L).

Abdominal imaging with X-ray and ultrasonography revealed no significant findings. CSF examination and CT of the brain were unremarkable. A urine sample for porphobilinogen spot test was positive. On the basis of his clinical findings, positive urine porphobilinogen, a positive family history, and no cutaneous involvement, he was diagnosed as a case of AIP.

The patient was managed prudently with intravenous dextrose and electrolyte correction. Two days later, he developed status epilepticus with deterioration in Glasgow Coma Scale (GCS) and inability to regain consciousness despite the administration of antiepileptic medicines such as Gabapentin and Benzodiazepines. Subsequently, he was shifted to the ICU where he was sedated with Propofol and placed on a ventilator along with Levetiracetam and IV magnesium sulfate. Dextrose saline kept serum sodium adequately high. Electrolyte correction was used to measure treatment response as quantitative tests for porphobilinogen were unavailable. The patient made a full recovery, was discharged, and treated as an outpatient.

Counselling included suggestion of intake of high carbohydrate diet and avoiding triggering drugs and prolonged periods of fasting. The patient was given Tab Levetiracetam 250 mg BD for two weeks. Follow-up after two weeks showed relief of clinical symptoms.

Discussion

According to a literature review by Kaplan et al of cases from 1907–1986, AIP in children is rare, with 141 cases reported in paediatrics and adolescents up to 19 years old.[4] The prevalence in Pakistan is unknown.

Seizures occur in 20% of patients having an acute attack and may evolve into life-threatening status epilepticus.[5] The unique feature that sets this patient apart is status epilepticus. A survey of the literature showed a few cases of status epilepticus in AIP, with no local literature available.

An acute porphyria attack is characterised by a urine porphobilinogen (PBG)-to-creatinine ratio 10 or more times the upper limit of normal (ULN) and the presence of two or more porphyria manifestations (involving the visceral, peripheral, autonomic, and/or central nervous systems) persisting for more than 24 hours in the absence of other likely explanations.[6] A number of mechanisms have been postulated to explain the neurotoxicity induced by ALA and PBG, including the production of reactive oxygen species and the disruption of specific neurotransmitters by ALA. Furthermore, heme synthesis deficiency throws several enzyme systems into disarray, which disrupts energy generation, detoxification, and blood vessel tone, all of which can result in neurovisceral attacks.[7] A limitation in the tests for porphobilinogen for diagnosis and assessment of treatment current case was non-availability of quantitative response. Non-availability of quantitative urine testing, genetic, enzyme and fluorescence analysis, along with strong clinical suspicion and a suggestive family history, warranted relying on urine porphobilinogen in this particular case.[8]

Heme therapy, which reduces ALA synthase expression, is the first line therapy for managing AIP, especially in patients with neurological symptoms, causing improvement within 48 hours. However, it has its adverse effects, which underlines the significance of avoiding precipitating factors as the core of care. Due to its unavailability in our setting, sufficient caloric support was the cornerstone of treatment in this case.

In the current patient, presenting with seizures, first line anti-epileptics like Carbamazepine and Valproate could

have worsened acute attacks by inducing the cytochrome p450 system and inducing ALA synthase.[9] Hence, it is critical to investigate porphyria as a differential diagnosis in patients presenting with seizures and abdominal pain to prevent further deterioration of clinical outcomes.

Experts suggest intravenous magnesium sulfate as the first-line therapy for treatment of porphyric seizures due to its safety.[10]

Levetiracetam, as seen in the current case, was determined to be safe and was likely useful in eliminating seizures. Its low hepatic metabolism, high bioavailability, and rapid steady-state concentrations, make it a promising treatment for seizures in patients with hepatic porphyrias. Propofol administration controlled the seizures and is an established anaesthesia. It is an effective and quick agent for the treatment of porphyric status epilepticus, as evident in multiple cases.[11]

Daily electrolyte monitoring and pain management was addressed foremost in order to avoid hyponatraemia and stress induced exacerbations respectively.[12] In order to maintain electrolytes, the patient was given potassium replacement and 10% dextrose water every twelve hours. Target sodium was above 135 mEq/L with a correction rate of 10-12 mEq/L in the first 24 hours with hypertonic saline.

In recent advances, a novel agent, Givosiran, working as a small interfering RNA proves to be a potential option in management. It has been available in Europe since 2020 but has yet to enter American guidelines.[13]

Porphyria patients over 50 years age should undergo an annual check-up for hepatocellular carcinoma, which is a chronic complication. The patient's uncle, a known case, being over 50 years of age was advised an ultrasound and LFT assessment annually. Liver transplant is the final therapeutic option available.[14]

Conclusion

This case highlights status epilepticus as a clinical challenge in patients with AIP and underscores the importance of high clinical suspicion for AIP when abdominal pain and seizures occur. Levetiracetam and magnesium sulfate show efficacy in treating porphyric status epilepticus. Further research is needed to improve the literature and confidence in managing seizures in porphyria patients, particularly using medications widely available in resource-poor countries like Pakistan.

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