CASE REPORT

Acute Intermittent Porphyria: Flaccid Quadriplegia and Encephalopathy due to Posterior Reversible Encephalopathy Syndrome (PRES)

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Abstract

A deficiency of the enzyme HMB Hydroxymethylbilane synthase function, also known as porphobilinogen deaminase, leads to the emergence of acute intermittent porphyria (AIP). AIP is an uncommon form of hepatic porphyria inherited in an autosomal dominant fashion. We present a case involving a young girl who experienced a sudden onset of quadriparesis, a severe neurological condition that necessitated ventilator support due to respiratory distress. Her condition was consistent with motor axonal neuropathy, which is a characteristic feature of Acute Intermittent Porphyria (AIP). During her last hospital admission, she developed new-onset generalized tonic-clonic seizures, and MRI findings at that time indicated the presence of hyperintense lesions in the posterior parietal region, likely attributed to Posterior Reversible Encephalopathy Syndrome (PRES). To manage her symptoms, she received Dextrose saline due to the elevated levels of urinary porphobilinogen. This case underscores the significance of recognizing two alarming complications associated with porphyria, namely PRES and acute motor axonal neuropathy. Despite an appropriate and timely diagnosis, our efforts were unsuccessful in averting these complications. The unavailability of Hematin, a vital treatment for acute porphyria attacks, was the primary reason for her unfortunate demise.

Keywords: *Female, porphyria, quadriplegia, porphobilinogen, seizures.*

INTRODUCTION

Porphyrias represent a collection of uncommon metabolic conditions identified by various clinical symptoms. Among these, a specific subtype of acute porphyria can develop due to genetic mutations affecting the enzyme pathway responsible for heme production [1]. One of its hallmark features is the occurrence of severe abdominal pain and the excessive excretion of porphobilinogen (PBG) in urine. Although porphyria cutanea tarda holds the distinction of being the most frequent type of porphyria, acute intermittent porphyria stands as the second most commonly encountered variant [2]. Neurological manifestations associated with acute intermittent porphyria encompass symptoms like hyponatremia, central pontine myelinolysis, seizures, neuropathy, and posterior reversible encephalopathy syndrome.

An analysis of the existing literature indicates that the prevalence of porphyria ranges from 0.6 to 10 cases per 100,000 individuals in the population [3]. Additionally, data from the Longitudinal Study, which focuses on HMBS mutations and patients with Acute Intermittent Porphyria (AIP), revealed that among a total of 204 AIP patients, eleven individuals (comprising 5% of the group, including 10 females and 1 male) reported experiencing their initial symptoms before reaching the age of fourteen. This observation underscores the limited availability of data on the pediatric population affected by AIP [4].

Because symptoms can resemble those of other medical conditions, it is crucial to approach the diagnosis of porphyria with a strong sense of suspicion. Here, we describe a case involving a young girl who required ventilator assistance due to severe neurological issues, including PRES and the abrupt onset of quadriparesis.

CASE HISTORY

A 15-year-old patient was brought to our hospital's Emergency Department with a complaint of being unable to move all four limbs for the past three days. Given the severity of her condition and the presence of severe respiratory distress, she was referred to a tertiary care hospital for potential ventilatory support.

Upon examination, she appeared as a young, lean girl with vital signs indicating low blood pressure (90/60 mmHg), a pulse rate of 88 beats per minute, and an oxygen saturation level of 88 percent while receiving 6 liters of oxygen. Her respiratory rate was elevated at 44 breaths per minute. During the neurological assessment, her higher mental functions and cranial nerves were found to be intact. However, the motor evaluation revealed normal muscle bulk with reduced muscle tone in all four limbs. Muscle power was notably diminished, graded at 0/5, suggesting severe muscle weakness. Reflexes were absent, and plantar reflexes were flexor. Sensory examination involving pin-prick testing indicated that her sensory perception was intact.

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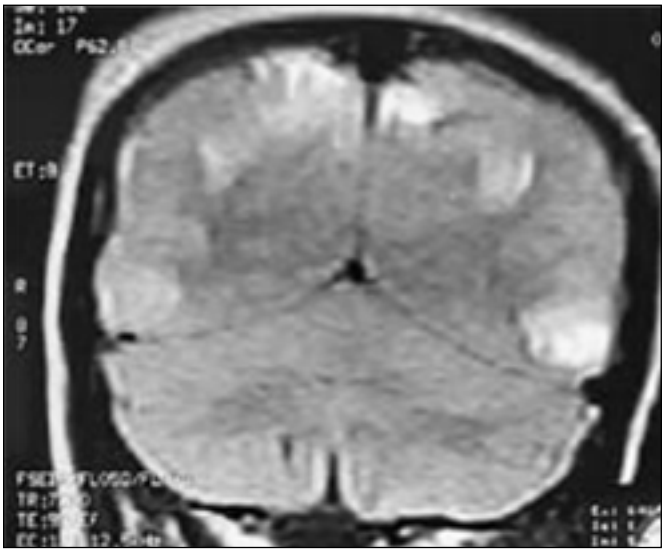

Fig. (1a): MRI flair sequence showing hyperintense lesions in parieto-occipital region.

These findings collectively pointed toward a serious neurological condition affecting the patient's motor function, prompting the need for intensive care and further evaluation.

Arterial blood gas analysis revealed a PaO2 (partial pressure of oxygen) of 60 and a pH of 7.22, indicating impaired oxygen exchange and potential respiratory acidosis with PCO2 of 60 and HCO3 of 24. Consequently, she was electively intubated and transferred to the intensive care unit for further management.

Upon a thorough review of the detailed medical history obtained from the patient's attendants, it became evident that she had been seeking medical attention due to significant abdominal pain on multiple occasions over the past year. During her most recent admission, which occurred 8 months ago, she experienced generalized tonic-clonic seizures. At that time, neuroimaging was conducted, as depicted in Fig. **(1a)**, revealing the presence of hyperintense lesions in the bilateral parieto-occipital region on Flair and T2 sequences. Importantly, there was no post-contrast enhancement observed in these lesions.

During that period, the medical team considered the possibility of acute demyelinating pathology as a diagnosis. As a result, the patient received a pulse of methylprednisolone, and her anti-epileptic medications were maintained. Additionally, a lumbar puncture was performed, and the results from this procedure were within the normal range (**Table 1**).

Table 1: Comparison of two lumbar puncture reports performed eight months apart.

CSF D/R (During last admission eight months ago)		**CSF D/R (Repeat sample during the current admission)-**	
Glucose	98 mg/dl	Glucose	119 mg/dl
Protein	17 mg/dl	Protein	19 md/dl
WBC	Nil	WBC	Nil
RBC	Nil	RBC	250 /cumm
		CSF G/S	Negative
		CSF C/S	Negative

Subsequently, after her previous hospitalization, the patient was discharged and sent home. However, she continued to experience intermittent episodes of lethargy and vomiting, which resolved on their own. Throughout this timeframe, her family noted a gradual dark-reddish or brownish discoloration in her urine persisting for several months.

When she was brought to our hospital, we urgently requested a urine sample for porphobilinogen analysis. Despite our inability to uncover any history of a triggering factor, we conducted this test in light of suspecting a severe and recurrent episode of acute intermittent porphyria. The results from the urine sample confirmed our suspicions, as the levels of porphobilinogen were found to be four times higher than the normal range, providing a critical diagnostic clue. Concurrently, we requested additional samples to explore potential diagnoses such as Wilson's disease and autoimmune disorders. Despite our suspicions, these investigations yielded negative results, eliminating these possibilities from consideration (**Table 2** and **3**).

Following her admission to our hospital, we decided to repeat the Magnetic Resonance Imaging (MRI) of her brain, specifically using the Flair sequence. Surprisingly, this repeat MRI (**Fig. 1b**) showed normal findings. Additionally, we performed a second lumbar puncture, which also yielded completely normal results.

These normal findings raised the possibility that the abnormal neuroimaging observed previously might have been related to Posterior Reversible Encephalopathy Syndrome (PRES) rather than an inflammatory or demyelinating pathology. This suspicion was supported by the fact that any demyelinating changes typically do not resolve within just eight months, making PRES a more likely explanation for the earlier abnormal neuroimaging findings.

Table 2: Laboratory workup and urinary porphobilinogen level.

ANA Profile	Negative
ENA Profile	Negative
24-hour Urinary Copper	19 (> 200 for Wilson disease)
Urinary Porphobilinogen /24 hours	51 (0-4 mg/hour)

Table 3: Biochemistry workup.

Urea/creatinine	69/1.1 mg/dl (0.7-1.3)
Sodium	131 mmol/litre (135-145)
Potassium	3.9 mmol/litre (3.5-4.2)
Chloride	96 mmol/litre (96-106)
Bicarbonate	25 mmol/litre (22-32)
SGPT	20 units/litre (29-33)
Hemoglobin	11.7 g/dl (12-15)

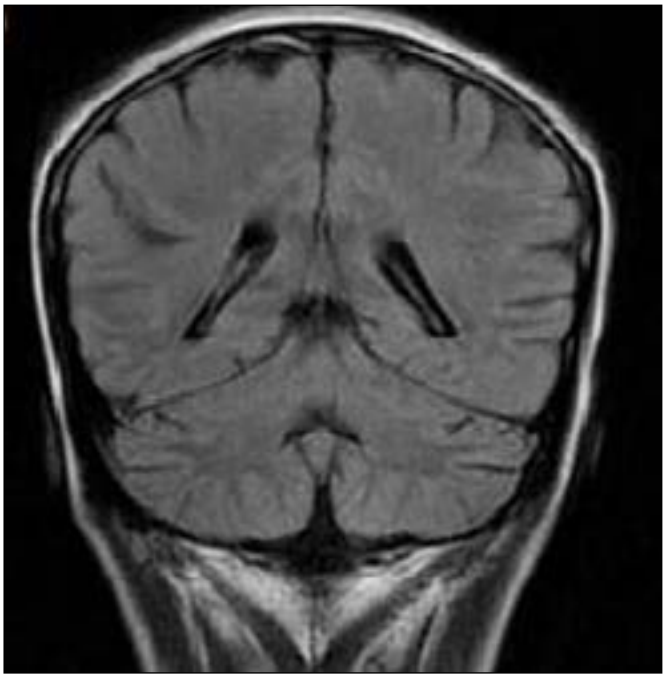

Fig. (1b): MRI brain flair sequence-normal.

The Electromyography (EMG) and nerve conduction studies revealed specific results. In the motor nerve conduction study, the recorded amplitudes fell within the normal microvolt range, and both distal latencies and conduction velocities were normal. It is worth noting that the sensory nerve conduction study produced entirely normal outcomes.

Based on these findings, the conclusion from the nerve conduction study was that the patient was suffering from acute motor axonal neuropathy, a condition that aligns with the diagnosis of acute intermittent porphyria. This particular neuropathy pattern, characterized by a decline in motor nerve function, corresponds with the symptoms and clinical presentation of her porphyria.

Upon admission, the patient was initiated on a 5% dextrose saline solution, administered at a rate of 2 liters over 24 hours. Unfortunately, Hematin, a crucial treatment for acute porphyria attacks, was not available at our hospital. Despite our efforts to procure it from other pharmacies in the city, we were unable to obtain Hematin.

As a result, her condition deteriorated progressively, with an increased reliance on ventilatory support. Tragically, she also contracted a hospital-acquired infection, which ultimately progressed into refractory septicemia, further complicating her medical condition. This underscores the critical importance of timely access to appropriate treatments in managing acute intermittent porphyria and preventing severe complications.

DISCUSSION

In the case presented, two less common neurological complications associated with Acute Intermittent Porphyria (AIP) were highlighted. One of these complications is PRES (Posterior Reversible Encephalopathy Syndrome), which can manifest with symptoms like headaches, seizures, altered consciousness, and visual disturbances. The other complication is acute neuropathy, which can lead to respiratory failure and is characterized by muscle weakness and nerve dysfunction. These complications illustrate the diverse and potentially severe neurological consequences of AIP.

It's worth noting that PRES (Posterior Reversible Encephalopathy Syndrome) is a relatively rare complication in the context of Acute Intermittent Porphyria (AIP), as reported in only four cases [5-7]. PRES typically presents with symptoms such as headaches, seizures, altered levels of consciousness, and visual disturbances.

PRES is more commonly observed in cases of hypertensive encephalopathy in adults, and its pathophysiology in the context of AIP may involve autonomic system involvement. In this particular case, there was a lack of prior hospitalization records detailing the patient's blood pressure variability during her seizures. However, the subsequent neuroimaging findings, which were completely normal upon repeat examination, suggested a potentially reversible etiology, as is often seen in PRES. This suspicion was further supported by the normal results from two lumbar punctures, ultimately favoring the diagnosis of PRES over other potential causes.

The higher prevalence of Acute Intermittent Porphyria (AIP) in females compared to males can be attributed to the strong correlation between hormonal changes and the onset of AIP attacks [8]. Hormonal fluctuations, especially during the menstrual cycle and pregnancy, can trigger or exacerbate AIP symptoms.

In the case presented, the patient had a history of abdominal pain, seizures, severe weakness affecting all four limbs, and respiratory muscle involvement due to severe peripheral neuropathy. These symptoms may be explained by axonal dysfunction resulting from an energy malfunction in the Na+/K+ pump, which can occur due to heme scarcity. Additionally, the direct neurotoxic effects of porphyrin precursors may contribute to the neurological manifestations observed [3].

The pattern of weakness, described as acute flaccid paralysis, is reminiscent of the presentation of acute motor axonal neuropathy (AMAN), a variant of Guillain-Barré Syndrome (GBS). However, making the correct diagnosis necessitates clinical correlation and considering other factors. In this case, the absence of cyto-albumin dissociation in the cerebrospinal fluid (CSF) favors AIP as the underlying cause of the neuropathy, as this finding is more characteristic of AIP-related neuropathies.

The main treatment strategy for porphyria entails a diet rich in carbohydrates, along with intravenous glucose and the use of hematin during episodes of acute illness. Typically, hematin is started at a dosage of 4 mg/kg/day for four days. It should be promptly administered to patients facing life-threatening symptoms during acute attacks, much like the scenario described [5].

Once hematin treatment is initiated, the use of dextrose saline becomes unnecessary, as hematin addresses the underlying metabolic issues more effectively. Givosiran (Givlaari), another treatment endorsed by the FDA for porphyria, is a small interfering RNA that facilitates the breakdown of aminolevulinate synthase messenger RNA in hepatocytes, leading to a decrease in elevated ALA levels. Givosiran is delivered through monthly subcutaneous injections [6].

Additionally, managing AIP requires avoiding certain medications, such as specific antibiotics and anti-epileptics (*e.g.*, phenytoin, phenobarbital, and carbamazepine), to prevent overstimulation of the cytochrome P450 pathway, which can exacerbate the condition. Similarly, it is important to avoid known triggers like hormonal changes in females, fasting, and excessive alcohol consumption, as these factors can induce AIP attacks [7].

Unfortunately, the fatal outcome in the presented scenario was due to the unavailability of these essential treatments in the local healthcare setup. In Pakistan, many children with porphyria are either misdiagnosed [9] or experience delayed diagnoses, often leading to unfavorable outcomes because of the unavailability of necessary treatments. The case report published by Anum *et al.* from Aga Khan University Hospital [10] demonstrated the reversibility of symptoms with hematin, albeit after importing it from Europe. This case highlighted the significant challenge of unregistered availability and regulatory obstacles associated with hematin in Pakistan, underscoring the complexity of managing such cases in the country.

CONCLUSION

The key to improving outcomes and preventing fatal complications in patients with acute intermittent porphyria (AIP) lies in prompt recognition, early intervention, and ensuring access to appropriate treatments like Hematin. These measures are crucial in managing this rare genetic disorder effectively.

CONSENT FOR PUBLICATION

Consent was obtained from the attendant of the patient.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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None declared.

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