

# Acute intermittent porphyria: A critical diagnosis for favorable outcome

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## Abstract

Acute intermittent porphyria (AIP) is an inherited metabolic disorder characterized by the accumulation of toxic metabolites of the heme pathway. It rarely presents in the prepubertal age group. AIP often presents with nonspecific and nonlocalizing symptoms. Moreover, several commonly used medications and stress states are known to precipitate an attack. We present the case of a previously healthy 5 years female who was diagnosed as acute central nervous system infection/inflammation at admission. It was the presence of red flags that led to a correct diagnosis. Besides supportive management, a dedicated search for intravenous hemin (chemically heme arginate, aminolevulinic acid synthase inhibitor, and drug of choice) was attempted. Unexpected help was rendered by doctors from a medical college in Gujarat, and two ampoules could be obtained. The patient received three doses of intravenous hemin; however, she succumbed later. This case is presented for the diagnostic and therapeutic challenges faced in developing countries.

**Keywords:** Acute porphyria, child, developing countries, diagnostic challenge, hemin, therapy

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## Introduction

Acute intermittent porphyria (AIP) may present with a paradigm of nonspecific symptoms, often resulting in a mistaken/missed/or delayed diagnosis. AIP is uncommon in children, particularly in prepubertal age.<sup>[1,2]</sup> Early diagnosis with timely therapy for this life-threatening (yet treatable) condition is essential. We present the diagnostic dilemma and difficulties encountered in the treatment of such a child.

## Case Report

A 5-year-old girl, second of twins, born of a nonconsanguineous marriage presented with complaints of fever since 3 days and complex partial seizures. She had tonic-clonic movements of the left lower limb on the day of admission without evidence of any other neurological findings. There was no history of head

trauma or tuberculosis. She was developmentally normal and previously healthy. At admission, her heart rate was 100 beats/min, respiratory rate was 28/min, and blood pressure was 100/70 mmHg. The systemic examination was unremarkable. Investigations (including liver function tests and renal function tests on admission) were normal, except for a total leukocyte count of 14,800/cumm and serum sodium of 113 meq/L. Magnetic resonance imaging brain was suggestive of acute demyelinating encephalomyelitis (ADEM) or meningoencephalitis [Figure 1]. She was treated with injectable methylprednisolone, acyclovir, and phenytoin.

Over the next 4 days, she developed multiple episodes of generalized tonic-clonic convulsions with interictal

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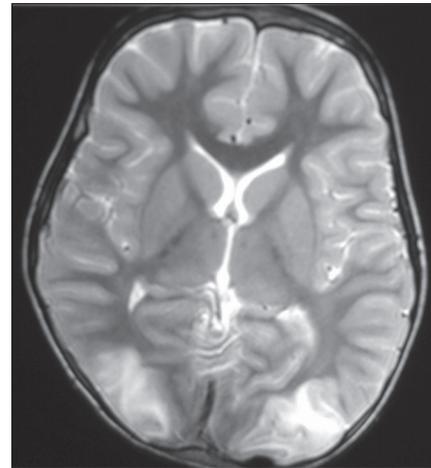
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drowsiness necessitating valparin and levetiracetam. Subsequently, the seizures were controlled and her sensorium improved over the next 3 days. Owing to hypertension encountered on the 3<sup>rd</sup> day of steroid therapy, methylprednisolone was discontinued and nifedipine was given to control hypertension. Hyponatremia (119 meq/L) was persistent despite electrolyte correction. On day 17 after admission, she acutely developed flaccid quadriplegia with areflexia and drowsiness with poor respiratory efforts mandating mechanical ventilation in the Pediatric Intensive Care Unit. A computed tomography scan of the brain done thereafter was suggestive of posterior reversible encephalopathy syndrome (PRES) [Figure 2]. Her urine collected in the urine bag was noticed (for the first time) to be dark colored which turned reddish brown on standing [Figure 3]. Workup for hematuria, hemoglobinuria, and myoglobinuria was negative and porphyria was considered. History of skin rash, abdominal pain, or family history of similar complaints was negative. Urinary screening for porphobilinogen (PBG) by the Watson-Schwartz, ultraviolet fluorescence, and the Hoesch's methods was positive. Urinary screening of siblings and parents were negative for porphyria.

Considering the diagnosis of AIP (and after a thorough literature search), harmful drugs such as phenytoin, valparin, and nifedipine were substituted with safer alternatives such as gabapentin and prazosin. High dextrose (10%) infusion therapy was initiated and the search for Hemin (intravenous drug of choice) began. Hemin, an orphan drug, is not manufactured in India and has to be procured from Europe or the USA. While its procurement was difficult and tedious due to logistic and financial constraints, we were fortunate to obtain it from doctors in Vadodara (Gujarat) who had undergone a similar sequence of events and had managed to procure it from Europe for their patient.<sup>[3]</sup> Our patient was given two doses of hemin at 3 g/kg for 2 days; however, she succumbed before her dosage schedule could be completed.

## Discussion

Acute porphyrias are disorders of heme synthesis which present with acute attacks, often life-threatening. AIP, an autosomal dominant condition, is the most common acute (hepatic) porphyria. It is characterized by deficient activity of PBG deaminase in the heme biosynthetic pathway.<sup>[4,5]</sup> The depletion of heme (substrate) and aggregation of intermediate heme metabolites causes neurovisceral manifestations.<sup>[4,6]</sup>



**Figure 1:** Magnetic resonance imaging of brain showing cortical and subcortical T2 hyperintensities along bilateral occipital lobes, parafalcine neuroparenchyma on either side and right frontal lobe suggestive of acute demyelinating encephalomyelitis or meningoencephalitis



**Figure 2:** Computed tomography of the brain showing hypodense regions in bilateral occipital lobes white matter extending into high parietal regions and frontal region suggestive of posterior reversible encephalopathy syndrome with dilated ventricular system



**Figure 3:** High coloured urine turned reddish brown on standing

The classic triad of AIP described is of abdominal pain, mental changes, and autonomic dysfunctions.<sup>[1,6]</sup> However, 90% of them manifest as autonomic changes (tachycardia and labile hypertension) associated with abdominal pain, constipation, nausea, and vomiting, while 10% present with central nervous system changes in the form of seizures, impaired consciousness, mental status changes, and encephalopathy.<sup>[1,6]</sup> Due to its variable penetrance, AIP may remain undiagnosed lifelong.<sup>[7]</sup> It is often precipitated by environmental and hormonal factors such as drugs, starvation, infection, surgery, stress, menstruation, and steroidal hormones.<sup>[2,4,6]</sup> However, due to its varied and nonspecific/nonlocalizing manifestations, it is commonly misdiagnosed.<sup>[3,5,8,9]</sup> In our case, the initial diagnosis of ADEM led us to treat her with steroids and anticonvulsants which were probably detrimental and pushed our patient toward precipitating a crisis. There have been many such reports of AIP being misdiagnosed as epilepsy, PRES, psychosis, Guillain-Barré syndrome, and acute abdomen leading to appendectomy (and even oophorectomy).<sup>[1,5,8-13]</sup> Many of the above cases were treated with precipitating drugs, which further aggravated their clinical course.<sup>[8,9,11]</sup> It was the presence of clues such as dark/reddish urine, new onset hypertension, hyponatremia, proximal weakness (upper limb more involved than lower limb),<sup>[14]</sup> and temporal association with the recent use of drugs/illness exacerbating the disease that led to a correct diagnosis.

Principles of treatment in AIP generally involve avoidance of porphyrigenic states (triggers of crisis as discussed above) and downregulation of heme synthesis by avoiding fasting and treating the intercurrent illness early. Once an attack is established, treatment modalities available include high carbohydrate diet, use of beta blockers for autonomic manifestations, and substrate reduction by hemin infusion (recommended).<sup>[6,7,14]</sup> Hemin is an orphan drug manufactured in Europe as heme arginate (Normosang<sup>TM</sup>/CR) and the United States (hemin<sup>TM</sup>/CR). Its procurement is expensive; it has to be imported, requires special permissions and has a time lag in completing the entire procedure. Although we were fortunate to be extended prompt help by our fraternity, obtaining hemin in India remains a difficult challenge. Other therapies that have been tried are the use of cimetidine and hemodialysis.<sup>[15,16]</sup> Hemodialysis was contraindicated in our patient due to the presence of deep vein thrombosis.

Thus, acute porphyrias can present as diagnostic dilemmas, unfortunately leading to misdiagnosis/delayed diagnosis, under treatment and under

reporting. Such a patient may present to varying specialties (including the critical care unit) due to a broad spectrum of manifestations, due to which awareness of red flags and a low threshold for screening should be encouraged. Besides acknowledging the benevolent gesture by our medical fraternity in another institution across the country, we wish to highlight the difficulties in obtaining an essentially lifesaving drug due to its orphan status.

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### Contribution of each author

Dr. Chhaya Divecha and Dr. Milind S. Tullu were involved in conceptualization of the manuscript, collecting patient data, conducting literature search and drafting the manuscript. Both Dr. Chhaya Divecha and Dr. Milind S. Tullu are designated as First Authors of the manuscript. Dr. Akanksha Gandhi and Dr. C.T. Deshmukh supervised the data collection, helped in literature search and revised the manuscript for scientific content. All the authors were involved in clinical management of the patient. Dr. C.T. Deshmukh will act as the guarantor of the paper.

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### Conflicts of interest

There are no conflicts of interest.

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