CASE REPORT

Acute Intermittent Porphyria in Prepubertal Child-diagnostic and Therapeutic Challenges in India: A Case Report and Literature Review

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Abstract

Acute intermittent porphyria (AIP) is autosomal dominant metabolic disorder of adulthood with limited case reports in children. Literature review from Western countries shows that most children present with non-specific gastrointestinal and neuropsychiatric symptoms with no family history. Moreover, the attacks are recurrent and precipitated by various factors (drugs/infection). We describe the case of 11-year-old male child who presented with acute abdominal pain, seizures, hypertension, quadriparesis, neuropathy, and respiratory weakness necessitating ventilatory and intensive care. Diagnosis of AIP was suspected on basis of bedside urine testing and confirmed with hydroxymethylbilane synthase gene mutation study. Besides supportive therapy, child was managed successfully with intravenous hemin, an orphan drug, which was procured with great difficulty. This case is presented for highlighting the diagnostic and therapeutic challenges faced in management of such cases in a developing country. We also review Indian literature for similar cases and discuss the clinical presentation, diagnosis, and management of AIP in children.

Keywords: Acute intermittent porphyria, Hemin, Hydroxymethyl bilane synthase gene mutation, Pediatric intensive care unit, Prepubertal child.

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Introduction

Acute intermittent porphyria (AIP), resulting from decreased activity of enzyme porphobilinogen deaminase, is characterized by classical triad of abdominal pain, neurologic dysfunction, and behavioral changes. The vague nonspecific symptoms, multisystem involvement, variability in clinical vignettes, absent family history, low childhood prevalence, and unfamiliarity with diagnostic and therapeutic aspects among pediatricians often cause delay in diagnosis and management of such children, despite a well-characterized molecular genetics.[1] We here report a prepubertal boy with clinical features suggestive of AIP, managed successfully with injection hemin. We also systematically review the Indian literature for similar cases.

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Case Description

A 11-year-old male child, presented with projectile vomiting and epigastric pain for 10 days and multiple seizure episodes for 7 days, managed conservatively with antiepileptics (phenytoin and leveraticetam). After 5 days of admission outside, he developed weakness of all four limbs, left-sided facial deviation and abnormal behavior over next three days. This was followed by onset of breathing difficulty, fever, and burning micturition for one day for which he was referred to our emergency. There was no history of tuberculosis contact or any similar complaints in family. On admission, child was conscious, oriented, anxious with mild respiratory distress, and high blood pressure (147/107 mm Hg). Neurological examination revealed quadriparesis (proximal power 2/5 and distal power 3/5 in both upper and lower limbs), hypotonia, absent reflexes, and upgoing plantars. Cranial nerve examination was suggestive of right upper motor neuron facial palsy. Rest systemic examination was essentially normal. Investigations done revealed metabolic alkalosis, hyponatremia (118 meq/dL), hypokalemia (2.7 meq/dL), and transamnitis (SGOT/SGPT-118/169 IU/L). Child was shifted to PICU and hypertension was managed with antihypertensive drugs (amlodepin and labetalol). Respiratory distress worsened on day 2 with evidence of diaphragmatic weakness in the form of paradoxical respiration and child was put on invasive mechanical ventilation. Investigation panel including sputum CBNAAT for tuberculosis, antinuclear antigen, lumbar puncture, whole abdomen ultrasound, renal Doppler, ECHO, magnetic resonance imaging of brain was within normal limits. It was observed that color of urine turned black on storage for 3–4 hours (Fig. 1A). A strong clinical suspicion of AIP was kept and urine for porphobilinogen by Schwartz test was sent which came positive. Child was started on high-dose dextrose therapy and low-dose benzodiazepines for anxiety and insomnia. Drugs (phenytoin) were modified to avoid further precipitation of attack. Nerve conduction study revealed motor axonal neuropathy. Genetic analysis for exome sequencing was sent for hydroxymethylbilane synthase (HMBS) gene analysis. Child was planned for injection

hemin administration in view of life-threatening attack. Hemin is an orphan drug manufactured in Europe (heme arginate) and the United States (hematin). Procuring hemin in India was an immensely difficult task due to high drug cost (approx INR 2 lakh for four vials, 250 mg each) and extensive legal documentation and permission required from the Customs and Central Drugs Standard Control Organization of India. The drug (brand name Injection Normosang) was procured with help of Indian Pharmaceutical company and arrived after almost 2 weeks of paperwork and money transfer. Child received hemin (dose 3–5 mg/kg/day for 4 days) and was monitored for side effects. After 6 days of starting hemin, there was improvement in respiratory muscle power, urine color (Fig. 1B), and biochemical parameters. On Day 35 of PICU admission, child was gradually weaned of ventilator and successfully extubated (previous extubation failure prior to hemin). Genetic testing revealed heterozygous mutation c.331 G>A (p.Gly111Arg) in HMBS gene confirming the diagnosis of AIP. No other family member was affected. Quadriparesis remained static; however, psychiatric manifestations and hypertension improved and child was discharged on day 50. On 2-week follow-up, child showed improvement in motor weakness (power –4/5 at each joint with elicitable reflexes) and respiratory weakness was completely resolved. Child had a repeat milder attack in the form of abdominal pain and altered urine color after 4 months which was again treated with hemin. At present, the child is ambulatory with no new symptoms and is doing well.

Discussion

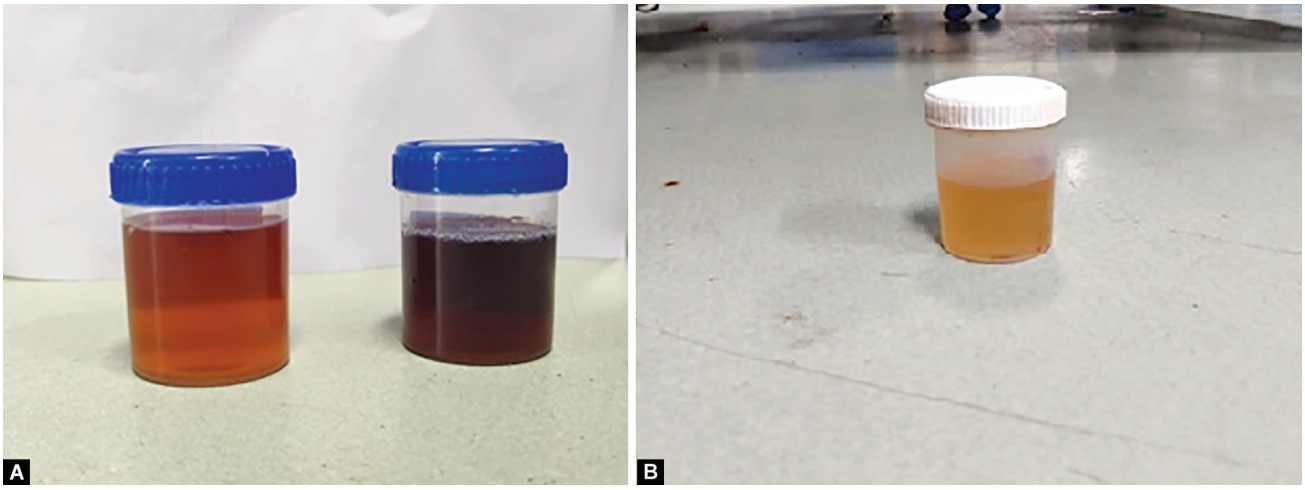
Heterozygous AIP is typically a disease of adult females with rare incidence in prepubertal children. By searching Pubmed and Medline, the available literature on Indian children with AIP was collated and summarized in Table 1. In contrast to adults, the majority of children below 14 years were males including our case. Most presented with abdominal (pain, vomiting), neurological (seizures, altered sensorium, motor weakness, nerve palsies), and psychological symptoms (anxiety attack, aggression). In addition, hypertension and hyponatremia were almost universally present similar to our case. These symptoms were associated with fever or use of drugs like chloroquine or antiepileptics (phenytoin-in present case), which maybe important precipitating factors in this age-group. These clinical findings are similar to published literature review on childhood AIP from Western countries.[2,3]

The diagnosis in majority of cases was based on clinical features and urine porphobilinogen detection by Watson Schwartz test or quantitative estimation. The diagnosis of AIP often gets missed due to rarity of disease and unavailability of testing facility at majority of places. Change in urine color on standing provides bedside test for screening in suspected patients. The definite confirmation is by genetic testing for HMBS gene mutation; however, it is expensive and rarely done. Of the total 16 cases in this review, only 3 had HMBS gene mutation analysis done including the patient reported in the present study (c.331 G>A (p.Gly111Arg)). Over 400 types of HMBS gene mutations are known worldwide including missense (majority), nonsense, and splice mutation. The c.331 G>A (p.Gly111Arg) mutation on exon 7 is a known variant of probably damaging pathogenicity leading to protein with approximately 4% residual HMBS activity, and has been widely implicated in cases worldwide.[4]

Therapeutic options involve definitive therapy in the form of hemin and supportive therapy like high carbohydrate loading (300–500 g/day), symptomatic management, and removal of precipitating factors. Intravenous dextrose in high doses blocks enzyme induction and prevents accumulation of precursors. In severe life-threatening cases, hemin therapy is indicated at 3–5 mg/kg/day for 3–5 days which acts by reducing the ALA synthetase enzyme. Only two cases in the review (including the present case) received hemin injection, while the rest were managed conservatively. The timely import and availability of this orphan drug is a big challenge especially in resource-limited settings like ours. The second important consideration is drug cost and affordability as majority patients belong to lower socioeconomic status. These patients may need hemin to prevent attacks for lifetime and thus need financial and multidisciplinary support for management of disease.

Conclusion

This report emphasizes the importance of early diagnosis of AIP, intensive care management, and treatment of life-threatening events as well as the challenges faced by us in procuring an orphan drug and its feasibility.



Figs 1A and B: (A) Darkening of urine color on storage (on admission to ICU); (B) No change in urine color after administration of hemin

Table 1: Literature review of Indian children presenting with acute intermittent porphyria

S. No	*References*	*Age/Sex*	*Clinical features*				*Precipitating factor*	*Urinary porphobilinogen*	*HMBS gene mutation*	*Treatment*	*Family history*	*Outcome and recurrence*
			Abdominal	*Neurological*	*Psychological*	*Others*						
1	Gupta et al.[5]	13yr/F	Abdominal pain	Quadriparesis hypotonia, respiratory muscle weakness	–	Fever, respiratory difficulty	Not known	Watson Schwartz test positive	Not done	Steroids, vitamin B1 and B12	Negative	Discharged with recurrence after 1 year
2	Puri et al.[6]	7yr/M	Pain abdomen, bilious vomiting	Confusional state			Fever which was treated with Chloroquine	Watson Schwartz test positive	Not done	Conservative	One sibling had positive Watson test	Discharged with no recurrence
3	Ghosh et al.[7]	16yr/F	Abdominal pain	–	Excessive irritability, aggressive behavior, panic attack	Paroxysmal tachycardia	Chloroquine given for acute onset fever	Watson Schwartz test positive	Not done	Conservative	Negative	Discharged with no recurrence
4	Bhat et al.[8]	12yr/M	Abdominal pain	Altered sensorium, sudden onset bilateral blindness		Bilateral papilledema, hypertension	None	20 mg/day	Not done	Antihypertensives	Negative	Discharged with no recurrence
5	Mehta et al.[9]	13yr/M	Pain abdomen	Status epilepticus, altered sensorium	h/o Hyperactive behavior, poor school performance	k/c/o recurrent seizures on multiple antiepileptics	Not known	Urine PBG positive	Not done	Propofol infusion, leveraticetam, gabapentin. Ventilation for poor sensorium	Unknown	Discharged
6	Dosi et al.[10]	16yr/F	Severe abdominal pain	Progressive quadriparesis, EPS—axonal neuropathy	Spells of altered behavior and confusion	Low-grade fever	Not known	Positive	Not done	Conservative Injection hemin	Not known	Discharged
7	Bolia et al.[11]	9yr/ M	Pain abdomen	seizures	None	Hypertension hyponatremia	Not known	Positive	Not done	10% dextrose, nitroglycerine, prazosin, atenolol	Negative	Discharged with no recurrence
		10yr/F	Recurrent episodes of acute pain abdomen	Seizures, right lower limb motor neuropathy	None	Hypertension	Not known	Positive	Not done	10% dextrose, atenolol, enalapril	Negative	Discharged

8	Balwani et al.[3]	9yr/ M	Pain, vomiting, constipation	Seizures, progressive flaccid quadriparesis	–	Palpitation, headache, limb pains, hypertension	Fever	152 µmol/L	Consensus splice site mutation IVS4-1G>A	Gabapentin, high-dose dextrose, propranalol	Heterozygous mutation in mother and 2 brothers	Discharged followed by two recurrences and death in the second recurrence
9	Divecha et al.[12]	5yr/ F		Generalized seizures, acute flaccid paralysis and poor respiratory efforts		Fever with complex partial seizures treated with phenytoin and methylprednisolone for ADEM; hypertension and hypo natremia	?Phenytoin	Positive	Not done	Hemin started but not completed as patient expired	Negative	Expired
10	Mohanlal et al.[13]	11yr/M	Abdominal pain	Seizures, quadriparesis, hypotonia, areflexia, altered sensorium, respiratory depression, cranial nerve palsies		Hypertension, hyponatremia, transamnitis	Not known	Fluorescence positive	Not done	Conservative	Negative	Discharged
11	Varshney et al.[14]	9yr/M	Abdominal pain and vomiting	Tingling sensation in lower limbs, seizures		k/c/o congenital ichthyosis, hyponatremia, hypertension	Fasting	92.1 mg	Not done	Conservative	Negative	Discharged
12	Aggarwal et al.[15]	15yr/F	Pain abdomen, vomiting	Nil	Nil	Pain lower limbs, purple urine	Every month 1 week before menses	Watson Schwartz test positive	Mutation in HMB synthase gene	High-dose dextrose and steroids for attack; GnRH analogues for ovarian suppression and prevention	Unknown	Discharged and attacks reduced in frequency with GnRH analogs and OCPs

(Contd...)

Table 1: (*Contd...*)

S. No	References	Age/Sex	Clinical features				Precipitating factor	Urinary porphobilinogen	HMBS gene mutation	Treatment	Family history	Outcome and recurrence
			Abdominal	Neurological	Psychological	Others						
13	Bhattiprolu et al.[16]	16yr/M	Pain abdomen, constipation	Peripheral neuropathy, bulbar palsy	Psychiatric symptoms	Fever, hypertension, hyponatremia	Fever	Urine color change on light exposure	Not done	5% Dextrose Metoprolol Pregabalin Escitalopram Midazolam Tramadol	Positive	Expired in 20 days
		15yr/M	Pain abdomen, vomiting	Seizures and status epilepticus	Psychiatric symptoms +	Hypertension hyponatremia	Not known	Urine color change on light exposure	Not done	5% Dextrose Metoprolol Pregabalin Escitalopram Midazolam Leveraticetam	Negative	Discharged
14	Present case	11yr/M	Vomiting abdominal pain	Seizures, quadriparesis, facial palsy, peripheral neuropathy	Anxiety attack, altered behavior	Hypertension, hyponatremia, transamnitis	?Phenytoin induced	Schwartz test positive	Heterozygous mutation c.331 G>A (p.Gly111Arg)	Injection hemin Dextrose, benzodiazepines	Negative	Discharged and mild recurrence within 4 months

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