

CASE REPORT

INTENSIVE CARE

Generalized tonic clonic fits precipitated by drotaverine as initial presentation of acute intermittent porphyria: a case report

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ABSTRACT

Acute intermittent porphyria is caused due to deficiency of porphobilinogen deaminase and usually presents with classic triad of neurologic dysfunction, abdominal pain and psychiatric disturbances. A 16-year old unmarried girl presented with 1-day history of recurrent episodes of generalized tonic clonic fits. There was history of mild diffuse abdominal pain for 15 days partially relieved by taking drotaverine. On examination, she was vitally stable and afebrile. Once the fits had stopped, there was no focal motor, sensory or cerebellar neurologic deficit and negative signs of neck rigidity. Initial investigations revealed microcytic anemia and a low normal sodium. Her ESR, CRP, CSF analysis, MRI scan (brain), EEG and aerobic cultures were normal. Urine had a pinkish red color and her 24-hour urine porphobilinogen were raised at 23 mg/24 h (normal range 0-3.4 mg/24 h) with normal fecal porphyrin levels. A diagnosis of Acute Intermittent Porphyria (AIP) was made and 10% dextrose infusion was started which resulted in recovery. Her attack was most likely precipitated by drotaverine and it was withdrawn. Counseling and education about her diagnosis and possible triggering factors was done. She was asymptomatic at discharge and remained stable on follow-up at 4 weeks.

Abbreviations: AIP - Acute Intermittent Porphyria; ALA - Alpha-lipoic acid; PBGD - porphobilinogen deaminase; GABA - γ -Aminobutyric acid

Keywords: Acute Intermittent Porphyria, Fits, Drotaverine, Urine Porphobilinogen, Fecal Porphyrin, Heme, Dextrose Infusion.

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1. INTRODUCTION

A group of rare hereditary disorders, the porphyrias are caused due to catalytic enzyme defect employed in heme biosynthesis. Based on the clinical manifestations and involvement of neurovisceral systems, the porphyrias are classified as acute or non-acute clinically.¹ The most common type of hereditary acute porphyrias, Acute Intermittent Porphyria (AIP) is caused due to deficiency

of porphobilinogen deaminase (PBGD).² The usual presentations of acute porphyrias include peripheral neuropathy, neuropathic abdominal pain, mental disturbance, autonomic dysfunction and seizures. The classic triad of AIP comprises of neurologic dysfunction, abdominal pain and psychiatric disturbances.³ However diagnosing AIP may be challenging and often delayed due to diversity in clinical

manifestations ranging from asymptomatic to severe life-threatening acute attacks.⁴ The typical presentation of an acute AIP attack is severe abdominal pain and neurological dysfunction. In acute porphyrias, seizures may be seen in up to 20% patients with complex partial seizures and tonic-clonic seizures being the most common types seen.⁵ Seizures have been described in AIP with transient abnormalities on MRI scan brain that resolve as the attack settle.⁶ Furthermore, EEG documentation of seizures is also sparse.

Herein, we report the case of a young girl who presented with recurrent episodes of generalized tonic clonic fits after taking drotaverine for diffuse abdominal pain. She had microcytic anemia and a low normal sodium. Her urine had a pinkish red color and her 24-hour urine porphobilinogen were raised with normal fecal porphyrin levels. Subsequently she was diagnosed with AIP and managed with 10% dextrose infusion and withdrawal of offending agent. Counseling and education about her diagnosis and possible triggering factors was done.

2. CASE REPORT

We report the case of a 16-year old unmarried girl who presented with 1-day history of recurrent episodes of generalized tonic clonic fits. Each episode lasted 2-4 min and was associated with tongue biting, urinary and fecal incontinence with post-ictal drowsiness and confusion lasting 5-10 min. There was no history of fever, headache, vision disturbances, ear discharge, focal neurologic weakness, sleep abnormalities, nausea and vomiting. On exploration, there was history of diffuse abdominal pain for 15 days, mild to moderate in intensity, not having any specific aggravating factor but partially relieved by taking medicines (drotaverine) from a GP. There was no history of abdominal distension, altered bowels, urinary pain or burning, skin rashes, joint pains and bleeding from any site. There was no history of similar episodes in the past. She studied in 9th grade and did not smoke or use illicit drugs. Menstrual history was normal. There was no family history of any neurologic disease. On examination, she was vitally stable with temperature 98.5°F. Once the fits had stopped, there was no focal motor, sensory or cerebellar neurologic deficit with power 5/5 in all 4 limbs. Signs of neck rigidity (Kerning and Brudnizki) were negative. There were no abnormalities on abdominal, respiratory and precordial examination.

As shown in Table 1, initial investigations revealed mild microcytic anemia and a low normal sodium. Malarial Parasite (MP) slide was negative. Her CSF analysis demonstrated normal glucose, protein and LDH with no RBC or TLC seen and negative gram and AFB stains. Her blood, urine and CSF cultures did not reveal any

Table 1: Initial blood work-up of the patient

Investigation	Patient's Value	Reference Range
Hemoglobin (G/dl)	11.3	12.0-16.0
TLC (per mm ³)	5,200	4,000-11,000
Platelets (per mm ³)	246,000	150,000-450,000
Hematocrit (%)	28	35-46
MCV (fL)	66.5	77-91
MCH (pg)	25.1	26-32
MCHC (G/dl)	37.7	32-36
ESR (mm/h)	15	Upto 20
CRP (mg/dl)	<5	Upto 5.0
PT (sec)	13	13
APTT (sec)	32	34
Blood Urea (mg/dl)	25	10-50
Creatinine (mg/dl)	0.6	0.6-1.4
Albumin (G/dl)	4.0	3.5-5.0
Globulin (G/dl)	2.2	1.8-3.2
Bilirubin (mg/dl)	0.9	Upto 1.0
AST (U/L)	38	Less than 35
ALT (U/L)	39	Less Than 35
Sodium (mmol/L)	136	133-150
Potassium (mmol/L)	4.2	3.5-5.0

growths. Her MRI scan (brain) and EEG were within normal parameters. Urinalysis revealed a pinkish red color urine. Her 24-hour urine porphobilinogen were raised at 23 mg/24 h (normal range 0-3.4 mg/24 h). Subsequently her fecal porphyrin levels were done which were normal. She was diagnosed with Acute Intermittent Porphyria (AIP) and started on 10% dextrose infusion which resulted in recovery. Her acute attack was most likely precipitated by drotaverine prescribed by her GP and the offending agent was withdrawn. The patient and her parents were counseled and educated about her diagnosis and possible triggering factors. She was asymptomatic by time of discharge and remained stable on follow-up at 4 weeks.

3. DISCUSSION

The management of AIP encompasses treatment of acute attack and prophylaxis of acute attacks. During an acute attack, the treatment of choice is intravenous hematin.⁷ Hematin is not a curative treatment but helps to shorten the acute attacks and reduce its intensity. In addition, a high carbohydrate infusion may aid in recovery.⁸ Heme preparations are not widely available

especially in underdeveloped and developing countries like Pakistan. In such instances, acute attacks are managed with supportive treatment with fluid therapy and adequate nutrition.³ Our patient recovered after initiation of 10% dextrose infusion. Heme infusion could not be given due to non-availability.

In acute porphyrias, seizures may be seen in up to 20% patients with complex partial seizures and tonic-clonic seizures being the most common types seen.⁵ It is postulated that the pathogenesis of seizures in AIP relies on hepatic production of Alpha-lipoic acid (ALA) and PGB which interact with glutamate/GABA receptors in the brain.¹ In the setting of this neurotoxicity, a combination of hypoperfusion, endothelial dysfunction and vasoconstriction leads to brain edema and blood-brain barrier compromise which results in seizures and other neurologic manifestations.⁹ MRI scan may be able to detect these changes but the lesions are non-specific and may be reversible when the attack resolves.⁹ However MRI scan can be normal. In our patient the MRI scan did not reveal any abnormalities. Treatment of seizures can trigger or exacerbate an acute attack including valproic acid, carbamazepine, phenobarbital, lamotrigine, phenytoin, primidone, ethosuximide, topiramate, tiagabine and felbamate.¹⁰ Drugs that are relatively safe for AIP seizures include levetiracetam, gabapentin and oxcarbazepine.^{1,10}

Prophylaxis of acute attacks forms a mainstay of management and it is important to recognize and address the triggering factors. In up to 75% of acute attacks, triggers can be identified and usually include malnutrition, fasting, strenuous exercise, stress, infections, tobacco, alcohol, malignancy, illicit drug use, pre-menstruation and anemia.^{8,11} In addition to various Anti-epilepsy drugs, other medications which may precipitate an acute attack include antibiotics (sulfonamides, erythromycin and rifampicin) and sedatives (barbiturates and some benzodiazepines).¹² Drotaverine may also lead to worsening of acute porphyrias. An anti-spasmodic drug, drotaverine acts through PDE4-inhibition and is used to relieve pain in irritable bowel syndrome, menstrual periods, headaches and cervical spasm.¹³ In the present case, the acute attack was most likely precipitated by drotaverine prescribed by her GP and the offending agent was withdrawn. The patient and her parents were counseled and educated about her diagnosis and possible triggering factors. She was asymptomatic by time of discharge and remained stable on follow-up at 4 weeks.

4. CONCLUSION

In conclusion even though AIP is a rare condition, it is imperative for the clinicians to be aware of it as AIP may have non-specific and variable features. Early

recognition, withdrawal of precipitating factors and supportive therapy are key management steps for acute attacks to improve prognosis and prevent permanent damage.

5. Conflict of interest

Nil declared by the authors.

6. Ethical considerations

Institutional Ethical Committee approval was obtained. Written consent from the patient's NoK was obtained to publish this report for educational purposes.

7. Authors contribution

All authors took part in the management of the patient, retrieval of the data, literature search, manuscript drafting and final approval.

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