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Neurological Variability in Acute Intermittent Porphyria: Case Reports to Highlight the Focus on Different Neurological Manifestations

Case Report

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Abstract

Acute intermittent porphyria (AIP) is a genetic condition due to deficiency of porphobilinogen deaminase enzyme in the heme synthesis pathway. It has an autosomal dominant inheritance. Its manifestation includes abdominal pain, peripheral neuropathy, autonomic symptoms and renal involvement.[1]We report similar cases of a young female presenting as pure motor quadriparesis and another man with seizure and posterior reversible encephalopathy syndrome.

A 17-year-old female presented with severe intermittent abdominal pain, vomiting, followed by muscle weakness and thinning of all four limbs. She underwent various investigations before AIP was suspected. High levels of urine porphobilinogen and nerve conduction study suggestive of pure motor neuropathy were identified. Therefore, AIP was the possible diagnosis. She had a partial recovery; her clinical course of the attack episode lasted for 8 weeks.

Another 18-year-old man came with severe abdominal pain and vomiting 4 days following anterior cruciate ligament repair of right knee. He underwent endoscopy for the same and ended up with a diagnosis of erosive gastritis. A week later he developed an episode of generalised tonic clonic seizure and neuroimaging showed PRESS. He was detected to have heterozygous mutation in hydroxy-methyl bilane synthase gene, thus confirming the diagnosis of porphyria.

Keywords: Porphyria; Neuropathy; Press

Introduction

Porphyria has two major phenotypes: cutaneous and hepatic. The estimated prevalence is around 1 in 5500 to 5800 people in western world. Acute intermittent porphyria (AIP) is more common and due to deficiency of the porphobilinogen deaminase enzyme that converts porphobilinogen to hydroxymethylbilane, resulting in accumulation of porphobilinogen and aminolevulinic acid. The classic symptoms are severe unexplained abdominal pain along with nausea, vomiting, or constipation; neurological attacks, such as epilepsy, sensori-motor weakness; psychiatric symptoms, such as agitation, depression, insomnia, psychosis, delusions, hallucinations; autonomic disturbances, such as hypertension and tachycardia; and hyponatremia. These symptoms are triggered by sleep deprivation, stress, fasting, infections, some medications, and menstruation. The wide range of penetrance (1-38%) raises concerns about the

underdiagnosis of AIP and can lead to fatal complications. [2-4] Hence the aim is to review the varied presentation of porphyria.

Case 1

A 17-year female came with progressive weakness and thinning of limbs for 3 months which started in upper limb (distal followed by proximal weakness). A week later she had proximal lower limb weakness and by the end of 1 month she was bedbound. The weakness was maximum by the end of 6 weeks. She was given intravenous immunoglobulinat nearby health centerafter a diagnosis of possible acute inflammatory polyradiculopathy was made. The nerve conduction study done at that time showed pure motor axonal > demyelinating type of neuropathy. She did not improve with the treatment but noted progressive thinning in all four limbs subsequently. She presented to us after 3 months and we found that she had acute onset progressive, upper limb onset, painless, pure motor, areflexic disabling lower motor neuron type of quadriparesis (Upper limb – distal > proximal, Lower limb distal and proximal) without truncal or respiratory involvement, sensory, autonomic, cranial nerve or sphincter involvement.

The patient underwent several investigations before AIP was suspected. High levels of urine porphobilinogen and a follow up nerve conduction study suggestive of pure motor neuropathy were identified. Therefore, AIP was the possible diagnosis. She had a partial recovery; her episode lasted 8 weeks. She has been advised carbohydrate rich diet and asked to avoid the list of trigger medications.

Our case is similar to one presented by Mutluay et al where a 17-year-old female presented with rapidly progressive quadriparesis with autonomic dysfunction, initially suspected to be an acute motor axonal neuropathy variant of Guillain-Barre syndrome but later found to be due to porphyria.[5]

Case 2

18-year-old man presented with severe abdominal pain and vomiting 4 days following anterior cruciate ligament repair, which did not resolve with symptomatic medications. His imaging studies including ultrasonography and CT abdomen was unremarkable thus he underwent endoscopy and ended up with a diagnosis of erosive gastritis. A week later he developed an episode of generalised tonic clonic seizure and neuroimaging/ MRI Brain showed bilateral posterior predominant T2/FLAIR hyperintensities s/o PRESS.

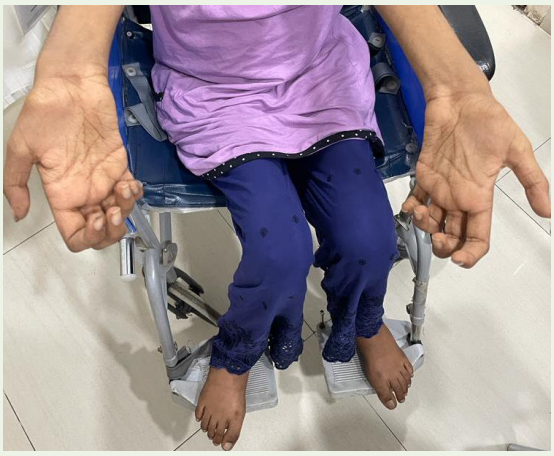

Figure 1: Above picture shows wasted hands and limbs

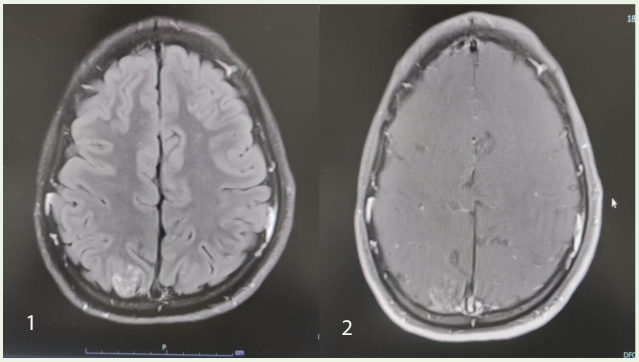

Figure 2: MRI Images 1) FLAIR; 2) Post Contrast

(MRI brain showed cortical edema with gyral swelling and altered signal changes of both frontal and right parietal and both occipital lobes along with clustered nodular enhancement of right pre cuneus with sulcal effacement s/o PRESS)

His mother also had similar h/o convulsion following similar episode of abdominal discomfort we suspected him to have porphyria. Surgery was the stressful event which precipitated the attack. Any surgery is a stressful procedure which when combined with factors like dehydration, fasting or exposure to certain drugs or anesthesia can increase the body"s demand for heme, leading to buildup of porphyria precursors which can trigger porphyria attack.[6] His urine for delta ALA was positive and subsequently he was detected to have heterozygous mutation in HMBS gene, thus confirming the diagnosis of porphyria. We managed him with dextrose containing intravenous fluids and symptomatic management with which he recovered well. Both the patients were advised to have carbohydrate rich diet and list of unsafe medications were explained.

Our case is similar to one published by Andrew et al wherein PRESS was found to be one of the complications in patients with porphyria. [7]

Discussion

Hemeconsists of 64 kDa tetrameric structure. Heme is present in hemoglobin, myoglobin, respiratory cytochromes, and cytochrome P450 enzymes. Heme is formed from glycine and succinyl coenzyme which consists of 8 enzymatic steps, four enzymes are present in the cytosol, and four enzymes are present in the mitochondria. Hepatic ALA synthase1 enzyme is the rate limiting enzyme which is inhibited by heme. [7] [8] [2] [3] [9] [10].

Neuropathy occurs in 10-40 % of porphyria cases and is due to neurotoxicity caused by accumulated porphyrin precursors and dysfunction of Na/K ATPase pump leading to abnormal axon transport and neural dysfunction. The neuropathy is usually pure motor, axonal, proximal upper limb onset and symmetric.

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Table 1: Various features of Porphyrias

Porphyrias	Causative enzyme	Systems involved	Inheritance	Symptoms
Aminolevulinate dehydratase deficiency	5-Aminolevulinate dehydratase	Hepatic	AR	Abdominal pain, Neuropathy
Acute intermittent porphyria	Hydroxymethylbilane synthase (HMBS) formerly porphobilinogen deaminase (PBGD)	Hepatic	AD	Periodic abdominal pain, psychiatric symptoms, peripheral neuropathy, autonomic symptoms
Congenital erythropoietic porphyria (CEP)	Uroporphyrinogen synthase	Erythropoietic	AR	Severe photosensitivity with erythema, swelling and blistering. Hemolyticanemia, splopioenomegaly
Porphyria cutanea tarda (PCT)	Uroporphyrinogen decarboxyase	Hepatic	AD/Sporadic	Photosensitivity with vesicles and bullae
Hereditary Coproporphyria	Coproporphyrinogen Oxidase	Hepatic	AD	Photosensitivity, Abdominal pain
Harderoporphyria	Coproporphyrinogen oxidase	Erythropoietic	AR	Jaundice, Anemia, HepatomegalySplenomegaly Often neonatal Photosensitivity later.
Variegate porphyria (VP)	Protoporphyria Oxidase	Hepatic	AD	Photosensitivity, Neurologic symptoms, Developmental delay
Erythropoietic Protoporphria (EPP)	Ferrochelatase (FECH)	Erythropoietic	AR	Photosensitivity with Skin lesions, Gallstones, mild liver dysfunction

Distal paresthesias are less common. Cranial nerve involvement is infrequent.[11]

Seizures are seen in approximately 10-20% patients with symptomatic porphyrias. The most common seizure types are tonic-clonic or complex partial seizures. Status epilepticus is less common. The possible mechanism may be due to neurotoxic substance presumably ALA/PBG which may interact with GABA or glutamate receptors. Endothelial dysfunction, hypoperfusion, vasoconstriction in the setting of neurotoxicity leads to compromise of blood brain barrier and brain edema. PRES may be a rare manifestation due to the same mechanism. Other neurological symptoms include autonomic dysfunction, encephalopathy, coma, agitation, anxiety, depression, insomnia and hallucinations.[1]

Precipitating factors for Acute Porphyria

- Drugs—barbiturates, oestrogens, methyldopa, danazol, diazepam, phenytoin, carbamazepine, sulphonylureas sulphonamides, chloramphenicol, tetracyclines, some antihistamines
- Fasting
- Smoking
- Surgery
- Alcohol
- Substance particularly marijuana, cocaine, ecstasy and amphetamines
- Infection
- Premenstrual attacks are common

Diagnosis

Patients with suspected signs and symptoms suggestive of AIP should be asked about potential triggers and family history of porphyria. A publicly available database of porphyrinogenic drugs enlists the causative agents. (https://porphyriafoundation.org/drugdatabase/) laboratory investigation may reveal hyponatremia, leukocytosis, mild transaminitis, red or brown urine (not related to hemoglobin or bilirubin) without any evidence of infectious, gastrointestinal, hepatobiliary, pancreatic, renal, or gynecologic cause. Mild to severe hyponatremia in seen in 25-60% of cases.[12]

During acute attacks, the urinary porphyrin precursor Porphobilinogen (PBG) is usually increased in AIP. The Trace PBG Kit detects elevated levels of urinary PBG. ALA and PBG levels are often elevated. Also, urinary (and fecal) porphyrin analyses can suggest a specific acute hepatic porphyria. Once a biochemical diagnosis is ensured, genetic mutation analysis for AIP should be undertaken. Molecular diagnostic studies also are to be done for confirming diagnosis of patients with symptoms, to identify at-risk family membersand to offer asymptomatic heterozygote counseling to avoid the drugs, fasting, hormones, and other precipitanting factors.[10]

Treatment

Initial management focuses on eliminating factors such as medications, caloric deprivation, and dehydration that may be precipitating factor. Rehydration using IV normal saline, glucose infusions, and discontinuation of any suspected inducer medications is a vital part of the management of the acute attack. Pain relief using opioids is considered safe. Definitive treatment is done with administration of IV hemin for 3-14 days, which reverses the increase in ALAS1. Research studies are being conducted with small interfering RNA (siRNA) to ALAS1 and appear promising. Givosiran was approved by the FDA in November 2019 for the treatment of acute hepatic porphyrias in adults.

Ongoing management: some patients may have recurring attacks. This includes females during menstruation. Gonadotropin-releasing hormone analogs have been found useful to

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prevent ovulation in female patients that present with recurrent pre-menstruation related acute porphyria.

Acute seizure management can be a challenging in acute porphyrias as most anticonvulsants induce the cytochrome P450 enzyme. Acute seizure management includes the following:

- First-line medication: Magnesium sulfate and diazepam
- For status epilepticus: Lorazepam, per rectal diazepam
- Correction of metabolic risk factors: Such as correction of hyponatremia with normal saline considering the volume status of the patient.
- Long-term seizure control: Gabapentin

Patients might have autonomic dysfunction, which can be managed by beta-blockers. An acute rise in blood pressure can be treated with appropriate emergency medication, such as labetalol.

Psychiatric symptoms are managed by giving phenothiazines, such as chlorpromazine.

Neuromuscular symptoms are treated with Gabapentin, early rehabilitation, mechanical ventilation for respiratory weakness and nasogastric feeds for severe dysphagia. Acute attacks of neuropathic pain can be managed with hemin infusion and opioids. In most cases recovery is often incomplete.[10] [11]

Statement and Disclosure

No person who had contributed substantially to the production of this manuscript had been excluded from authorship. Person who has contributed partially have been acknowledged in the manuscript.

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