Acute Intermittent Porphyria – A Rare Case with Neurovisceral Symptoms

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Abstract

Acute intermittent porphyria (AIP) is an autosomal dominant disorder resulting from partial deficiency of the porphobilinogen deaminase affecting the production of heme. It produces acute neurovisceral symptoms. The diagnosis of AIP is difficult. Symptoms are often nonspecific.As the penetrance is low in AIP, positive family history of disease may be absent. So high index of suspicion is required to diagnose AIP. Combination of neurologic and visceral symptoms gives clue to the diagnosis. In December 2018, we have diagnosed a case of Acute intermittent porphyria who presented with acute abdomen, hypertension, tachycardia and convulsion. His urine colour turned to purple red on exposure to sunlight. He had hyponatremia. MRI of brain revealed features of Posterior Reversible Encephalopathy Syndrome (PRES) and EEG was suggestive of focalseizure. Urine porphoblinigen was positive. He was treated with IV glucose, DNS, high carbohydrate diet, newer antiepileptic drug, opioid analgesic, antihypertensive medication and other supportive and symptomatic measures. Ultimately his condition improved gradually and discharged with advice to continue medicine and periodic follow up.

Key-words: Intermittent porphyria, acute abdomen, seizure, hypertension, hyponatremia, porphobilinogen, MRI of brain, PRES.

Introduction

Acute abdomen refers to sudden onset severe pain in abdomen. It is in many cases a medical emergency, requiring urgent and specific diagnosis. Several causes need surgical treatment. But there are medical causes of acute abdomen where there is no role of surgery. Appropriate medical management will cure the abdominal pain. Examples of medical causes are diabetic ketoacidosis, adrenal crisis, hypercalcemia, sickle cell anemia, dengue fever, mesenteric vasculitis, ischemic colitis, acute pyelonephritis, familial Mediterranean fever, acute intermittent porphyria etc[1].

Seizure is a medical emergency which may be idiopathic or due to secondary causes like neoplasm or intracranial space occupying lesson (ICSOL),stroke, trauma, infection or metabolic. One of the rare metabolic causes of seizure is acute intermittent porphyria. In CMH Dhaka we have diagnosed a case of AIP who presented with both acute abdomen and seizure. We are publishing the case to generate awareness regarding this uncommon disease[2].

Case Report

A 14-year-old boy was admitted to CMH Dhaka on 20/12/2018 with the complaints of severe pain in central and upper abdomen associated with anorexia, nausea and vomiting for 5 days prior to hospital admission. He had 2 episodes of convulsion during this period. There was no history of fever, skin rash, arthralgia, jaundice, dysuria, passage of blood with vomitus, stool or urine.He gave history of occasional pain in abdomen, constipation and high coloured urine associated with generalized weakness for last 2 years. His family history was unremarkable. With these, he was initially admitted to surgical HDU as a case of acuted abdomen and treated conservatively with proton pump inhibitors, opioid analgesics, antiemetics, antibiotics, IV fluid and anti-spasmodics etc without significant improvement.

General physical examination revealed the boy was anxious and mildly anemic. His pulse was 120b/min and blood pressure was 156/120 mmHg. There was mild epigastric tenderness. He was then referred to Medicine specialist due to convulsion and accelerated hypertension. Bedside urine examination revealed that his urine colour changed to reddish purple on exposure to sunlight (Figure-1).

Therefore, he was suspected as a case of acute intermittent porphyria. He was investigated thoroughly to confirm the diagnosis and to exclude the other possibilities. His CBC showed Hb%-11 gm/dL, TLC, DLC, platelet count and ESR was normal. Urine R/E showed WBCs 3-5/HPF, RBCs 1-2/HPF, granular cast +ve, and trace of protein. Urine for ACR was 3.5:1 mg/mmol. Urine ketone bodies were absent. Serum electrolytes revealed hyponatremia (Na-119 mmol/L). His serum creatinine, LFT, sugar,lipid profile, amylase, lipase, serum calcium, PT, aPTT, D-dimer, S.cortisol, TSH, serum rennin and aldosterone levels were normal. His HBsAg, anti-HCV, ANA, anti-DS-DNA, c-ANCA, p-ANCA were negative and serum IgA level was normal. Plain X-ray abdomen showed large gut distension. USG of whole abdomen and endoscopy UGIT, CT scan of abdomen was unremarkable. ECG and CXR were normal. EEG showed focal epileptic form of discharge predominantly in fronto-temporal area. CT scan of brain (Figure 2) showed prominent ventricles and external CSF space. MRI of brain (Figure 3) revealed leukoencephalopathy in both cerebral hemispheres suggestive of PRES with mild cerebral atrophy. Urinary porphobilinogen was positive which was done from Apollo Hospital Delhi with collaboration of Apollo Hospital, Dhaka.

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Therefore, finally he was diagnosed as a caseof Acute Intermittent Porphyria. He was treated with high carbohydrate diet, infusion normal saline and 5% DNS, Tab Levetiracetam, Tab Bisoprolol, Tab Fludrocortisone, Inj Nalbuphin HCl, antiemetic and laxative. Haematin could not be given due to non-availability and cost. His condition improved gradually and he was discharged on 15/1/19 with advice to continue medication, avoid precipitating factors and follow up periodically.

Figure 1: Changing urine colour on exposure to sunlight.

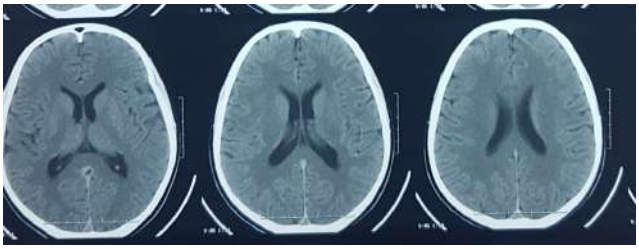

Figure-2: CT scan of brain showing Prominent ventricles and external CSF space.

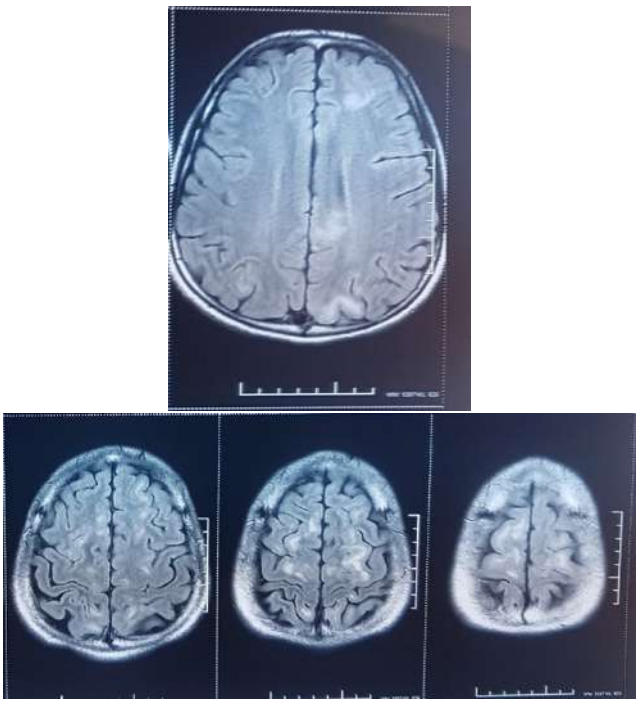

Figure-3: MRI of brain suggestive of leukoencephalopathy in both cerebral hemisphere.

Discussion

Porphyria is named from ancient Greek word porphura, meaning purple. The porphyrias are a heterogeneous group of inherited metabolic disorders of haem synthesis pathway. There are seven forms of porphyria, each of which is caused by a partial deficiency of one of the last seven enzymes in the haem biosynthetic pathway[3]. The seven forms of porphyria may be classified into acute and non-acute. Acute porphyrias include Acute intermittent porphyria, Variegate porphyria, Hereditary coporphyria, ALA dehydratase deficiency porphyria. Non acute porphyria include Porphyria cutanea tarda, Congenital erythropoietic porphyria, erythropoietic protoporphyria and X-linked dominant protoporphyria. Neurologic and/or cutaneous symptoms may manifest depending on which enzyme in the pathway is affected[4].

Acute intermittent porphyria (AIP) is the most common among acute porphyrias. It is also called Swedish porphyria, pyrroloporphyria. It has a 2:1 female to male ratio. It is an acute neurovisceral porphyria and is an autosomal dominant disorder with low penetrance. AIP results from a partial deficiency of enzyme porphobilinogen deaminase (PBGD)[5]. The diagnosis of AIP is challenging. Symptoms are nonspecific and because of low penetrance disease manifestation may be absent among family members[6,7].

ALA or other metabolites that are over-produced by the liver become neurotoxic. The enzyme activity in the acute porphyrias is only partially deficient. and in normal circumstances the remaining activity (<50% in AIP, VP and HCP) is usually sufficient to maintain normal haem homeostasis[8]. The enzyme deficiency predisposes patients to acute attacks, where there is an increased need for haem. The rate of haem synthesis is primarily controlled via ALA synthase. The activity of this enzyme in the liver is regulated by the free intracellular haem pool by a negative feedback mechanism[9]. ALA synthase activity increases as the basal haem concentration declines, resulting in increased levels of ALA and subsequently, increased levels of PBG and porphyrins. In patients with acute porphyria the conversion of ALA, PBG and porphyrins to haem is compromised by their enzyme deficiency. These are associated with characteristic clinical features[10].

Symptoms associated with AIP include GI symptoms which is the majority, which includes colicky abdominal pain, constipation, vomiting and diarrhea. Neuropathic and other symptoms like psychiatric symptoms, diffuse pain in upper body, hypertension, tachycardia, fever, seizures may also be present. Drugs that increase demand for heme in liver (specially cytochrome P450 enzymes), crash diets (decrease carbohydrate intake), endogenous hormones (progesterone), metabolic stresses (infections, surgery, psychological stress) and cigarette smoking (induces cytochrome P450) are potential precipitants of an acute attack of AIP[11].

A wide range of investigations is required to come to the diagnosis of AIP. Abdominal imaging may reveal small and/or large bowel

distension due to ileus. Brain imaging may show reversible densities in white matter resembling posterior reversible encephalopathy syndrome (PRES; also called reversible posterior leukoencephalopathy syndrome), a syndrome of deranged cerebrovascular function. During the time of an acute attack, AIP is characterized by increased urinary PBG, ALA, and porphyrins. Urinary PBG excretion is generally 20 to 200 mg/day during an attack, markedly raised from normal level of approximately 0 to 4 mg/day. Urinary ALA is generally also markedly increased, but less so than PBG. Plasma or serum ALA and PBG are also elevated. Normal or only slightly increased fecal porphyrin levels are seen in AIP. PBG in urine is oxidized to porphobilin upon standing in sunlight, which gives a dark-brown color to urine, and often referred to as 'port wine' reddish urine. Decreased erythrocyte porphobilinogen deaminase (PBGD) activity is seen in about 90% of patients[12,13].

Management is largely symptomatic. On mild to moderate attack, high dose of glucose, high carbohydrate and 5% DNS 02 liters/24 hrs should be given. Severe attack can be treated with hematin 4mg/kg/day for 04 days. Pain control is best achieved by narcotics. Laxatives and stool softener are used for constipation. Newer anti-epileptic drugs are given for convulsion. β blockers are preferable to manage hypertension. Liver transplantation cures AIP in case of recurrent attacks, life threatening conditions or when quality of life is severely affected. Comprehensive rehabilitation program by physiatrist is required to combat weakness. Research is still going on the field of gene therapy[14,15].

Adequate carbohydrate intake, I/V hematin, hepatocellular carcinoma screening, end-Stage renal disease prevention by controlling BP, and avoidance of alcohol, smoking, and exacerbating drugs are measures which must be taken as prognostic measures to prevent acute attacks and complications[16].

Conclusion

Before 1970, fatality rates were 50% which has now decreased to 10%. Since introduction of hemin and hematin, mortality has decreased. Overall death rate in patients with acute attacks is 3-fold higher than that of the general population. Delayed diagnosis and treatment contribute to higher mortality. Prompt diagnosis and efficient management is the key to successful and better prognosis to AIP.

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