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Minireview

Acute Intermittent Porphyria in children: A case report and review of the literature

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ABSTRACT

Acute Intermittent Porphyria (AIP), an autosomal dominant inborn error of heme metabolism, typically presents in adulthood, most often in women in the reproductive age group. There are limited reports on the clinical presentation in children, and in contrast to the adults, most of the reported pediatric cases are male. While acute abdominal pain is the most common presenting symptom in children, seizures are commonly seen and may precede the diagnosis of AIP. As an example, we report a 9 year old developmentally normal pre-pubertal boy who presented with acute abdominal pain, vomiting and constipation followed by hyponatremia, seizures, weakness and neuropathy. After a diagnostic odyssey, his urine porphobilinogen was found to be significantly elevated and genetic testing showed a previously unreported consensus splice-site mutation IVS4-1G>A in the *HMBS* gene confirming the diagnosis of AIP. Here, we discuss the clinical presentation in this case, and 15 reported pediatric cases since the last review 30 years ago and discuss the differential diagnosis and challenges in making the diagnosis in children. We review the childhood-onset cases reported in the Longitudinal Study of the Porphyrias Consortium. Of these, genetically and biochemically confirmed patients, 11 of 204 (5%) reported onset of attacks in childhood. Most of these patients (91%) reported recurrent attacks following the initial presentation. Thus, AIP should be considered in the differential diagnosis of children presenting with unexplained abdominal pain, seizures, weakness and neuropathy.

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1. Introduction

Acute Intermittent Porphyria (AIP, OMIM #176000), an autosomal dominant disorder of heme biosynthesis, rarely presents in childhood. AIP is due to mutations in the hydroxymethylbilane synthase (*HMBS*) gene that result in half-normal HMBS enzymatic activity, the third enzyme in the heme biosynthetic pathway [1,2,3] (HMBS, EC 2.5.1.61, also known as porphobilinogen deaminase). This enzymatic deficiency predisposes heterozygous patients to life-threatening acute neurovisceral

Abbreviations: ALAS1, Aminolevulinic acid synthase 1; HMBS, Hydroxymethylbilane synthase; ADP, Aminolevulinic acid dehydratase deficiency porphyria; PBG, Porphobilinogen; ALA, Aminolevulinic acid.

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attacks that are precipitated by various factors, including porphyrinogenic drugs (*e.g.*, P450 inducers), alcohol, infection, stress, prolonged fasting and chronic under nutrition, and steroid hormones. These factors induce the synthesis of aminolevulinic acid synthase 1 (ALAS1), the first and rate-limiting enzyme in the heme biosynthetic pathway. When hepatic ALAS1 is induced, the partial HMBS enzyme deficiency becomes limiting, resulting in the marked accumulation of the neurotoxic porphyrin precursors, aminolevulinic acid (ALA), and porphobilinogen (PBG). These porphyrin precursors act on the central and peripheral nervous systems to produce acute neurovisceral and psychiatric symptoms. The diagnosis of AIP is typically made by demonstrating markedly elevated urinary PBG levels during an acute attack, and by identifying a pathogenic *HMBS* gene mutation in the patient [1,4].

It is estimated that 10–20% of AIP heterozygotes experience acute attacks, while the majority are clinically asymptomatic throughout their lives [2,3,4]. The most common clinical presentation of an acute porphyric attack is severe abdominal pain, accompanied by vomiting, constipation, and abdominal distention, which can masquerade as an acute abdomen. Behavioral changes such as irritability, insomnia, emotional lability and hypertension and tachycardia due to sympathetic over-activity are important clues for the diagnosis [4]. Hyponatremia often occurs during severe attacks and can lead to seizures or an altered sensorium or even coma. The acute onset of progressive limb weakness due to motor axonopathy accompanied by myalgia can be extremely debilitating for patients. If these symptoms are not recognized and treated early, they can lead to residual morbidity and mortality due to bulbar and respiratory muscle paralysis [1,2,4]. Physical examination is usually unremarkable and patients may lie in the fetal position in response to extreme pain and debility. Due to the variable clinical presentation and non-specific symptoms of the neurovisceral attacks, and the fact that attacks are rare in children, a high index of suspicion is required to make the diagnosis in children.

Here, we 1) provide an instructive case that highlights the difficulty in diagnosis and attack progression in a pre-pubertal boy in whom porphyrinogenic drugs were used to treat an infection and seizures which further exacerbated, prolonged, and increased the severity of his acute attack, 2) review the literature describing AIP in children since the previous review 30 years ago by Kaplan and Lewis [5], and 3) report the frequency of childhood AIP manifestations among the 204 AIP patients enrolled in the Longitudinal Study of the Porphyrias Consortium of the NIH-sponsored Rare Diseases Clinical Research Network.

2. Case summary

The patient was a 9-year-old developmentally normal, pre-pubertal Indian boy (Tanner stage G1PH1), with no prior medical history. He was the son of unrelated parents. He was essentially well until he presented with acute abdominal pain, vomiting and constipation. He had a fever without an obvious localizing cause, which responded to paracetamol a day prior to the acute episode. The pain was severe and he was hospitalized for a presumed sub-acute intestinal obstruction, and fluids were restricted (NPO). He received intravenous antibiotics including ceftriaxone and metronidazole. An abdominal CT scan showed mild ascites, but no other cause of his symptoms. On day 3 of illness, he developed a tonic–clonic seizure that was treated using intravenous midazolam and phenytoin loading. His clinical condition remained unchanged and he was transferred to another hospital where he was treated conservatively with IV fluids and different antibiotics, including sulbactam and amikacin.

Laboratory studies showed leukocytosis and hyponatremia (serum sodium levels of 111 meq/L and 114 meq/L on days 4 and 5 of illness). Hyponatremia was treated with intravenous saline. On day 7 of illness, his abdominal pain and vomiting improved and he was discharged on multivitamins and an appetite stimulant. He was stable for a few days, but on day 12 he developed progressive weakness and pain of the lower extremities, and he was unable to support himself. On day 15 of illness, the weakness advanced to the proximal muscles of the upper limb and he continued to have severe pain in his extremities and back.

He was hospitalized again on day 20 of illness with truncal weakness and was unable to sit without support. He complained of headache, palpitations, and excruciating pain in the limbs that was not relieved by analgesics (Ibuprofen and Diclofenac). His appetite was poor and he was irritable, restless and had insomnia. His physical examination revealed a thin boy with a BMI of 14.5 kg/m^2 who was irritable and lethargic. He had tachycardia and hypertension (BP 150/90 mm Hg) with normal pulse volume and character, with all peripheral pulses palpable. The four limb BP did not reveal any discrepancy across different limbs and the fundus did not show any hypertensive changes. The pain was generalized in all limbs, trunk, and back. There were no objective signs of joint swelling/tenderness or inflammation and the examination of the musculoskeletal system was essentially normal. He was conscious, oriented, with an intact memory and intellect, with no cranial nerve involvement. He assumed a fetal posture because of the excruciating pain and resisted examination. The muscles of his upper and lower limbs had strength of 3/5 accompanied with truncal weakness. The deep tendon reflexes were difficult to elicit and the plantar reflexes were flexor. There were no meningeal signs, and his gait could not be examined as he was unable to stand unsupported. There was no evidence of musculoskeletal disease. An echocardiogram and ultrasound of the renal vessels were normal. He continued to have pain and progressive weakness and was given tramadol for pain control. His hypertension was managed using amlodipine. Evaluation for autoimmune disorders including Anti-Nuclear Antibody, Anti-ds DNA, RA factor and C-reactive protein was negative. The blood lead concentration was 0.1 μg/dL (<5). He was started on an empirical trial of Vitamin C, and Vitamin D3 was supplemented due to Vitamin D deficiency. A bone marrow aspiration to rule out an occult malignancy was negative.

The patient developed tachypnea and his breathing became labored indicating weakness of the intercostal muscles and the diaphragm. He was started on gabapentin as the pain appeared to be neuropathic, and he showed a slight improvement. Nerve Conduction Velocity (NCV) studies demonstrated a low conduction velocity in the left common peroneal nerve. He developed urinary retention, which was relieved by catheterization. The urine was red, which led to the suspicion of an acute porphyria (Fig. 1). A Hoesch test for PBG was strongly positive and a quantitative urine PBG level was 152 μmol/L (normal <10 μmol/L). *HMBS* mutation analysis identified a novel splice-site mutation, IVS4-1G>A, in the *HMBS* gene confirming the diagnosis of heterozygosity for AIP. Family studies revealed that his asymptomatic mother and two brothers were heterozygous for the novel consensus splice-site mutation (Fig. 2).

As hematin, the standard treatment for acute attacks [4], was not commercially available, the patient was started on a high dose dextrose infusion regimen (400 g/day). He received propranolol for hypertension and gabapentin was continued for his neuropathic pain. The patient improved significantly and was discharged on physical therapy. His repeat NCV at the end of 12 weeks demonstrated axonal motor sensory neuropathy. Follow up evaluation 12 weeks after his initial attack showed residual foot and wrist drop. The patient had two subsequent attacks during the nine months after discharge, precipitated by a minor viral illness and poor oral intake, respectively. These attacks were managed by hospitalization and intravenous dextrose (400 g/day).

3. Review

Heterozygous AIP typically presents in the second or third to fifth decade of life, most often in women, and very rarely presents before puberty [1,2,3,4]. Previously, Kaplan and Lewis reviewed the literature from 1907 to 1986 and reported 37 cases of acute porphyria with onset of symptoms in childhood [5]. These patients were predominantly males presenting before age 14 years, who had various manifestations,

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