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Axonal Polyneuropathy in a Man Treated for Pulmonary Cocci: A Case of Acute Intermittent Porphyrria

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 67
Final Diagnosis: Acute intermittent porphyria
Symptoms: Abdominal pain • bilateral thigh pain • weakness in all 4 limbs
Medication: Fluconazole
Clinical Procedure: —
Specialty: Hematology

Objective: Rare disease
Background: Acute intermittent porphyria (AIP) is a rare autosomal dominant disorder that is part of a group of acute porphyria disorders usually found in females of reproductive age. Although clinically there is low penetrance, with 90% of genetically diagnosed individuals never experiencing an acute flair, consequences of acute flairs may lead to devastating results. Debilitating paresis, seizures, respiratory failure, and even death may result from AIP. Early detection is key in preventing these devastating manifestations.

Case Report: A 67-year-old Hispanic man with a past medical history of pulmonary Coccidioides on fluconazole presented with bilateral thigh pain for 2 days. At baseline, the patient had no limitations, but now was limited to minimal walking due to his thigh pain subsequently progressing to diffuse weakness after the administration of IV Solumedrol. Over the next few months, EMG was notable for acute-on-chronic sensorimotor axonal denervation in upper and lower extremities, without evidence of myositis. Urine porphobilinogen was 58 mmol/L, which is 29 times the upper limit of normal. Treatment was started with hemin 4 mg/kg/day for 4 days.

Conclusions: Over our patient's clinical course, he was affected by a severe manifestation of repeated acute porphyria attacks, which started as anterior thigh pain and progressed to diffused weakness disproportionately affecting the muscles of the upper extremities. Although the patient was in his late 60's at the initial onset of AIP, his diffuse Coccidioides infection, use of azoles, and steroids likely contributed to his first AIP attack.

MeSH Keywords: Coccidioidomycosis • Polyneuropathies • Porphyrria, Acute Intermittent

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/917134>

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Background

Acute intermittent porphyria (AIP) is a rare autosomal dominant disorder that is part of a group of acute porphyria disorders usually found in females of reproductive age. Although of clinically low penetrance, with 90% of genetically diagnosed individuals never experiencing an acute flair, consequences of acute flairs may lead to devastating results. Debilitating paresis, seizures, respiratory failure, and death may all result from acute flairs. Polyneuropathy may be a confusing presenting symptom as it is hard to distinguish polyneuropathy secondary to AIP from that of Guillain-Barre syndrome (GBS), vitamin deficiencies, and toxin-induced nerve injury. As such, understanding and recognizing the symptoms consistent with AIP, prevention of flairs, and treatment can improve outcomes among these individuals.

Case Report

We report the case of a 67-year-old non-smoking Hispanic man with a past medical history of pulmonary *Coccidioides* infection, currently on Fluconazole, who presented with bilateral thigh pain of 2 days duration. Eleven days prior to admission, he was seen at Urgent Care for peri-umbilical abdominal pain resolving after the administration of normal saline, Simethicone, and Dicyclomine. There were several emergency and urgent care visits leading up to his current admission, during which he had an abdominal CT scan and basic laboratory testing, which were all negative for acute disease processes.

At baseline, the patient had no limitations in lower extremity movement, but now was limited to minimal walking due to bilateral thigh pain. He denied back pain, lower extremity weakness, constipation, and incontinence. No changes in urine were noted. A physical exam was notable for tenderness over the abdominal right lower quadrant, bilateral thighs, and right flank. He had normal strength and sensation throughout all extremities.

During his admission, in addition to thigh pain, he developed tenderness over his right forearm and was started on intravenous (IV) Solumedrol 20 mg due to a concern for polymyalgia rheumatica. After 1 dose of IV Solumedrol, his thigh pain improved; however, bilateral weakness of his hip extensor was noted. Over the next several days, he progressed to the point where he was unable to raise his arms over 90 degrees and became bed-bound due to proximal thigh weakness. An MRI scan of the lower extremities showed minimal focal muscle edema, with no evidence of myositis. There was progression of his weakness to involve multiple muscle groups over a period of days, most notably bilateral 1/5 strength on interosseous abduction, adduction, and flexion of all fingers and 2/5

Table 1. Important lab results on patient's admission, most notably a normocytic anemia, hyponatremia, and elevated liver enzymes. Urine porphobilinogen levels greater than 10 times the upper limits of normal confirmed the diagnosis.

Lab result	Patient's value	Normal range
Complete blood count (CBC)		
Hgb	11.7 g/dL	12.0–15.5 g/dL
Mean corpuscular volume	94.6 fL	80–100 fL
Complete metabolic panel (CMP)		
Sodium	129 mmol/L	135–145 mmol/L
AST	48 U/L	10–40 U/L
ALT	101 U/L	7–56 U/L
Others		
Creatinine kinase	121 mIU/mL	22–198 mIU/mL
ESR	69 mm/h	0–22 mm/h
Urine porphobilinogen	58 µmol/L	0–2 µmol/L

strength on wrist and arm extension and flexion. His thigh strength had also progressed, with 2/5 strength on hip flexion and extension bilaterally. Interestingly, ankle strength remained preserved throughout his admission.

Initial lab testing showed increased liver function tests (AST 48 U/L, ALT 101 U/L), normal TSH (3.1 U/mL), normal creatinine kinase (121 mIU/mL), and an elevated ESR of 69 mm/h. Hyponatremia and a normocytic anemia were noted, with a sodium of 129 mmol/L and hemoglobin of 11.7 g/dL (Table 1). Over the next month, additional testing results, including iron, lead, and a para-neoplastic panels, were all normal.

Three weeks after admission, a repeat MRI showed mild myositis involving the musculature of the hands. EMG was performed and was consistent with acute-on-chronic sensorimotor axonal neuropathy with active denervation in the upper and lower extremities, without evidence of myositis. At this time, the urine porphobilinogen test result was 58 µmol/L, which is 29 times the upper limit of normal (2 µmol/L). Treatment was started with hemin 4 mg/kg/day for 4 days. Throughout the rest of the hospitalization, he developed multiple complications leading to an ICU admission and subsequent death due to a retroperitoneal hemorrhage.

Discussion

Clinical symptoms

Acute intermittent porphyria (AIP) is due to a deficiency in the third enzyme, hydroxymethylbilane synthase (HMBS)/Porphobilinogen Deaminase (PBGD), in the heme biosynthesis pathway (Figure 1). AIP attacks may present in many ways, with gastrointestinal symptoms being the most common presenting sign. Abdominal pain, in particular, is present in 85–95% of cases and is the most sensitive sign [1]. A high index of suspicion is needed for correct diagnosis. A constellation of symptoms such as abdominal pain, autonomic dysfunction, hyponatremia, muscle weakness, or psychiatric symptoms in the absence of other obvious causes should raise clinical suspicion [2]. Of note, neuropathic symptoms usually develop within 1 month of the onset of pain symptoms [3]. As with this patient, neuropathic pain may involve the extremities, back, chest, neck, or head.

Differentiating the neuropathy of AIP and Guillain-Barre syndrome (GBS) may be confusing clinically, but there are some key features to be aware of. Unlike paresis from GBS, AIP typically affects the upper extremities rather than the ascending paralysis characteristic of GBS [4]. AIP also tends to present with focal weakness rather than global weakness. Nerve injury in both of these diseases may progress to proximal paresis, debilitating patients for months; the most devastating symptoms are convulsions and respiratory paralysis, which are seen in up to 20% of AIP patients [1]. Psychiatric symptoms are quite variable and include a spectrum of mood disorders, psychotic disorders, anxiety disorders, and sleep-wake disorders [3]. Other supporting characteristics include dark urine on exposure to sunlight, muscle weakness, new-onset hypertension, or recent initiation of porphyrogenic drugs [5].

Diagnosis and testing

Vital signs and laboratory assessment may be helpful in the diagnosis of AIP. Autonomic instability is often seen, and most patients present with hypertension and tachycardia. Hyponatremia has classically been found in AIP in up to 50% of cases, and is thought to be due to a mild form of SIADH [6]. Various case studies have also described mild transaminitis, although this is a topic of debate and not clearly described [7]. Normocytic anemia from reduced heme production is also often present [8].

Initial testing should begin with a Watson-Schwartz or Hoesch qualitative test, confirmed by quantitative testing. Urine PBG level greater than 5 times above the upper limits of normal is sensitive and specific for an acute attack and is usually elevated by 10-fold in acute attacks [8]. It is important to note PBG levels may be mildly increased in hepatic, hematologic, and

Figure 1. Heme biosynthesis pathway and AIP: Heme is produced in the mitochondria and cytoplasm of cells when Succinyl CoA and Glycine combine and undergo 8 important enzymic reactions, using Fe^{2+} in the final step. Heme acts on ALAS as a negative inhibitor. AIP results from defects in PBGD, the 3rd enzyme in the heme biosynthesis pathway. By not producing heme, there is overproduction of harmful intermediate byproducts. ALAS – 5-aminolevulinic acid synthase; ALAD – 5-aminolevulinic acid dehydratase; PBGD – porphobilinogen deaminase; UROS – uroporphyrinogen III synthase; UROD – uroporphyrinogen III decarboxylase; CPOX – coproporphyrinogen.

neurologic disease, and investigation of other causes should be undertaken, especially as an elevation of less than 5 times of normal is very non-specific for AIP [9].

Positive results should prompt further evaluation of quantitative urine ALA, urine porphyrin, serum porphyrin, and fecal porphyrin. This will help in differentiating between the most common types of porphyrias, as prognosis and recurrence vary [2]. Additionally, heavy metals, lead in particular, can mimic symptoms, and biochemical analysis in various porphyrias and levels should be checked. Confirmation can be made via plasma porphyrin emission spectrum testing and DNA analysis. The sensitivity of mutation analysis ranges from 90% to 100%, with about 400 HMBS gene mutations identified in the literature [2].

Treatment

The management of patients with AIP includes the following strategies: (1) treat with heme preparations; (2) symptomatic treatment of autonomic dysfunctions neuropathy and encephalopathy; (3) exclusion of precipitating factors; and (4) adequate nutrition and fluid therapy [2]. Guidelines for treatment vary by country [10]. UK and US guidelines recommend a high carbohydrate diet and supportive measures for mild

attacks during the first 48 hours [11]. Development of neurologic symptoms should prompt treatment with hemin, as this may decrease hospital stays and stop the progression of neuropathy [9,12]. Administration of hemin can reduce the levels of metabolically toxic byproducts of heme production. Hemin is infused daily for 3–4 consecutive days (3–4 mg/kg/day). A prolonged course may be needed if symptoms continue. New treatment options are being developed, including a phase 1 RNA interference therapy, which, among other things, showed a reduce rate of porphyria attacks [13].

Only the minority of patients have recurrent attacks [14]. Physicians play an important role in counselling on diet, limiting fasting, and avoiding porphyrogenic medication to prevent recurrent attacks. A guide to drug safety can be found on the Porphyria Drug Safety Finder website at www.porphyr-iadrugs.com.

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Conclusions

Over this patient's clinical course, severe manifestations of repeated acute porphyria attacks were seen, with weakness starting as anterior thigh pain and progressing to diffused weakness disproportionately affecting the muscles of the upper extremities. Of note, his abdominal pain was the first clinical sign of a porphyria attack, occurring 2 weeks before his weakness developed, representing the most sensitive sign of an AIP attack. Although the patient was in his late 60's at the initial onset of AIP, there were many inciting factors which led to the manifestation of his otherwise phenotypically silent disease, most notably the pulmonary *Coccidioides* infection, use of an azole medication, and possible exacerbation by steroid use and dehydration. An increased awareness of the clinical symptoms and possible precipitants of AIP may have led to prevention of multiple acute attacks.

Conflict of interest

None.