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ACUTE INTERMITTENT PORPHYRIA MIMICKING SEVERE COPROSTASIS IN A PATIENT ON OPIOID MAINTENANCE THERAPY

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ABSTRACT

Introduction: Acute intermittent porphyria (AIP) is a rare hereditary metabolic disorder in haem biosynthesis that presents with severe abdominal pain. Attacks may be triggered by caloric deprivation. Diagnostic delay is common and reflects non-specific clinical presentations, the rarity of the disease and cognitive biases in clinical decision-making.

Case description: A 30-year-old woman with opioid and benzodiazepine use disorder presented with abdominal pain and constipation and was initially treated for opioid-induced constipation. Persistent symptoms and hyponatraemia prompted further evaluation, revealing markedly elevated urinary porphyrin precursors. She was diagnosed with AIP and treated with intravenous hemin and high-carbohydrate therapy.

Discussion: This case illustrates the diagnostic challenge of AIP when plausible alternative explanations such as opioid-induced constipation are present. Persistent symptoms and hyponatraemia due to SIADH served as key clues prompting diagnostic reassessment. Diagnostic overshadowing may have contributed to delayed recognition in the context of substance use disorder. Concurrent severe malnutrition with caloric deprivation likely triggered the attack via accumulation of neurotoxic haem precursors, underscoring the importance of diagnostic flexibility in atypical or non-resolving cases.

Conclusion: This case underscores the need to consider AIP in patients with severe abdominal pain and atypical clinical courses.

KEYWORDS

Acute intermittent porphyria, abdominal pain, substance use disorder, SIADH

LEARNING POINTS

- Acute intermittent porphyria (AIP) can present as opioid-induced coprostasis, increasing the risk of diagnostic anchoring and delay.
- Coexisting factors (opioid therapy, psychiatric comorbidity, malnutrition) may act simultaneously as triggers, mimics and sources of cognitive bias.
- Reconsidering the initial diagnosis in atypical or non-resolving cases is essential to counter cognitive bias and improve outcomes in rare but treatable conditions.

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INTRODUCTION

Porphyrias comprise a group of eight metabolic disorders affecting the haem biosynthesis pathway, each resulting from dysfunction of a distinct enzymatic step[1]. The eight porphyrias are classified into two major categories based on clinical presentation: acute porphyrias and cutaneous porphyrias. Acute intermittent porphyria (AIP) is the most common acute form and has an estimated prevalence of symptomatic disease of approximately 1 in 100,000[2]. It predominantly affects women (80–90%) of reproductive age, with onset most commonly occurring between 15 and 50 years and a peak in the second to third decades[1,2]. AIP is an inherited disorder of haem biosynthesis caused by partial deficiency of hydroxymethylbilane synthase (HMBS), leading to accumulation of the neurotoxic porphyrin precursors delta-aminolevulinic acid (ALA) and porphobilinogen (PBG).

CASE DESCRIPTION

A 30-year-old woman with a history of persistent intravenous drug use presented to the emergency department with severe abdominal pain (VAS 9/10) and vomiting for three days. The abdominal pain involved the entire abdomen; it was continuous and persisted at night. She reported constipation with absence of bowel movements for 10 days.

Vital signs on admission were within normal limits (heart rate 78 beats/min; blood pressure 135/78 mmHg; temperature 36.5°C; respiratory rate 24 breaths/min). On physical examination, the patient was severely underweight (BMI 13.4 kg/m^2; height 175 cm, weight 41 kg). Abdominal examination revealed a soft, non-distended abdomen with mild, diffuse tenderness on palpation, without guarding or signs of peritoneal irritation.

Past medical history included a diagnostic laparoscopy with appendectomy 12 year prior to presentation as well as several emergency department visits for abdominal or back pain, during which no somatic cause was identified, and a somatoform disorder was suspected.

The patient was on opioid maintenance therapy, consisting of a total daily dose of 50 mg levomethadone and 340 mg diacetylmorphine (170 mg intravenously twice daily), corresponding to approximately 1,300 mg oral morphine equivalents per day. Concomitant sedative medication included clonazepam 4 mg/day and zolpidem 20 mg/day. In Switzerland, opioid maintenance therapy is widely implemented and well established[3]. In this case, however, the high doses were associated with recurrent episodes of reduced vigilance, particularly following substance use or periods of agitation prior to administration, resulting in a challenging clinical assessment during ward rounds. Administration of naloxone was not required.

Blood tests revealed hypo osmolar hyponatraemia, with a serum sodium level of 126 mmol/l and a serum osmolality of 272 mmol/kg. Urine analysis showed an elevated urine sodium concentration of 207 mmol/l and a urine osmolality of 848 mmol/kg. These findings were consistent with the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Urinalysis additionally revealed ketonuria, consistent with a catabolic metabolic state due to reduced nutritional intake. Due to severe abdominal pain of unclear aetiology and a history of prior abdominal surgery, computed tomography was performed, revealing marked faecal loading consistent with opioid-induced coprostasis.

Medical management was complex and resource-intensive due to psychosocial factors, addressing laxative therapy, hyponatraemia, nutritional support, pain control, optimisation of opioid substitution and social planning for post-discharge housing. Ongoing abdominal pain and the absence of a clinical response to laxative therapy led to a reassessment of the initial diagnosis of severe coprostasis. Analysis of a spot urine sample demonstrated markedly elevated delta-ALA, 85.3 µmol/mmol creatinine; reference <2.5) and porphobilinogen (PBG; 68.4 µmol/mmol creatinine; reference <1.25), confirming the diagnosis of AIP. Treatment with hemin (120 mg/day; 3 mg/kg) combined with high-calorie enteral nutrition led to pain relief, resumption of oral intake and normalisation of serum sodium levels.

DISCUSSION

AIP typically presents with severe abdominal pain accompanied by nausea, vomiting and constipation, despite unremarkable imaging findings. Severe or untreated attacks may be complicated by predominantly motor axonal neuropathy, as well as neuropsychiatric symptoms including anxiety, confusion or seizures. Laboratory findings are often unremarkable, apart from hyponatraemia. Although the term porphyria implies purple-coloured urine, freshly voided urine in patients with AIP may appear normal, as the haem precursors delta-ALA and porphobilinogen are colourless and only darken upon light exposure at room temperature[1,2].

This case illustrates four clinically relevant aspects of AIP:

First, caloric deprivation represented a key precipitating factor. In this case, the patient was severely malnourished (BMI 13.4 kg/m^2), with reduced caloric intake and ketonuria consistent with a catabolic state, likely related to substance use disorder and unstable living conditions. Caloric deprivation and fasting are recognised triggers for acute attacks in AIP and were the most likely precipitating factors in the present patient. Fasting upregulates hepatic ALAS1, the rate-limiting enzyme in haem synthesis, increasing toxic haem precursors that drive neurovisceral symptoms. Accordingly, a high-carbohydrate diet represents a key strategy for preventing exacerbations of porphyria[2]. In addition to caloric deprivation, acute AIP attacks may be triggered by porphyrinogenic medications including barbiturates, sulfonamide antibiotics, certain antiepileptic drugs and hormonal agents. Hormonal fluctuations, particularly during the luteal phase of the menstrual cycle, as well as physiological stressors such as infections, surgery

and excessive alcohol consumption, are also recognised precipitants[2,4].

Second, hyponatraemia represents an important clinical clue to AIP and is predominantly caused by the SIADH[5]. It frequently occurs during acute AIP attacks, with reported prevalence rates ranging from 25 to 61%[1]. In this context, generalised tonic–clonic seizures occur in up to 20–30% of acute AIP attacks and are often associated with severe hyponatraemia due to SIADH, which may significantly influence prognosis[6]. The development of SIADH is likely multifactorial, involving direct stimulation of antidiuretic hormone secretion by severe abdominal pain and secondary activation of the renin–angiotensin system in the setting of paralytic ileus, that frequently accompanies acute attacks[5].

Third, delayed diagnosis remains a major clinical challenge in AIP. In an observational study including 108 patients with acute porphyrias, of whom 90 had AIP, the diagnosis was delayed by a mean of 15 years[7]. This prolonged diagnostic latency can be explained by several factors. Clinical manifestations are largely non-specific and overlap with common conditions, making rare diseases unlikely to be considered in the emergency setting and often leading to initial misdiagnosis (e.g. unnecessary appendectomy or cholecystectomy)[7].

The diagnosis is further complicated by the fact that most patients with AIP experience only one or a few attacks during their lifetime, with more than 90% of symptomatic patients falling into this category[1,2]. In contrast, a small minority – 3–8% of patients – develop recurrent attacks, defined as four or more attacks per year[2]. Diagnostic testing for AIP is straightforward and should be performed at a low threshold when clinical suspicion arises. A spot urine sample is sufficient, as porphyrin precursor levels are markedly elevated during acute attacks, and samples must be protected from light to ensure analytical reliability[1,2].

Finally, this case illustrates the impact of diagnostic overshadowing on clinical decision-making. Diagnostic overshadowing refers to a phenomenon in which individuals with mental illness receive inadequate or delayed medical care due to misattribution of physical symptoms to their psychiatric condition, in this case substance use disorder[8]. In a study involving 39 emergency department clinicians, 77% reported at least one incident in which the presence of a psychiatric disorder led to misdiagnosis or delayed treatment[9]. Pain during acute attacks of AIP is often severe and poorly responsive to opioids[4]. Together with the absence of objective findings, this may lead to misattribution of symptoms to psychosomatic causes or substance use disorder. The risk of diagnostic overshadowing is particularly increased in patients with complex clinical presentations or medically unexplained symptoms, which are more likely to be attributed to underlying mental illness.

CONCLUSION

This case underscores the need to consider AIP in patients with severe abdominal pain and atypical clinical courses. Reconsidering the initial diagnosis in atypical or non-resolving cases is essential to counter cognitive bias and improve outcomes in rare but treatable conditions.

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