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CASE REPORT

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An easily overlooked disease in the early stages: acute intermittent porphyria

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Abstract

Background Acute intermittent porphyria (AIP) is an inherited metabolic disorder that can affect the central, peripheral, and autonomic nervous systems. Therefore, its clinical presentation is diverse and may include abdominal pain, as well as neurological and psychiatric symptoms. Abdominal pain, though a common initial symptom, is often overlooked or misdiagnosed due to its lack of specificity. But early diagnosis and treatment are crucial, as untreated symptoms can progressively worsen.

Case presentation This report describes a 26-year-old male who was admitted due to seizures and PRES changes on brain magnetic resonance imaging (MRI) for over 30 days, along with a 20-day history of sudden proximal weakness in both upper limbs. Additionally, he experienced recurrent vomiting and excessive sweating. Five months before admission, he was diagnosed with a urinary tract infection due to severe abdominal pain and tea-colored urine, and the symptoms resolved after treatment. Multiple examinations before and after admission consistently revealed hypertension, tachycardia, and hyponatremia. Electromyography (EMG) suggested axonal damage to the motor nerves of both upper limbs. During hospitalization, the patient's upper limb weakness progressively worsened, and around 12 days after admission, he began experiencing recurrent episodes of abdominal pain and limb pain. Then he was diagnosed with AIP based on the detection of positive PBG in urin and the identification of a c.445C > T (R149X) mutation in the hydroxymethylbilane synthase (HMBS) gene.

Conclusions This case unveils that AIP is a disease that can be easily overlooked in its early stages. When a patient presents with central, peripheral, or autonomic nervous system symptoms and common causes are ruled out, AIP should be considered as a potential diagnosis. Additionally, unexplained symptoms such as abdominal pain, changes in urine color, hyponatremia should also raise suspicion. Timely screening through biochemical testing, including measurement of ALA, PBG and porphyrins in a random urine sample, is recommended. Timely administration of intravenous hemin and avoidance of precipitating factors can lead to a better prognosis.

Keywords Acute intermittent porphyria, Porphyric neuropathy, PRES, Seizures, Case report

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Background

Porphyrias are inherited metabolic disorders characterized by defects in the enzymes involved in heme biosynthesis, leading to the abnormal accumulation of porphyrins or their precursors [1]. These disorders can be classified into eight types based on the specific enzyme defect. Among them, acute intermittent porphyria (AIP), an autosomal dominant inherited disease, is caused by mutations in the hydroxymethylbilane synthase (HMBS) gene, which encodes the third enzyme in the heme biosynthesis pathway [2]. The prevalence of pathogenic variants in the HMBS gene is approximately 1 in 1700, with about 0.5–1% of carriers in the general population developing clinically overt AIP with acute porphyria attacks [3, 4]. Female patients with AIP experience a higher proportion of acute exacerbations compared to male patients. These attacks are commonly triggered by factors such as progesterone elevations during the luteal phase of the cycle, progesterone-containing oral contraceptives, cytochrome P450-inducing drugs, stress, alcohol consumption, smoking, fasting, strict carbohydrate-restrictive diets, or infectious diseases. Factors that precipitate acute attacks induce the synthesis of δ-aminolevulinic acid synthase 1 (ALAS1), the first and rate-limiting enzyme in the heme biosynthetic pathway, by directly promoting its transcription through mechanisms such as dieting or fasting or by increasing hepatic heme demand or consumption due to factors like drug use or illness [5]. When hepatic ALAS1 is induced, the deficiency in HMBS becomes the rate-limiting step in hepatic heme biosynthesis, leading to a significant accumulation of the potentially neurotoxic porphyrin precursors aminolevulinic acid (ALA) and porphobilinogen (PBG) [6].

AIP is an inherited metabolic disorder that can affect the central, peripheral, and autonomic nervous systems. Therefore, its clinical presentation is diverse and may include abdominal pain, as well as neurological and psychiatric symptoms. Abdominal pain, though a common initial symptom, is often overlooked or misdiagnosed due to its lack of specificity. Thus, early diagnosis and treatment are challenging. Herein, we report a case of a male patient with AIP who initially presented with seizures and imaging findings consistent with PRES, followed by the onset of bilateral proximal upper limb weakness. Notably, the patient had a prior history of abdominal pain, which had been misdiagnosed as a urinary tract infection. The patient lacked an accurate diagnosis and appropriate treatment in the early stages, resulting in progressively worsening symptoms that ultimately affected the central, peripheral, and autonomic nervous systems.

Case presentation

On April 2, 2024, a 26-year-old male was admitted to our department with a one-month history of sudden loss of consciousness accompanied by generalized body convulsions, fixed gaze, and foaming at the mouth, as well as a twenty-day history of bilateral upper limb weakness. There was no family history of any medical illness. Five months prior to admission, the patient developed severe right lower abdominal pain, darkened urine, and recurrent vomiting. A urinary tract infection was considered, and after receiving corresponding treatment, the abdominal pain and vomiting resolved within two weeks. One month ago, he had two episodes of generalized tonic–clonic seizures, along with recurrent vomiting and profuse sweating. The subsequent admission examination revealed hypertension, sinus tachycardia, and hyponatremia. Based on the asymmetrical scattered patchy abnormal signals in the bilateral parieto-occipital cortical areas and cerebellar hemispheres observed on brain magnetic resonance imaging (MRI), he was diagnosed with PRES (Fig. 1). After receiving treatment with antihypertensive therapy, levetiracetam for seizures, and metoclopramide as an antiemetic, no further seizures occurred. Approximately 20 days before, the patient suddenly noticed an inability to lift either arm above shoulder level, accompanied by proximal upper limb muscle atrophy and strength graded as 3/5. Additionally, he experienced recurrent vomiting and excessive sweating. Follow-up brain MRI indicated that most lesions had disappeared, leaving only a few dot-like abnormal signals in the right parieto-occipital lobe (Fig. 2). Blood tests including creatine kinase revealed no significant abnormalities. However, liver function tests were abnormal, with alanine aminotransferase levels at 145 U/L (normal range: 9–50 U/L) and aspartate aminotransferase levels at 81 U/L (normal range: 15–40 U/L). The electromyography (EMG) conducted at an outside hospital suggested acute axonal damage to the motor fibers of the bilateral median, ulnar, radial, musculocutaneous, and axillary nerves. One week after the onset of weakness, a lumbar puncture was performed, and the patient's cerebrospinal fluid (CSF) biochemical analysis and routine tests were all normal.

The physical examination upon this admission revealed significant atrophy of the bilateral upper limb muscles, particularly the biceps brachii, deltoid, supraspinatus, and infraspinatus (Fig. 3). Proximal muscle strength in both upper limbs was assessed at 3/5, distal strength was 4/5, and lower limb strength was 5/5, with normal deep tendon reflexes. And sensory system examination was normal. Examination still revealed autonomic hyperactivity primarily characterized by hypertension (166/125 mmHg), sinus tachycardia (112 beats per

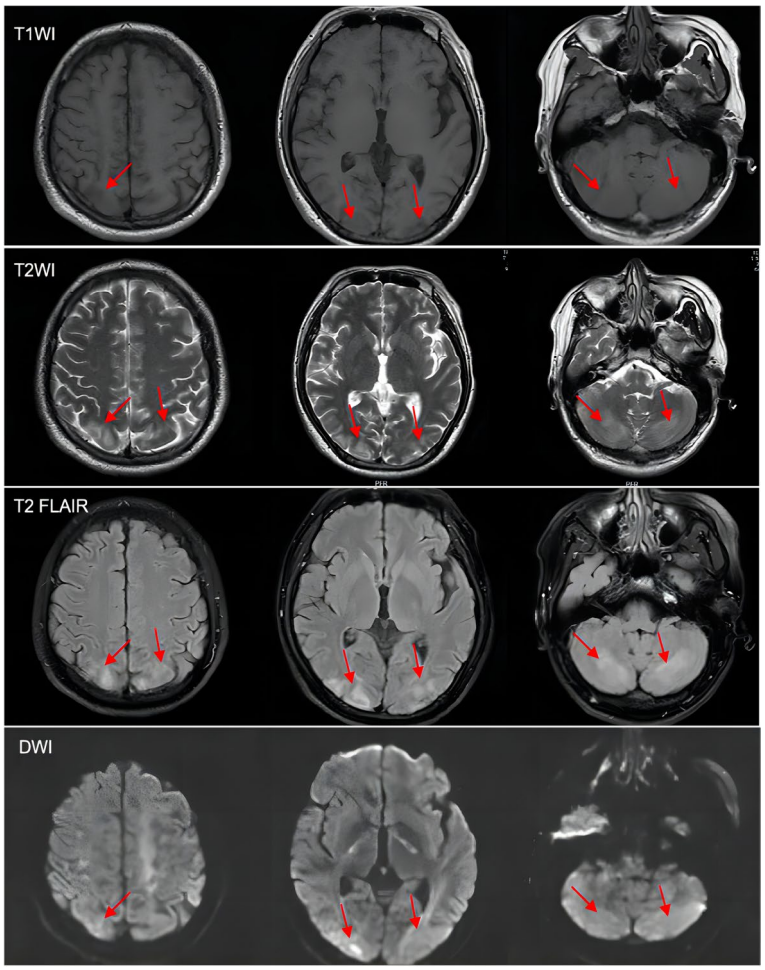

Fig. 1 The brain MRI conducted on February 28, 2024, revealed asymmetrical, scattered patchy abnormal signals in the bilateral parieto-occipital cortical areas and cerebellar hemispheres. These signals were hypointense on axial T1-weighted MRI and hyperintense on axial T2-weighted and fluid-attenuated inversion recovery (FLAIR) MRI sequences. The diffusion-weighted images (DWI) localized high signal intensity

minute), and hyponatremia. Brain MRI showed no significant abnormalities compared to the second brain MRI (Fig. 4). The follow-up electromyography (EMG) showed indicated peripheral motor axonal neuropathy, with significant involvement of the upper limbs, particularly pronounced in the proximal regions compared to the distal regions (Supplementary Table 1). His proximal upper limb weakness was assessed as motor axonal neuropathy, raising an initial high suspicion of Guillain-Barré syndrome (GBS). But there was no improvement in his proximal upper limb weakness after receiving intravenous immunoglobulin therapy at a dosage of 0.4 mg/kg/d for 5 days.

Approximately 10 days after admission, the patient began experiencing recurrent limb pain, followed by the gradual onset of constipation, abdominal bloating, abdominal pain, and bowel obstruction in the subsequent days. At the same time, his proximal upper limb weakness gradually extended to the distal regions, leading to difficulty in holding objects steadily. Overall, the patient presented with central nervous system (CNS) manifestations, including PRES and seizures. The peripheral nervous system (PNS) involvement began with bilateral proximal upper limb weakness accompanied by muscle atrophy, which progressed to include bilateral distal upper limbs and both lower limbs. Additionally, the patient exhibited significant gastrointestinal symptoms and generalized pain including abdominal pain and limb pain. mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) and AIP were considered as possible diagnoses. However, no elevated lactate levels were detected after exercise, and muscle biopsy findings showed no ragged red fibers (RRFs) but indicated neurogenic damage, thereby ruling out MELAS

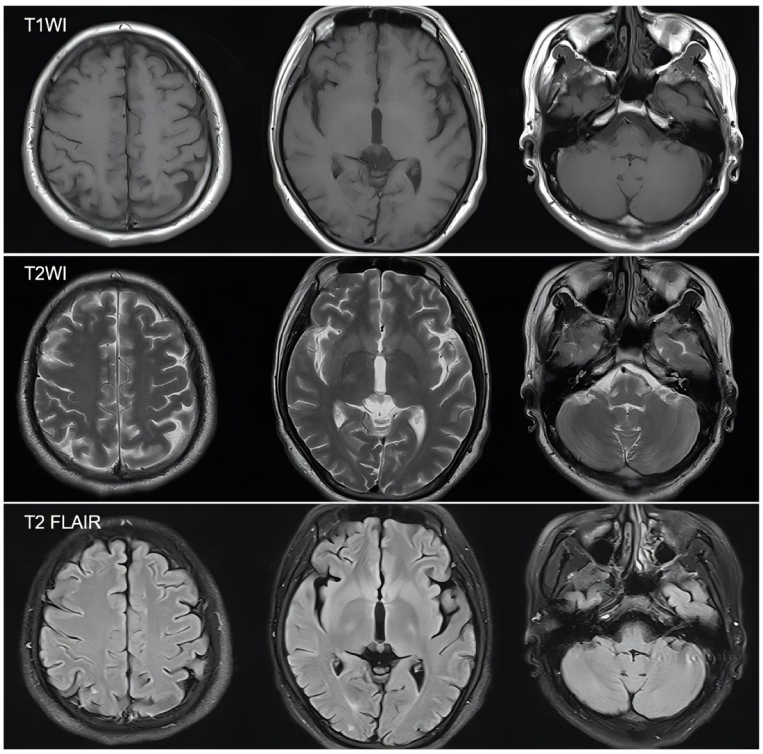

Fig. 2 A follow-up brain MRI conducted on March 15, 2024, indicated that most lesions had disappeared, leaving only a few dot-like abnormal signals in the right parieto-occipital lobe. These signals appeared hypointense on axial T1-weighted MRI and hyperintense on both axial T2-weighted MRI and axial FLAIR MRI

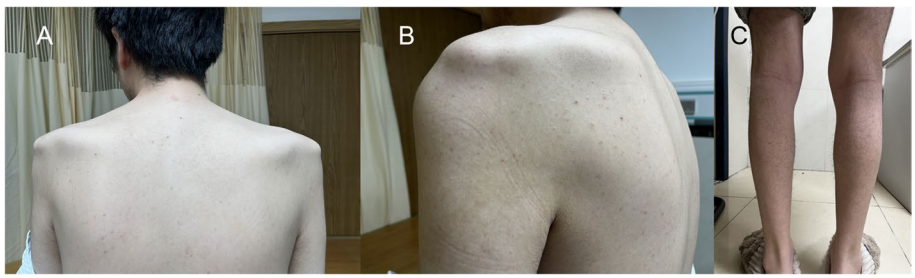

Fig. 3 **A** and **B** exhibited significant atrophy in the bilateral upper limb muscles, including the biceps brachii, deltoid, supraspinatus, and infraspinatus. In contrast, **C** indicated that the atrophy in the bilateral lower limb muscles was not obvious

and strongly supporting the diagnosis of AIP. On the 16th day after admission, due to the difficulty in obtaining hemin in China, carbohydrate-loading therapy was initiated. Approximately 20 days after admission, the diagnosis of AIP was confirmed by positive PBG in a urine sample, which was tested using the qualitative Watson-Schwartz method at PUMC, along with genetic testing that identified a c.445C > T (R149X) mutation in the HMBS gene.

The guideline recommends that acute attacks of AHP severe enough to require hospital admission should be treated with intravenous hemin [7]. Due to the fact that the demand for hemin is very low and hemin can only be obtained through importation, its purchasing process is extremely time-consuming. Only carbohydrate-loading therapy can be temporarily administered. After one week of carbohydrate-loading therapy with oral glucose administration, a follow-up EMG again revealed a further progression of peripheral motor axonal neuropathy (Supplementary Table 2). After nearly 20 days of carbohydrate-loading therapy with intravenous glucose, his limb weakness worsened, and he developed lower back weakness, rendering him bedridden and unable to sit or stand. He also had difficulty swallowing and experienced

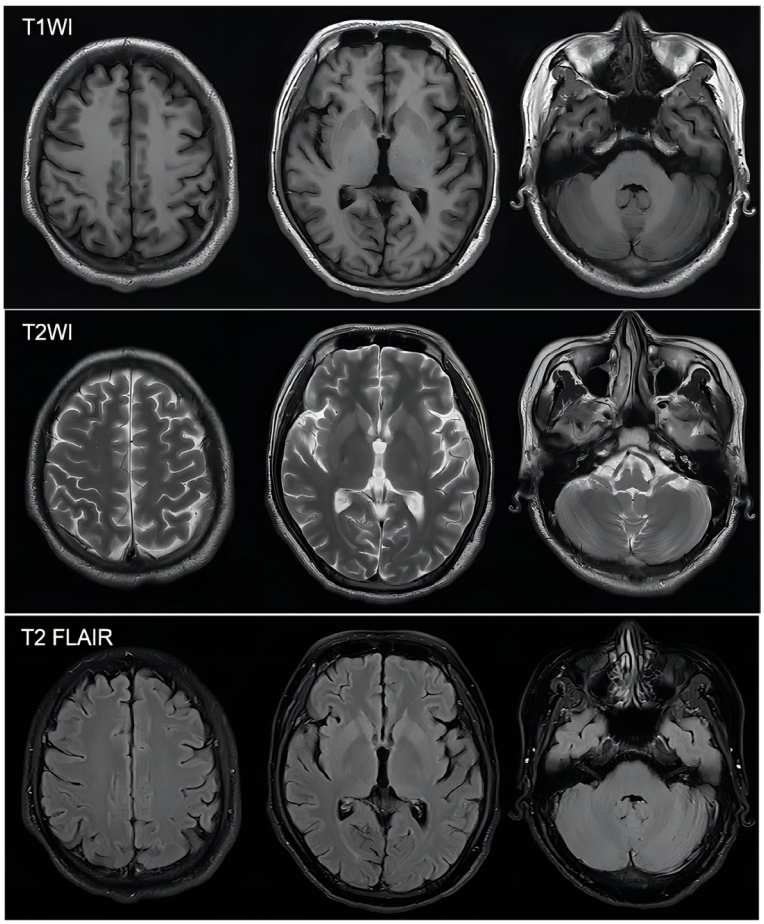

Fig. 4 A third brain MRI conducted on April 10, 2024, revealed no abnormal lesions. The previously observed few single dot-like abnormal signals in the right parieto-occipital lobe had also disappeared

coughing episodes while drinking. Additionally, the patient exhibited psychiatric symptoms, including hallucinations, self-talk, and delusions. However, there was some improvement in his recurrent vomiting, bowel obstruction, and intermittent abdominal pain. Five weeks after admission, the patient began receiving a central intravenous infusion of heme arginate (Normosang) at a dose of 4 mg/kg body weight once daily, imported from abroad, in conjunction with carbohydrate-loading therapy through intravenous glucose administration at another hospital. After 8 days of treatment, the urine color normalized, and the psychiatric symptoms, recurrent vomiting, bowel obstruction, and intermittent abdominal pain resolved. The patient was also able to stand independently. Two months later, the patient was able to walk slowly with assistance, and a muscle EMG was re-examined. The results are detailed in Supplementary Table 3.

Three months after admission, the patient experienced generalized muscle pain, abdominal pain, mild nausea, and ted-colored urine. An acute episode of porphyria was suspected and the patient received a daily hemin infusion for 4 days. Following the infusion, the symptoms resolved. By four months, the patient's blood pressure and heart rate had returned to normal. Four and a half months after admission, the patient was able to walk several hundred meters independently and could move his arm in a circular motion. However, he still exhibited wrist drop and was unable to straighten his fingers (Fig. 5).

Discussion

We present a AIP case of a 26-year-old male whose symptoms progressively worsened due to the absence of an accurate diagnosis and appropriate treatment in the early stage, ultimately involving his CNS, PNS, and autonomic nervous system (ANS). His primary manifestations were seizures, PRES, and peripheral neuropathy and was sequentially misdiagnosed with PRES, GBS, and MELAS. We conducted a literature search on PubMed and Web of Science and found a total of 10 previously reported

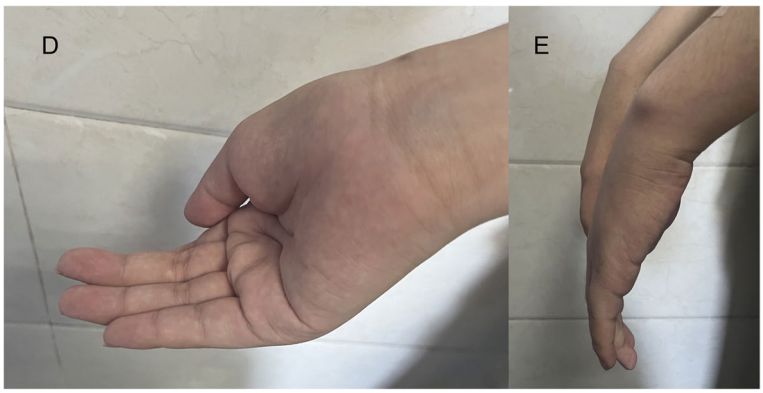

Fig. 5 **D** showed that the patient was unable to straighten his fingers. **E** showed that he had wrist drop and was unable to extend his wrists

cases of AIP patients with symptoms including seizures, PRES, and peripheral neuropathy. We have summarized these 10 cases in Table 1. Among the 10 cases, 4 were male, with ages ranging from 11 to 60 years, although the majority of patients were approximately 25 years old. In the majority of cases, there are delays in the diagnosis and treatment of AIP, during which time the patient's symptoms progressively worsen. More than half of the patients had identifiable triggers. In female patients, elevated progesterone levels during the luteal phase of the menstrual cycle or pregnancy were the primary triggers. Among the six female cases, four developed symptoms during pregnancy, premenstrual periods, or postpartum. Symptoms improved significantly in most cases when these clear triggers were removed. Abdominal pain was the most common presenting symptom, occurring in 8 out of the 10 cases. For patients with such prominent symptoms, treatment with hemin is the optimal choice or glucose loading if hemin is not initially available. The majority of patients had a favorable prognosis, with mild residual symptoms, primarily manifesting as limb weakness. A small subset of patients experienced disease relapse, with 2 out of the 10 cases documenting recurrence.

These cases reveal that AIP is a disease that can easily be overlooked in its early stages. The early symptoms of AIP are nonspecific, making early diagnosis challenging. However, early diagnosis is crucial, as clinical symptoms may progressively worsen before appropriate treatment is administered. Therefore, it is essential to strengthen screening for AIP in cases with unclear diagnoses. When a patient presents with central, peripheral, or autonomic nervous system symptoms, and common causes are ruled out, AIP should be considered as a potential diagnosis. Particular attention should be given to patients exhibiting significant autonomic hyperactivity symptoms, such as hypertension, tachycardia, excessive sweating, constipation, intestinal obstruction, diarrhea, nausea, vomiting, and bladder dysfunction, as almost all AIP patients present with autonomic neuropathy. In addition, many AIP patients also exhibit nonspecific symptoms such as abdominal pain, tea-colored urine, and hyponatremia, which should also raise suspicion. The history of abdominal pain in suspected AIP patients may need to be traced back several months or even years. Timely biochemical testing, including measurements of ALA, PBG and porphyrins in random urine samples, is recommended, as early testing aids in the diagnosis and treatment of AIP.

Signs of CNS involvement in this case include PRES, seizures, and psychiatric symptoms [3]. PRES is a clinical and radiological condition characterized by reversible subcortical cerebral vasogenic edema [18]. The pathogenesis of PRES involves endothelial dysfunction, compromising the integrity of the blood–brain barrier and resulting in capillary leakage. This process can be triggered by hyperperfusion resulting from impaired autoregulation and, in some instances, focal vasoconstriction [19]. During porphyric attacks, several mechanisms may independently or collectively contribute to the development of PRES, including dysfunction of hemoproteins due to heme deficiency, elevated levels of the potentially neurotoxic ALA, arterial vasospasm due to autonomic involvement, decreased nitric oxide production, and hyponatremia [20]. Common presentations of PRES include seizures, headaches, altered mental status, visual disturbances, and other focal neurological deficits. Neuroimaging typically reveals bilateral vasogenic edema, primarily in the parieto-occipital regions, which is usually reversible with appropriate treatment. Affected areas typically appear hyperintense on T2-weighted and FLAIR MRI sequences and hypointense on T1-weighted MRI. Diffusion-weighted imaging (DWI) demonstrates low signal intensity in these regions, indicating nonrestricted diffusion, which is corroborated by high signal intensity on apparent diffusion coefficient (ADC) maps

Table 1 Review all reported AIP cases with symptoms including seizures, PRES, and peripheral neuropathy

Case	Author (year)	Age/Sex	Inducement	Initial symptom	CNS	PNS	ANS	gene	Treatment	Recurrence	Prognosis
1 [8]	M Celik 2002	20/F	After a caesarean section	Seizure	Seizure, disturbance of consciousness, seizure, visual hallucinations, PRES	Quadriplegic, hoarseness, facial diplegia, respiratory failure	Tachycardia, hypertension , hyponatremia	NA	NA	NA	Recovered spontaneous respiration after 3 months but remained quadriplegic
2 [9]	C Gürses 2008	25/F	NA	Abdominal pain, dysuria	Generalized tonic–clonic seizure, disturbance of consciousness, PRES	Quadriplegic	Tachycardia, hypertension , hyponatremia	NA	NA	Seizures recurred after 5 months	Walk slowly but without assistance, and still has mild limbs weakness after 18 months
3 [10]	Feng-Chih Shen 2008	60/M	NA	Abdominal pain, nausea, vomiting	Generalized motor seizure, PRES, acute confusional state including disorientation, psychosis, and agitation	Quadriplegic, facial diplegia, hoarseness, respiratory failure	Tachycardia, hypertension, acute pancreatitis	NA	Received intravenous glucose therapy at a rate of 10 g/h for 2 days (still developed) and hematin (4 mg/kg/day) was administrated for another 14 days	NA	Mild residual polyneuropathy was noted after 4 months
4 [11]	Almazán, MCD 2012	29/M	NA	Abdominal pain, nausea, vomiting, Constipation, dark colored urine	tonic–clonic seizure, consisting of drowsiness, incoherent speech, hallucinations, PRES	Multilevel axonal polyneuropathy	abdominal pain, hypertension, tachycardia, hyponatremia	A N272H mutation in the HMBS gene	Treatment with glucose and hemin	NA	At discharge from the ICU after 15 days, only impaired tendon reflexes persisted
5 [12]	Smilu Mohanlal 2016	11/M	NA	Abdominal pain, generalized tonic–clonic seizure	seizure, PRES	Quadriplegic, respiratory muscle weakness, right Lower Motor Neuron (LMN) facial nerve palsy, IXth and Xth cranial nerve palsy (sensory motor axonal polyneuropathy)	Abdominal pain, hypertension , hyponatremia	NA	Treated symptomatically, physiotherapy and nutritional rehabilitation	NA	Quadriplegic resolved in over 6 months and no further attacks of abdominal pain and seizure

Table 1 (continued)

Case	Author (year)	Age/Sex	Inducement	Initial symptom	CNS	PNS	ANS	gene	Treatment	Recurrence	Prognosis
6 [13]	Mohammed Alqwaifly 2019	27/F	Pregnancy	Abdominal pain, nausea, vomiting	Seizure, PRES	Multilevel axonal polyneuropathy	Abdominal pain, nausea, vomiting, hyponatremia	NA	Received injection of hemin intravenously and supportive therapy	NA	Resolution of weakness and seizures but had a spontaneous abortion
7 [14]	Yang Yang 2020	36/F	Pregnancy	Abdominal pain	Seizure, blurred vision, impaired speech, memory impairment, PRES	Quadriplegia	Abdominal pain	c.405-406delAA in exon 8 of the HMBS gene	Treated by intravenous infusion of 300 g/day of glucose	NA	Complete recovery was achieved after 2 weeks of conservative treatment and then terminate the pregnancy
8 [15]	Mohamed Ahmed Ahmed 2020	23/M	Drug	Abdominal pain, tachycardia, hypertension	Generalized tonic–clonic seizure, PRES, psychiatric symptom including depression and anorexia nervosa	Motor axonal polyneuropathy	Abdominal pain, tachycardia, hypertension	NA	Treated with a high carbohydrate diet, a continuous intravenous infusion of 10% dextrose solution delivered by a nasogastric tube and hemin therapy	NA	The symptoms had resolved within 2 weeks
9 [16]	Vachiravit Sriprakoon 2022	14/F	Fasting	Abdominal pain, nausea, vomiting	Generalized tonic–clonic seizure, PRES	Quadriplegia	Abdominal pain, nausea, vomiting, hypertension	a c.517C > T (p.Arg173Trp) mutation in the HMBS gene	Received intravenous glucose therapy and a high carbohydrate diet	1 to 2 acute attacks per year	Returning to normal at 8 weeks after the onset of the acute attack

Table 1 (continued)

Case	Author (year)	Age/Sex	Inducement	Initial symptom	CNS	PNS	ANS	gene	Treatment	Recurrence	Prognosis
10 [17]	Jie Lin 2024	23/F	Menstruation	Insomnia, unresponsiveness	Seizures, PRES, insomnia, unresponsiveness, psychiatric symptoms, depression, irritability	Quadriplegic, dysphagia, shortness of breath (sensory motor axonal polyneuropathy)	Abdominal pain, lumbago, urination difficulties, intestinal obstruction	a c.518G > A (p.R173Q) mutation in the HMBS gene	Progesterone injections of 20 mg once daily intramuscularly to delay menstruation, injections of glucose 150 g twice daily intranasally and intermittent high-sugar diet after discharge	NA	Stand on her own and could breathe on her own, but emotional irritability

[20]. Seizures are relatively common in patients with AIP, with a prevalence of 10%–20%. The types of seizures observed in AIP include myoclonic jerks, tonic–clonic seizures, partial seizures that may generalize, and generalized seizures [21]. Severe hyponatremia, caused by the syndrome of inappropriate antidiuretic hormone secretion (SIADH) resulting from damage to the hypothalamic-hypophyseal tracts due to excess PBG and ALA, is considered a pathogenic factor for seizures [22, 23]. Seizures are the most common presenting symptom of PRES, and vasogenic edema leading to PRES-like changes is suggested as an alternative pathophysiological mechanism of seizures in AIP. Furthermore, ALA, potentially toxic to neuronal and glial cells and structurally similar to γ-aminobutyric acid (GABA), can impair GABA function by acting as a partial agonist or antagonist at GABA receptors, thereby contributing to the occurrence of seizures [24].

Peripheral neuropathy is a common complication of AIP, affecting 10% to 40% of cases. This neuropathy typically emerges 4 to 12 weeks after the onset of other clinical features, such as abdominal pain and CNS symptoms, with severity peaking 3 to 4 weeks later [6]. In acute porphyric neuropathy, motor symptoms are more prominent than sensory symptoms, mainly starting in the proximal muscles of the upper extremities [25]. In severe cases, these conditions can progress to quadriplegia and respiratory insufficiency, occasionally necessitating mechanical ventilation [5]. Ana Ponciano et al., Wu et al., DYJAS et al., and Fltigel et al. have provided detailed records and analyses of the electromyographic characteristics of peripheral neuropathy in porphyria [26–29]. This type of neuropathy generally presents as an acute to subacute, motor-predominant axonal neuropathy [27]. Sensory nerve conduction studies reveal minimal abnormalities compared to motor nerve conduction studies [29]. Additionally, chronic porphyric neuropathy, characterized by symptoms and signs lasting more than 6 weeks, is more likely to present as distal sensorimotor polyneuropathy [28]. In the few cases that progress to chronic porphyric peripheral neuropathy, later-stage electromyography may reveal sensory nerve damage and demyelinating changes. Most instances of porphyric peripheral neuropathy have a favorable prognosis, with near-complete recovery typically achieved within one year of onset [28]. In our cases, based on three follow-up electromyograms (Supplementary Table 1–3), we noted that the patient's motor-predominant axonal neuropathy began in the proximal upper limbs, extended to the distal upper limbs, and progressed to the lower limbs. Furthermore, as the disease advanced, sensory nerves also showed damage by the third EMG follow-up, as indicated by a decrease in their wave amplitude. The accumulation of ALA may cause impairment of the axonal Na + /K + pump function, leading to changes in membrane potential and subsequent axonal degeneration. This mechanism aligns with the rapid recovery observed in acute motor paresis with axonal neuropathy on electrophysiological testing [30]. An alternative hypothesis posits that axonal degeneration may occur due to reduced energy capacity resulting from decreased heme production caused by deficiencies in enzymes of the heme biosynthesis pathway [31].

The patient's ANS symptoms include abdominal pain, abdominal distention, constipation, intestinal obstruction, diarrhea, nausea, vomiting, bladder dysfunction, unusual sweating, tachycardia, and hypertension. These manifestations of autonomic neuropathy are associated with splanchnic autonomic dysfunction, as evidenced by symptom relief after ganglionic blockade and splanchnicectomy [19]. Additionally, autopsy findings reveal demyelination, axonal degeneration of the vagus nerve, and reduced density of sympathetic ganglia cells, highlighting significant ANS involvement [32]. One hypothesis suggests that increased serotonergic activity may be linked to autonomic dysfunction. Specifically, a decrease in the activity of the tryptophan-degrading enzyme tryptophan dioxygenase, due to heme deficiency in the liver, results in elevated tryptophan levels, which subsequently enhances serotonin (5-HT) production through the activation of tryptophan hydroxylase [24]. Moreover, excitation of the sympathetic nervous system results in increased catecholamine production, contributing to the manifestations of autonomic neuropathy. Abdominal pain is typically the earliest and most common symptom of AIP, often indicating the onset of an acute attack. This pain is hypothesized to arise from gastroparesis and disturbed intestinal motility caused by autonomic neuropathy, or possibly from intestinal ischemia due to vasospasms [31]. Autonomic cardiovascular manifestations, such as hypertension and tachycardia, are likely attributable to cardiovagal neuropathy or may be a response to visceral pain [33].

Environmental exposures and unidentified modifying genes play a significant role in AIP. In this case, we suspect that the patient's progressive worsening of symptoms may be attributed to metoclopramide, which was administered for vomiting during the course of the illness and has been reported in the literature to cause attacks in a few AIP patients [34]. The patient was found to have the c.445C > T (R149X) mutation in the HMBS gene. The R149X mutation is a nonsense mutation located in exon 9, first associated with AIP in Finland by Kauppinen et al. [35]. Studies suggest that the severity of clinical symptoms and the progression of AIP are mutation-specific [36]. A study on the clinical and biochemical characteristics and genotype–phenotype correlations in Finnish and

Russian porphyria patients revealed that individuals with the R149X mutation have a higher risk of acute attacks, an increased recurrence rate, and elevated urinary PBG excretion during remission, exceeding 30 μmol/L [37]. In the literature, there is a case report of a 23-year-old Black South African man with the R149X mutation who presented with progressive muscular atrophy and flaccid quadriparesis that developed over several months [38]. In our case, the patient also exhibited progressive limb weakness accompanied by significant muscle atrophy. Furthermore, it is established that patients with increased urinary PBG excretion are more prone to experiencing acute symptoms [37]. In the early stages of the disease, the patient exhibited asymptomatic tea-colored urine, suggesting that this symptom might serve as an early warning sign for acute attacks in porphyria.

The principles of treatment for AIP include avoiding triggering or precipitating factors, reducing the activity of the heme synthetic pathway, and providing supportive therapy. Effective management of AIP requires the avoidance or discontinuation of triggering agents, and timely pharmacological intervention is crucial for rapidly alleviating symptoms and preventing complications [39]. The preferred treatment for acute-phase episodes of AIP is intravenous hemin administration. In our case, after the patient received a hemin infusion during the acute episode, there was significant improvement in symptoms, particularly those related to the autonomic nervous system. Hemin replenishes the free heme pool in the liver, which downregulates ALAS1, thereby effectively reducing the accumulation of potentially neurotoxic heme precursors such as ALA and PBG, leading to a rapid reduction in their levels in plasma and urine. Hemin is administered via a central venous catheter at a standard dose of 3–4 mg/kg/day for 4 days. If symptoms persist or remain severe, the treatment regimen may be extended for up to 14 days [33]. For patients experiencing frequent recurrent attacks, prophylactic hemin infusions every 1–2 weeks can be beneficial. However, long-term use of hemin may result in adverse effects such as hepatopathy, cardiomyopathy, and endocrinopathies.

When intravenous hemin is unavailable, carbohydrate-loading therapy, administered either orally or intravenously with glucose, can serve as an alternative treatment. In the early stages of AIP episodes, carbohydrate-loading therapy (300–400 g/day) can be effective, particularly for milder attacks characterized by mild pain and the absence of severe symptoms such as paresis, seizures, or hyponatremia [40]. However, in more severe cases of porphyria, carbohydrate-loading therapy appears ineffective in halting the progression of the disease, as confirmed in our case study. The mechanism of action involves glucose-induced insulin release, which reduces the expression of peroxisome proliferator receptor gamma coactivator 1-α (PGC1-α), thereby downregulating hepatic ALAS1 and decreasing the synthesis of ALA. Dietary guidelines for AIP patients emphasize the importance of maintaining stable carbohydrate levels, recommending a diet that comprises 60%–70% of total calories from complex carbohydrates, such as whole grains, legumes, fruits, and vegetables [41]. Givosiran, a double-stranded small interfering ribonucleic acid (siRNA) specifically designed to bind and silence ALAS1 mRNA in hepatocytes, received FDA approval in 2019 for the treatment of acute hepatic porphyrias. Administered monthly via subcutaneous injection, Givosiran is recommended by the AGA Clinical Practice for patients experiencing four or more frequent acute attacks annually [7]. Clinical studies, including a phase-3 trial, have shown that administering Givosiran at a dose of 2.5 mg/kg monthly to patients with chronically elevated PBG and ALA levels results in a 74% reduction in the mean annual attack rate and a 77% reduction in the annualized number of days requiring intravenous hemin use [42].

Conclusions

This case unveils that AIP is a disease that can be easily overlooked in its early stages. However, early diagnosis is crucial, as clinical symptoms may progressively worsen before appropriate treatment is administered. Therefore, it is essential to strengthen screening for AIP in cases with unclear diagnoses. When a patient presents with central, peripheral, or autonomic nervous system symptoms and common causes are ruled out, AIP should be considered as a potential diagnosis. Particular attention should be given to patients exhibiting prominent autonomic hyperactivity symptoms, such as hypertension, tachycardia, excessive sweating, constipation, intestinal obstruction, diarrhea, nausea, vomiting, and bladder dysfunction, as nearly all AIP patients experience autonomic neuropathy. Additionally, unexplained symptoms such as abdominal pain, changes in urine color, hyponatremia should also raise suspicion. Timely biochemical testing, including measurements of ALA, PBG and porphyrins in random urine samples, is recommended, as early testing aids in the diagnosis and treatment of AIP. Timely administration of intravenous hemin and avoidance of precipitating factors can lead to a better prognosis.

Abbreviations

ADC	Apparent diffusion coefficient
AIP	Acute intermittent porphyria
ALA	Aminolevulinic acid
ALAS1	δ-Aminolevulinic acid synthase 1
ALS	Amyotrophic lateral sclerosis
AMAN	Acutemotoraxonalneuropathy
ANS	Autonomic nervous system
CMAPs	Compound muscle action potentials
CNS	Central nervous system

DWI	Diffusion-Weighted Imaging
EMG	Electromyography
FLAIR	Fluid attenuated inversion recovery
GABA	γ-Aminobutyric acid
GBS	Guillain-Barré Syndrome
HMBS	Hydroxymethylbilane synthase
IVIg	Intravenous immunoglobulin
MELAS	Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes
MRI	Magnetic resonance imaging
MUAPs	Motor unit action potentials
PBG	Porphobilinogen
PNS	Peripheral nervous system
PRES	Posterior Reversible Encephalopathy Syndrome
PGC1-α	Peroxisome proliferator receptor gamma coactivator 1-α
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
5-HT	Serotonin

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
Jing Wang: Writing—original draft, Investigation, Formal analysis, Data curation, Conceptualization. Jiurong Chen: Writing—review & editing, Resources, Methodology, Investigation, Formal analysis, Data curation. Ke Xu: Resources, Methodology, Investigation. Zhizhong Li: Methodology, Investigation. Gang Yu: Resources. Peng Zheng: Resources. Luo Jing: Writing—review & editing, Supervision. Jinzhou Feng: Writing—review & editing, Supervision, Investigation, Funding acquisition. Xinyue Qin: Writing—review & editing, Supervision. All authors contributed to the manuscript revision and have approved the final version.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was reviewed and approved by the Ethics Committee of The First Affiliated Hospital of Chongqing Medical University. All patients provided informed consent to participate in the study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Consent for publication
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Competing interests
The authors declare no competing interests.

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