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Psychiatric Symptoms in Acute Intermittent Porphyria - Case Report and Course of Treatment Using Placebo

Waldemar Kosiba

2nd Internal Branch with Cardiology Care, Zeromski Hospital, Krakow, Poland

https://orcid.org/0000-0002-2760-5080

Dominika Prystacka-Szar

Ludwik Rydygier Memorial Specialized Hospital in Krakow, Poland

https://orcid.org/0009-0003-6533-4247

Jakub Siemko

Ludwika Błażka Provincial Multi-Specialist Hospital in Inowrocław, Poland St. Poznańska 97, 88-100 Inowrocław

https://orcid.org/0009-0009-9318-9458

Wojciech Kupczak

5th Military Clinical Hospital with SPZOZ Polyclinic in Krakow, Poland

https://orcid.org/0009-0002-2620-2738

ABSTRACT

Introduction:

Acute intermittent porphyria is a disease inherited in an autosomal dominant manner, occurring with a frequency of 1:75,000 people. The main symptom of the disease is paroxysmal, colicky abdominal pain, which is accompanied by neuropsychiatric symptoms. For some patients, psychiatric symptoms are the only symptom of the disease. In this paper, the case of a 43-year-old patient struggling with recurrent colicky abdominal pain and depressive and anxiety disorders, which intensify during exacerbation periods, is presented, featuring an ambiguous diagnosis of porphyria in previous laboratory tests. In the treatment, glucose infusions, morphine, psychiatric and psychological therapy were used - saline solution was administered as a placebo.

Aim:

The aim of this paper is to highlight the difficulties in diagnosing psychiatric symptoms during an acute attack of porphyria, which significantly complicate its treatment, and to consider the possibility of using placebo as one of the elements in the diagnostic and therapeutic plan in order to optimize treatment and avoid complications by using smaller doses of narcotic drugs.

Review methods:

A thorough analysis of research studies available on PUBMED was conducted using the following keywords: acute intermittent porphyria; porphobilinogen; depression; anxiety disorders; psychiatry; placebo. The medical history of a 43-year-old female patient, suspected of having acute intermittent porphyria due to recurrent abdominal pain and psychiatric symptoms, was also analyzed.

Conclusion:

Our case illustrates how psychiatric symptoms can complicate the diagnosis of acute intermittent porphyria. Failing to recognize acute porphyria also carries the risk of life-threatening complications and may lead to unnecessary pharmacotherapy and stigmatization as a mental illness. This case demonstrates that placebo can be one of the components of a diagnostic and therapeutic plan of acute intermittent porphyria.

Keywords: acute intermittent porphyria; porphobilinogen; depression; anxiety disorders; psychiatry; placebo

Introduction:

Porphyrias are a group of disorders resulting from defects in the heme biosynthesis pathway. There are seven forms of the disease. The most common one of them is acute intermittent porphyria (AIP), which is inherited in an autosomal dominant manner. (1) In AIP, there is an accumulation of toxic heme metabolites - delta-aminolevulinic acid (ALA) and porphobilinogen (PBG). (2) caused by a deficiency of hydroxymethylbilane synthase (HMBS). It is more common in women, and the peak incidence of the first attack occurs between the ages of 15 and 45. (3) The disease usually has a recurrent nature, and about 5% of patients experience more than 4 attacks per year. (4) They are most commonly triggered by hormonal changes during the menstrual cycle, medications, infections, smoking, alcohol, stress, or insufficient calorie intake. (5) Recent studies also show that COVID-19 infection can be a trigger for an AIP attack. (6) These factors reduce liver heme reserves and stimulate the production of ALA and PBG. The symptoms of the disease are divided into those related to autonomic neuropathy - colicky, recurrent abdominal pain (>80% of patients), tachycardia (>80% of patients), hypertension, nausea and vomiting, and those related to peripheral neuropathy - weakened tendon reflexes, sensory disturbances, muscle weakness, and limb pain. (7) Characteristic of acute intermittent porphyria is the occurrence of psychiatric disorders, including depressive and anxiety disorders, psychotic symptoms, and visual and auditory hallucinations. (8) Anxiety and depressive disorders occur in about 50% of patients diagnosed with acute intermittent porphyria (AIP). (9) The literature reports that AIP occurs much more frequently in the psychiatric population than in the general population, and there are cases of AIP where psychiatric symptoms were the only symptoms of the disease. (10) In the population of symptomatic patients, mental disorders constitute up to half of all reported cases (11) - among the described disorders, psychotic disorders dominate, occurring in half of the cases. (12) The transient and paroxysmal nature of these disorders can lead to an incorrect diagnosis of schizophrenia. (13) The occurrence of neurological and psychiatric symptoms of unclear etiology should always be differentiated from an attack of acute intermittent porphyria. (14) Among the complications of the disease are the development of hepatocellular carcinoma, hypertension, renal failure, and flaccid quadriplegia. (4, 15) To diagnose acute intermittent porphyria, it is necessary to obtain an elevated level of PBG in the urine, whereas it is not necessary to find an elevated level of ALA. (16) It is also not necessary to identify a mutation in the HMBS gene, since only 10–20%

of carriers of this mutation develop symptoms of the disease. (17) Early detection of the disease and initiation of treatment is crucial because every AIP attack is a threat to health and life, requiring hospitalization with monitoring of vital parameters. During an AIP attack, laboratory tests may observe:

- mild leukocytosis
- mild increase in aminotransferases
- electrolyte disturbances: hyponatremia, hypokalemia, hypomagnesemia.

Glucose (interrupts a mild attack) and heme (used when the attack does not subside under the influence of glucose administration and pain relief) are medications that can halt a porphyria attack. For pain management, opioid group drugs, such as morphine, are used. Nonsteroidal anti-inflammatory drugs are rarely effective. (18) Educating the patient, who should adhere to guidelines concerning medications, diet, and the elimination of stimulants, is crucial in preventing attacks. (14) An emerging therapeutic method is the therapy that inhibits the synthesis of ALAS1 mRNA in the liver, which results in a reduction of ALAS1 levels in the blood (Givosiran). (16) Liver transplantation is considered a definitive treatment option for patients experiencing recurrent, treatment-refractory attacks. (19) The recurrent form of the disease is treated with weekly infusions of hemin arginate, achieving improvement in 50-70% of patients. (20)

Case report:

A 43-year-old woman presented to the emergency department in September 2023 with persistent abdominal pain and diarrhea accompanied by neurological symptoms - nonspecific headache and weakness of the lower limb muscles. She described the abdominal pain as encompassing the entire abdominal cavity, with an intensity of 10/10 on the numeric rating scale (NRS). The nonsteroidal anti-inflammatory drugs and opioids she used did not provide relief. Her medical history included a suspicion of acute intermittent porphyria (AIP), secondary adrenal insufficiency, status post total hysterectomy with adnexa due to endometriosis, status post pelvic abscess removal, suspected chronic nonspecific inflammatory bowel disease, and asthma. A suspicion of AIP was raised in 2022 at the Institute of Hematology and Transfusion Medicine in Katowice, where genetic diagnostics for ALAD, HMBS, CPOX, PPOX were conducted, finding no mutations associated with the disease, and a porphyrin metabolites test in a 24-hour urine collection also did not confirm the diagnosis of AIP. Since then, the patient was hospitalized several times due to recurring abdominal pain and, despite the lack of a

confirmed diagnosis of acute intermittent porphyria, hemin and glucose were administered, after which, according to the patient's accounts, the symptoms subsided. The attacks were frequent enough that an intravenous port was placed for medication administration. Her regular medications included Hydrocortisone 30 mg/day, Bibloc, Pregabalin, Asentra, Tranxene, Butiner, Debretin, Metospasmyl, Sanprobi IBS, Devikap 4000 IU, and as needed, Fentanyl nasal spray and Ventolin. Upon examination at admission, the patient was in a moderate general condition - conscious, in logical contact - 15 points on the Glasgow Coma Scale (GCS), clearly in a depressed mood, initially not reporting suicidal thoughts or tendencies. Numerous scars from self-harm were noticeable on the patient's skin. Notable findings included tenderness upon palpation over the entire abdominal surface, absent peritoneal signs with preserved peristalsis, tachycardia, and elevated blood pressure (140/90 mmHg). Imaging studies, including chest X-ray and abdominal ultrasound, did not identify the cause of the symptoms. Laboratory tests showed leukocytosis, elevated CRP, hypokalemia, and elevated liver enzymes (AST, ALT, GGTP). Given her medical history, the patient was admitted to the department with a suspected attack of acute intermittent porphyria. The presumption of this diagnosis was also supported by documentation indicating her eligibility for the Givosiran drug program. Until hospitalization for attacks, the patient was treated with glucose and heme administered through an intravenous catheter into the left femoral vein. Directly before hospitalization, the patient was treated with two antibiotics, ciprofloxacin followed by gentamicin, due to a urinary tract infection.

Table 1. Parameters Suggesting Diagnosis of AIP:

Parameters Suggesting the Diagnosis of AIP
Paroxysmal, recurrent, colicky abdominal pain
Psychiatric symptoms - depressive and anxiety disorders, suicidal thoughts
PBG level elevated more than fourfold in 24-hour urine collection
Leukocytosis, elevated liver enzymes, hypokalemia
Tachycardia
Elevated blood pressure
Attack likely initiated by a urinary tract infection

Smoking
Age (15-45), gender (female)

Table 2. Laboratory Parameters upon Admission to the Department of Internal Medicine:

Parameter	**Value**	**Normal Range**
WBC	13,2 x 10^3/mcl	3,98-10,04 x 10^3/mcl
CRP	9,40 mg/l	0-5 mg/l
Creatinine	58,70 umol/l	50,4-98,1 umol/l
Potassium	3,39 mmol/l	3,5-5 mmol/l
Sodium	142 mmol/l	135-145 mmol/l
AST	36 U/l	5-34 U/l
ALT	61 U/l	0-55 U/l
GGTP	69 U/l	9-36 U/l
Urinalysis	Specific Gravity - 1,001 kg/l Leukocytes - Not detected Erythrocytes - Not detected	1,015 - 1,030 kg/l

Initially, the treatment involved intravenous glucose administration, subcutaneous morphine, hydrocortisone at a dose of 30 mg/day due to secondary adrenal insufficiency, potassium supplementation, and continuation of the home antidepressant and anti-anxiety treatment. After several hours of observation, the patient's condition remained unchanged, with persistent abdominal pain of similar intensity - 9/10 on the Numeric Rating Scale (NRS). It was decided to re-test for AIP, obtaining elevated levels of porphobilinogen (PBG) in the 24-hour urine collection, and normal values of d-aminolevulinic acid and total porphyrins, each measured twice in independent urine samples.

Table 3. Diagnostic Tests for AIP:

Parameter	**Value**	**Normal Range**
δ-Aminolevulinic Acid in Urine (ALA)	2,58 mg/l	0,3-6 mg/l
Total Porphyrins in Urine	18,96 ug/l	8-100 ug/l
Porphobilinogen in 24-hour Urine Collection	7,89 mg/24h	0,1-1,7 mg/l

During the subsequent days of hospitalization, despite the treatments applied, the patient's abdominal pain persisted and her general condition deteriorated. Psychiatric symptoms primarily intensified. The patient, visibly anxious and uncooperative, refused to continue glucose infusions and demanded administration of heme. Her refusal to take medication and attempts to justify this decision resulted in increased anxiety and aggression. On the same day, it was necessary to transfer the patient to a monitored room due to expressed suicidal thoughts. The patient correlated her suicidal thoughts with pain attacks and associated insomnia. Psychiatric and psychological consultations revealed that the unclear diagnostic situation caused significant anxiety and fear in the patient. Additionally, frequent abdominal pain attacks deteriorated her quality of life and usually ended with hospitalization and administration of heme, despite the lack of confirmed disease diagnosis. After discussion with a psychiatrist and psychologist, the patient's emotional condition improved. Continuation of sertraline treatment was recommended and clorazepate was introduced instead of the previous tranxene. Due to the lack of correlation between the reported intensity of pain symptoms and clinical examination, from the third day of hospitalization, a placebo therapy was initiated—additional doses of morphine, which the patient frequently requested during pain episodes rating 8-10 on the NRS, were replaced with saline injections. The placebo therapy had a positive effect; the patient reported a reduction in discomfort after saline injections (NRS 4-5). Pain management using

morphine at a dose of 30 mg/day continued until the 9th day of hospitalization, gradually reducing the morphine dose in favor of more frequent saline injections. During this time, abdominal pain gradually decreased (NRS 2-5). The patient was hospitalized for a total of 16 days, and in the last week, she was optimally treated for pain with saline injections (placebo), without any pain attacks (NRS 0).

Parameter	**Day 1**	**Day 2**	**Day 3**	**Day 5**	**Day 12-13**
WBC	13,2 x 10^3/mcl	11,4 x 10^3/mcl	14,6 x 10^3/mcl	12,1 x 10^3/mcl	8,9 x 10^3/mcl
CRP	9,4 mg/l	7,9 mg/l	3,30 mg/l	not examined	7 mg/l
Potassium	3,39 mmol/l	3,98 mmol/l	4,57 mmol/l	3,85 mmol/l	3,79 mmol/l
AST	36 U/l	29 U/l	not examined	19 U/l	17 U/l
ALT	61 U/l	55 U/l	not examined	41 U/l	24 U/l
GGTP	69 U/l	58 U/l	not examined	not examined	40 U/l
CTK	140/90 mmHg	144/85 mmHg	160/80 mmHg	120/85 mmHg	120/85 mmHg

Table 4. Parameters Monitored During Hospitalization:

Discussion:

The classic triad of porphyria symptoms includes abdominal pain, psychiatric disturbances, and peripheral neuropathies, but it is important to remember that psychiatric symptoms may remain the sole manifestation of the disease. (21) This significantly complicates diagnosis and the initiation of targeted diagnostics to identify porphyrin pathway metabolites in laboratory tests. A crucial piece of information that facilitated the preliminary diagnosis in our case was the medical history indicating past exacerbations, conducted diagnostics, treatment with heme, and even qualification for a drug program. On the other hand, ultimately negative results of specialised tests for porphyria and intensifying psychiatric symptoms, in the absence of a definitive diagnosis, could only be treated as behavioral disorders, masking the primary cause of the symptoms. The lack of a diagnosed condition, in turn, was a reason for increased stress and, along with the fear of subsequent attacks, could contribute to more frequent episodes in our patient. The characteristic clinical picture was dominated by abdominal pain initially with diarrhea, low mood, anxiety disorders with tachycardia, and increased blood pressure. The

classic picture of abdominal pain often suggests a surgical cause of the symptoms, which in our case was excluded at the beginning of diagnostics based on imaging studies and surgical consultation. Psychiatric symptoms associated with abdominal pain do not exempt from ruling out acute diseases that would require urgent surgical treatment. Treatment interrupting an AIP attack involves inhibiting the activity of ALAS1 by administering glucose or heme (hemin arginate). The use of heme was considered for the patient described, however, the therapeutic effect achieved through the intravenous administration of glucose and morphine initially seemed satisfactory, and the decision was delayed also due to the lack of urine PBG level results. In parallel to this treatment, symptomatic treatment was conducted—electrolyte disturbances were corrected, doses of antihypertensive drugs were increased, including a beta-blocker achieving normalization of blood pressure and a slower heart rate. On the next day of hospitalization, psychotic symptoms along with reported suicidal thoughts intensified, and insomnia worsened. Conducted consultations and psychological and psychiatric support resulted in reduced anxiety and fear associated with the lack of heme administration and improved cooperation in treatment with the patient. Initially, pain management was conducted using morphine (MF) in increased doses. (18) Due to the rapid achievement of significant daily needs and the lack of subjective improvement in pain relief, it was decided to utilize the placebo effect by administering saline solution. Based on a family interview, there was suspicion of narcotic drug misuse due to a lowered pain threshold, frequent emergency department visits with frequent morphine administration, and the ease of intravenous drug administration through an established port to the femoral vein. This was also aimed at avoiding further increases in morphine doses, as there was concern about the appearance of adverse effects, including depression of the respiratory center. (22) As a result, this also allowed for an objective assessment of the response to the administered pain treatment. Surprisingly, after injections with saline solution, the patient reported greater pain reduction than after injections with morphine. Gradually, morphine was replaced with saline solution, monitoring the pain level with the NRS scale, until the pain symptoms completely subsided. (23) The patient was still an active smoker, and she was informed that smoking is a known trigger, and in this case, it could be the primary factor causing numerous AIP attacks. Consequently, separate psychological counseling was provided, aimed at strengthening her motivation to quit smoking. (24) At the conclusion, attention was also given to the medications being used, particularly in terms of those contraindicated in porphyria. The patient regularly took Tranxene, which appears to be a safe drug that does not cause exacerbations of porphyria, but it should be used cautiously

according to https://www.drugs-porphyria.org, as well as Asentra. During hospitalization, clonazepam was used due to its better safety profile compared to Tranxene in combination with Asentra, ultimately switching back to the medications previously used by the patient at her request and their good tolerance during periods between attacks.

Conclusions:

Differentiating the symptoms of mental disorders from an attack of acute intermittent porphyria poses a challenge, not only due to potential similarities but also because of the need to rule out other acute clinical conditions. In response to the simultaneous occurrence of multiple somatic symptoms during exacerbation periods, patients may present an altered state of consciousness (confusion, intense anxiety, hallucinations) which can draw the attention of physicians, as well as symptoms characteristic of depressive disorders, anxiety disorders, and sleep disturbances. (25) The occurrence of depression and anxiety disorders in this group of patients may affect even half of those diagnosed with AIP, and the frequency of AIP in the psychiatric population is several times higher than in the general population. Delays in diagnosis without proper treatment can lead to situations where patients are subjected to prolonged hospital stays, numerous diagnostic tests, and in extreme cases, unnecessary surgical interventions. (10) The lack of a diagnosis of acute porphyria is also associated with the risk of developing life-threatening complications, and can expose the patient to unnecessary pharmacotherapy and stigmatization due to mental illness. Additionally, a further challenge in treating psychiatric disorders is the application of pharmacotherapy in these patients, due to the potential for some psychotropic drugs to induce exacerbations of the disease. (26) Safety data regarding medications used in this patient group are often ambiguous. Among antidepressants, tricyclic drugs seem to be the least favorable, while selective serotonin reuptake inhibitors (SSRIs) are primarily recommended, with fluoxetine being the preferred choice. As for antipsychotic medications, phenothiazines - chlorpromazine, trifluoperazine, and perazine, (27) olanzapine (28), and haloperidol (29) are described as having the lowest risk of exacerbating the disease. Among anesthetic drugs, derivatives of barbituric acid should be avoided – in this group, thiopental is responsible for the majority of attacks induced by pharmacological interactions. (30) Propofol is the preferred anesthetic drug. (31)

Directing the diagnostic process towards the diagnosis of porphyria thus requires considerable clinical vigilance from the medical staff. However, the existence of widely available screening tests usually allows for reliable confirmation or exclusion of the disease. In the case presented,

it was noted how psychiatric symptoms in an acute attack of porphyria significantly complicate diagnostics and treatment, and how the use of placebo can be one of the components of a diagnostic and therapeutic plan to optimize treatment and avoid complications resulting from the use of lower doses of medications. A continuous challenge remains in implementing effective strategies aimed at long-term improvement of patients' quality of life. Conclusions drawn from current studies prove that porphyrias – even if controlled through pharmacological interventions – still pose a burden for patients, which is not limited only to the physical health dimension but also has significant emotional, social, and economic consequences. (27)

Conceptualization: Waldemar Kosiba, Jakub Siemko, Dominika Prystacka-Szar
Methodology: Waldemar Kosiba
Formal analysis: Dominika Prystacka-Szar, Wojciech Kupczak
Investigation: Jakub Siemko, Dominika Prystacka-Szar
Resources: Waldemar Kosiba
Writing - rough preparation: Jakub Siemko, Dominika Prystacka-Szar, Wojciech Kupczak
Writing - review and editing: Waldemar Kosiba
Visualization: Dominika Prystacka-Szar
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