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Psychiatric Presentation of Hereditary Coproporphyria with Coproporphyrinogen Oxidase Gene Mutation c.734 C>T: A Case Report

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ABSTRACT

Introduction: Porphyrias constitute a collection of hereditary metabolic disorders arising from disturbances in the enzymatic activities inherent to the heme biosynthetic pathway. Eight subtypes of porphyria, each associated with enzymes in the heme biosynthesis pathway, have been identified. Hereditary coproporphyria is one of the porphyria subtypes characterized by neuropsychiatric clinical features. It develops as a result of a deficiency in coproporphyrinogen oxidase enzyme activity. Consequently, an accumulation of coproporphyrin and its precursor metabolites is observed. Hereditary coproporphyria exhibits autosomal dominant inheritance. Following clinical suspicion, a diagnosis is made with biochemical and genetic tests. The presence of nonspecific symptoms and the lack of consideration for porphyria in differential diagnosis complicate the diagnosis.

Case: An 18-year-old male patient was referred to our psychiatry clinic only with psychiatric complaints. The mental status examination revealed affective signs, along with visual hallucinations and delusions. Blood tests and cranial scans at admission showed no abnormalities. After initiating treatment with valproic acid and olanzapine for a presumptive diagnosis of bipolar I disorder, a manic episode with psychotic features, the patient's general medical condition worsened. During clinical observation, the appearance of neurological and gastrointestinal system findings led to a reconsideration of the diagnosis, and porphyria was considered. Urine tests revealed elevated levels of porphyrin intermediates. The diagnosis of hereditary coproporphyria was confirmed by genetic testing, which identified the c.734 C>T mutation in the coproporphyrinogen oxidase gene. Symptomatic relief was observed following a carbohydrate-rich diet without the need for psychotropic treatment.

Conclusion: Although their subtypes exhibit distinct clinical features, porphyrias typically present with involvement of multiple systems. Cases that initially present with symptoms specific to a single system can pose diagnostic challenges. In our case report, we aimed to present the psychiatric onset of hereditary coproporphyria, a rare subtype of porphyria known for its potentially fatal attacks when untreated.

Keywords: Case report, coproporphyrinogen oxidase, hereditary coproporphyria, porphyrias

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INTRODUCTION

Porphyrias are hereditary metabolic disorders arising from disturbances in the enzymatic activities inherent to the heme biosynthetic pathway. Eight distinct porphyria subtypes have been identified, each associated with specific enzymes (1). Hereditary coproporphyria (HCP), a subtype of porphyria, is caused by impaired coproporphyrinogen oxidase (CPOX) activity (2).

Clinical manifestations in porphyrias can include gastrointestinal, neurological, and dermatological signs (1). Hereditary coproporphyria is one of the subtypes characterized by psychiatric symptoms (3). The measurement of porphobilinogen, aminolevulinic acid, and porphyrins, and their confirmation through genetic testing, is crucial for diagnosis during the episode (2). HCP's rarity and nonspecific symptoms make diagnosis challenging, leading to the management of patients under alternative diagnoses. Untreated episodes can result in mortality.

In our paper, we aim to present a case of HCP that began with isolated psychiatric symptoms and had not previously been diagnosed with porphyria, a presentation rarely reported in the literature.

CASE

An 18-year-old male was referred to the psychiatry clinic due to the belief that magic was being cast through lights, thoughts of having died and been resurrected multiple times, rapid and incoherent speech, and reports of seeing humanoid figures.

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Highlights

- **HCP may initially present solely with psychiatric symptoms.**
- **A missed diagnosis of HCP can result in recurrent admissions to psychiatric wards.**
- **Undiagnosed porphyria attacks can lead to fatal outcomes.**

He had no prior psychiatric admissions or known chronic illnesses. His psychosocial development was reported to have progressed in line with his peers. There was no family history of psychiatric disorders. His parents were fifth-degree relatives. The family reported he had started consuming alcohol before the onset of symptoms. It was noted that although his alcohol consumption was irregular, it had increased, with the last use occurring one and a half months ago.

Mental status examination revealed increased speech, heightened emotional expression, visual hallucinations, tangential responses, scattered associations, grandiose and mystical delusions, and psychomotor agitation. The patient reported seeing humanoid figures, which he identified as girlfriends. He noted unclear faces on the figures. Believing he was immortal, the patient claimed to have died and been revived and considered himself capable of directing vehicles mentally and linked these thoughts to a mystical mission. The physical examination revealed no pathological abnormalities. The ethanol level was zero. There were no signs of dehydration or alcohol withdrawal. Routine blood tests at admission were normal. Non-contrast cranial tomography and both contrast-enhanced and non-contrast magnetic resonance imaging showed no abnormalities.

For the patient suspected of having bipolar I disorder, manic episode with psychotic features, the regimen was initiated with olanzapine 20 mg/day and valproic acid (VA) 1500 mg/day, increasing doses gradually. Although partial improvement was observed, the hallucinations and affective elevation persisted. The patient reported periumbilical pain, but abdominal examination and imaging revealed no abnormalities. Hyponatremia (117 meq/L) was detected. Valproic acid and ammonia levels were within the normal range. Liver function tests showed elevations (AST: 90 U/L, ALT: 184 U/L). Tests for liver viral panel, autoimmune antibodies, immunoglobulins, septic parameters, endocrinopathies, iron and copper metabolism found no significant abnormalities. The sodium level was gradually corrected. During clinical deterioration, the patient on olanzapine 20 mg/day and VA 1500 mg/day planned to taper off psychotropic drugs by reducing doses every other day. A re-evaluation for differential diagnosis was planned.

Two days later, prolonged response latency, drowsiness, and confusion were observed. Encopresis developed, and autonomic instability was present. The electroencephalogram showed marked slow-wave activity, especially in the temporal region, suggesting encephalopathy; a lumbar puncture was performed, but cerebrospinal fluid analysis revealed no definitive results.

The emergence of gastrointestinal and neurological symptoms alongside psychiatric manifestations, particularly following VA, raised suspicion of porphyria. The urine sample, exposed to sunlight for three days, showed remarkable reddening. Consultations were requested from the departments of metabolic diseases and genetics. Tests targeting porphyria were scheduled. Urine analysis revealed uroporphyrin I, III: 1190 nmol/L (N: 0–30 nmol/L), coproporphyrin I, III: 1531 nmol/L (N: 0–110 nmol/L), aminolevulinic acid (ALA): 71.61 µmol/L (N: 0–34.32 µmol/L), ALA urine/creatinine ratio: 6.14 mg/g crea (N: 0–4.5 mg/g crea), heptacarboxyporphyrin: 20.51 nmol/L (N: 0–7.01 nmol/L), hexacarboxyporphyrin: 8.86 nmol/L (N: 0–1.99 nmol/L), and pentacarboxyporphyrin: 139.6 nmol/L (N: 0–5.0 nmol/L), indicating a diagnosis of HCP. The diagnosis of HCP was confirmed through genetic analysis, identifying a c.734 C>T mutation in the CPOX gene.

A carbohydrate-rich diet was initiated, resulting in positive outcomes. Within five days, confusion, drowsiness, and prolonged response latency decreased. Autonomic stability was achieved. No hallucinations or delusions were observed. However, euphoria, increased speech, and psychomotor agitation reappeared. These symptoms gradually subsided after one day of continued carbohydrate-rich nutrition. The follow-up electroencephalogram showed no signs of encephalopathy. The patient was psychiatrically evaluated as having a mental disorder due to another medical condition. As a result, the patient achieved complete symptom resolution without psychotropic medication. Written informed consent was obtained from the patient.

DISCUSSION

Hereditary coproporphyria is a rare form of acute hepatic porphyria. A comprehensive European study found that the prevalence of acute porphyria is 10 cases per million, with an annual incidence of 0.2 cases per million. Specifically, HCP's annual incidence was 2 cases per 100 million (4). Hereditary coproporphyria exhibits autosomal dominant inheritance (2). However, there was no known porphyria in patient's family.

Alcohol, infections, and fasting are known triggers of porphyria attacks (1,5). In our case, the initiation of alcohol consumption before symptom onset suggests that the episode may have been triggered by alcohol. Alcohol use in genetically predisposed individuals can shift the disease from a compensated latent phase to a decompensated phase. Once clinical symptoms manifest, it takes time for biochemical abnormalities to normalize (5). The patient was initially diagnosed with bipolar I disorder, manic episode with psychotic features, and VA was introduced. However, VA is a porphyrinogenic agent (6). The emergence of neurological and gastrointestinal symptoms in our case suggested that VA's porphyrinogenic properties contributed to clinical deterioration. Worsening symptoms after VA administration should prompt suspicion of porphyria.

Affective and psychotic symptoms often co-occur with systemic manifestations during porphyria episodes. The delta-ALA accumulation and the kynurenine pathway play a key role in the pathophysiology of porphyria's psychiatric symptoms (3,7–9). Aminolevulinic acid activates gamma-aminobutyric acid (GABA) autoreceptors, disrupting GABA/glutamate balance and leading to neuronal toxicity (7,8). The kynurenine pathway plays a regulatory role in heme biosynthesis and modulates dopamine and glutamate activity in neurons (3,9). In addition to affective and psychotic symptoms, anxiety, obsessive-compulsive, and depressive disorders have been reported in porphyria (3,10). Considering the variety of symptoms, it is difficult to define specific psychiatric signs for porphyria. Literature includes porphyria cases similar to ours, with reported visual hallucinations (10). Isolated psychiatric appearance at the onset of episodes, compared to accompanying psychiatric symptoms, is less common. Though porphyria cases starting with psychiatric complaints are rarely documented in the literature, this presentation is even less commonly reported in HCP (10,11).

Abdominal pain is the predominant symptom in HCP. Other gastrointestinal symptoms include vomiting, constipation, and encopresis (2). Autonomic dysfunction is frequently observed due to increased

sympathetic activity and electrolyte imbalances. Hyponatremia can be present in about 40% of cases, and maintaining electrolyte balance is crucial (1). If left untreated, hyponatremia can lead to seizures, while rapid correction may cause neurological complications. In this case, sodium levels were carefully monitored and corrected gradually to prevent complications.

Neurological symptoms, including drowsiness, delayed responses, and confusion, were supported by electroencephalogram findings consistent with encephalopathy. Reversible posterior encephalopathy syndrome, has been reported during episodes, often presenting cerebral edema on imaging (12). However, in our case, no signs of cerebral edema were detected. Although the lumbar puncture yielded no significant results, in porphyria cerebrospinal fluid analysis often fails to provide notable results, even with neurological symptoms (1). While neurovisceral symptoms usually dominate in HCP our case was distinct in that psychiatric symptoms were the initial presentation.

A carbohydrate-rich diet and intravenous hemin therapy are recommended for porphyria attacks due to their inhibitory effects on ALA synthase (13). The role of intravenous carbohydrate administration remains controversial, as it can induce hyponatremia and lead to neurological complications (2). Recent studies suggest that givosiran, an RNA interference-based drug, is effective in the treatment of porphyria (14). In our case, a carbohydrate-rich diet significantly improved neurological and gastrointestinal symptoms within five days. In our case, before a carbohydrate-rich diet, hyponatremia was corrected, electrolytes balanced, and porphyrinogenic agents discontinued. This might have shortened the clinical response time to oral carbohydrate supplementation. The psychotic symptoms in our case were resolved without the need for antipsychotic. However, institutions such as the American Porphyria Foundation and the Nordic Drug Database have evaluated the safety of psychotropics. Olanzapine and clozapine are classified as probably safe antipsychotics by both databases. Fluoxetine is classified as safe, while sertraline, paroxetine, venlafaxine, and duloxetine are categorized as probably safe antidepressants. Among benzodiazepines, alprazolam, diazepam, and midazolam are classified as probably safe by both databases (6,15).

Although porphyrias typically involve multiple organ systems, they may present solely with psychiatric symptoms. In cases where psychiatric symptoms coexist with systemic findings, considering porphyria in the differential diagnosis is crucial for early intervention and prevention of potentially fatal outcomes. Additionally, clinical deterioration following the administration of porphyrinogenic psychotropic drugs should raise suspicion of porphyria.

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