Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2021;46(4):1719-1724
DOI: 10.17826/cumj.982619

OLGU SUNUMU / CASE REPORT

Diagnostic difficulty in a patient with recurrent attacks of acute polyneuropathy: Acute intermittent porphyria

Akut polinöropatinin tekrarlayan atakları olan bir olguda tanı güçlüğü: Akut intermittant porfiria

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Cukurova Medical Journal 2021;46(4):1719-1724

Abstract

Acute intermittent porphyria is one of the most common porphyria subtypes. There is a critical need to diagnose porphyria, given its multisystem nature and the poor prognosis associated with incurable cases. Here we present the case of a 27-year-old female patient who had severe abdominal pain and who was operated on due to ileus with tetraparesis that manifested following an operation. The patient had muscle weakness in four limbs and symptoms of sympathetic hyperactivity and electrolyte imbalance. Moreover, neurophysiological studies supported acute axonal polyneuropathy. Owing to the neurological symptoms, electrophysiological studies, metabolic disorders, and the severe abdominal pain noted, porphyria was suspected. Porphobilinogen and ALA levels increased in the 24-hour urine test, and the patient was diagnosed with acute intermittent porphyria. In patients who have unexplained recurrent abdominal pain with additional autonomic dysfunction, neurological and / or psychiatric findings, porphyria, a rare disease, should come to mind.

Keywords:. Porphyria, acute intermittent porphyria, acute polyneuropathy, motor axonal polyneuropathy

Öz

Akut intermittant porfiri, porfirinin en yaygın alt tiplerinden biridir. Multisistemik bir hastalık olması ve tedavi edilemeyen olgularda prognozun kötü olması nedeniyle tanı koymak çok önemlidir. Burada şiddetli karın ağrısı ile acil servise başvuran ve ileus ön tanısıyla opere edilen, operasyon sonrası tetraparezi gelişen 27 yaşında bayan hasta sunulacaktır. Hastanın dört ekstremitesinde kas güçsüzlüğü, sempatik hiperaktivite bulguları ve elektrolit dengesizliği vardı. Yapılan elektrofizyolojik çalışmalar akut aksonal polinöropatiyi destekledi. Hastanın nörolojik semptomları, elde edilen elektrofizyolojik bulguları, metabolik bozukluklar ile birlikte şiddetli karın ağrısı olan hastada porfiriden şüphelenildi. Bakılan 24 saatlik idrar testinde porfobilinojen ve ALA düzeylerinin yükseldiği gösterilen hastaya akut intermittant porfiri tanısı konuldu. Açıklanamayan tekrarlayan karın ağrısı, otonom disfonksiyon, nörolojik ve/veya psikiyatrik bulguları olan hastalarda, nadir görülen bir hastalık olan porfiri akla gelmelidir.

Anahtar kelimeler: Porfiri, akut intermitant porfiri, akut polinöropati, aksonal motor polinöropati

INTRODUCTION

Porphyrins are precursors involved in the biosynthesis of hemoglobin, myoglobin, and cytochromes. Porphyrins contribute to the heme structure, an important substance in oxygen transport. Porphyria is a disease that manifests due to the accumulation of intermediate metabolites of the heme synthesis pathway and is caused by deficiencies in the pathway's enzymes. Porphyrias are classified as acute or nonacute, hepatic or erythropoietic. Acute porphyrias include acute intermittent porphyria (AIP), variegate porphyria, hereditary coproporphyria, and aminolevulinic acid dehydratase deficient porphyria. These are related to severe

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Geliş tarihi/Received: 18.08.2021 Kabul tarihi/Accepted: 19.10.2021 Çevrimiçi yayın/Published online: 23.11.2021

attacks, including abdominal, psychiatric, neurological, or cardiovascular symptoms[1].

Here, we report an acute intermittent porphyria case characterized by recurrent attacks of acute polyneuropathy, abdominal pain, central neurological involvements, cardiovascular findings, and electrolyte abnormalities with the exception of skin photosensitivity. Notably, a deficiency in hepatic porphobilinogen deaminase enzyme causes the collection of porphobilinogen and delta amino-levulinic acid (D-ALA). Disease diagnosis relies on both clinical findings and urine tests that demonstrate an increase in the levels of these substances. The diagnosis of this metabolic disorder is vital, given its life-threatening nature. Accordingly, we aimed to present this case to emphasize the importance of consistently considering a diagnosis of acute intermittent porphyria when investigating similar symptoms while also being mindful of the difficulties and clinical findings encountered during the diagnosis phase. Written informed consent was obtained from the patient during this process.

Table 1. The ENMG findings of patient;1. ENMG: at the beginningof the disease, 2. ENMG: control ENMG after disease duration, 3. ENMG: In the recurrent period of disease

NCS	1.ENMG	2.ENMG	3.ENMG
Left peroneal nerve DML	7.4 ms	3.5 ms	7.6ms
CMAP amplitude	2.4 mV	2.2 mV	1.3 mV
Motor conduction velocity	50.1 m/s	43.2 m/s	39.1 m/s
Right tibial nerve DML	7.3 ms	4.5 ms	4.2 ms
CMAP amplitude	8.6 mV	9.2 mV	7.4 mV
Motor conduction velocity	45.1 m/s	43.1 m/s	37.0 m/s
Right Sural nerve SNAP amplitude	11.0 μV	20.1 μV	18.7 μV
Sensory conduction velocity	51 ms	52 ms	40.0 ms
Left Sural Nerve SNAP amplitude	10.8 μV	23.0 μV	23.0 μV
Sensory conduction velocity	40.0 m/s	51 m/s	40.1 m/s
Right Ulnar nerve DML	3.2ms	3.5 ms	3.6 ms
CMAP amplitude	3.9 mV	7.6 mV	3.3 mV
Motor conduction velocity	51 m/s	55 m/s	43.9 m/s
SNAP amplitude	14 μV	12.8 μV	22.1 μV
Sensory conduction velocity	56 m/s	42.7 m/s	55.6 m/s
Muscle studies			
Right tibialis anterior	Spontaneous activity+ Neurogenic pattern MUAP+	Neurogenic pattern MUAP+	Polyphasic, Neurogenic pattern MUAP+
Left gastrocinemius	Spontaneous activity+ Neurogenic pattern, polyphasic MUAP+	Neurogenic pattern MUAP+	Polyphasic, Neurogenic pattern MUAP+
Right abductor digiti minimi	Spontaneous activity+ polyphasic MUAP+	Neurogenic pattern MUAP+	Polyphasic, Neurogenic pattern MUAP+
Right biceps brachii	Spontaneous activity+	Neurogenic pattern MUAP+	Normal

ENMG, electroneuromyography; NCS, nerve conduction studies; DML, dystal motor latency; CMAP, compound muscle action potential; SNAP, sensory nerve action potential, MUAP, motor unit action potential; ms, milisecond; mV, milivolt; m/s, meter/second; μV, microvolt

CASE

A 27-year-old female patient experiencing the sudden onset of abdominal pain underwent a subtotal colectomy–ileorectal anastomosis procedure with a pre-diagnosis of ileus and was discharged with colostomy. One week later, she applied to our neurology department with a complaint of weakness in her limbs. Her medical history included a stillbirth at 25 weeks due to intrauterine growth restriction, but she had no other comorbidities.Following a neurological examination, she was diagnosed with tetraparesis and all four limbs and deep tendon reflexes were hypoactive. In the patient's first electroneuromyography (ENMG) examination, both the left fibular motor and ulnar motor compound muscle action potential (CMAP) amplitudes were found to be low (Table 1).

Laboratory blood tests, including the creatinine kinase level, were normal. Contrast-enhanced cranial and spinal magnetic resonance images (MRI) were performed and transverse myelitis was excluded. Anti-acetylcholine receptor, anti-musk and anti-titin antibodies were tested for myasthenia gravis; however, they were within normal limits.

The patient developed sinus tachycardia and resistant hypertension during follow-up and was subsequently referred to cardiology. Nonetheless, the cardiological examination was normal. Intravenous immunoglobulin G (IVIG) treatment was started, but was discontinued because of increases in the creatinine level. During follow-up, the patient developed hypercalcemia, hyperpotassemia, and hypomagnesemia. Moreover, an anastomotic leak at the colostomy site was also identified, thereby necessitating the patient undergoing an emergency operation. Postop septic shock and thrombocytopenia developed and the patient was followed up in the intensive care unit for 70 days where she received antibiotherapies and apheresis treatments. Once the patient's general condition improved, she was transferred to the neurology department, where she underwent a lumbar puncture procedure to address the motor axonal polyneuropathy identified during the ENMG examination (Table 1).

Cerebrospinal fluid protein was found to be high at 53mg/dl and there were no cells supporting albuminocytological dissociation. Cerebrospinal fluid cytology was also examined and found to be normal. The patient was given 0.4g/kg/day IVIG treatment for 5 days and infectious markers examining polyneuropathy etiology were negative. Since the patient had a history of stillbirth, a rheumatology consultation was requested due to suspicion of vasculitis. However, no signs of vasculitis were detected. Subsequent examinations and electrophysiological measurements showed almost complete improvements with the help of physiotherapy and IVIG. Approximately 10 months later, the patient was reoperated on for colostomy and two weeks after discharge, the patient presented to the emergency service with intense body pain and generalized tonic-clonic seizures twice a day. However, no pathology was observed except for postictal changes in contrast-enhanced cranial MRI (Figure 1).

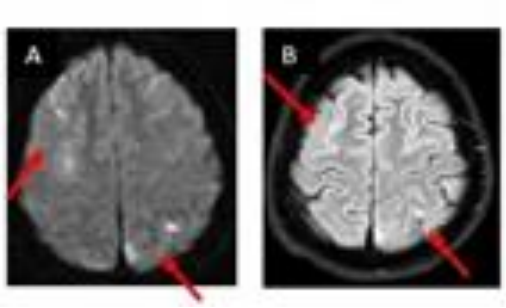

Figure 1. Brain MRI firdings on the 1st day showed high intensity on DWI (A) and the lesions improved on the 9th day FLAIR images (B)

Electroencephalography (EEG) was normal; however, levetiracetam was started for seizure control. Intense body pain continued, and muscle weakness developed in all limbs within a few days. Acute axonal polyneuropathy was detected in ENMG and IVIG treatment of 0.4g/kg/day was given for 5 days. During this period, tachycardia and hypertension attacks were observed again. Collectively, this led to a suspicion of porphyria, as the patient had multiple neurological involvement with occasional severe abdominal pain accompanied by autonomic disorder and electrolyte imbalance. Subsequent measurements identified a total porphyrine of 1598.9 µg/day (0-150 µg/day) and D-ALA levels of 30.6 mg/L (0-4.5mg/L) in the 24-hour urine test. The porphobilinogen level was 2.2 µmol/mmol (< 1.5µmol/mmol), the D-ALA level was 44.9 µmol/mmol (<3.8 µmol/mmol), and the total porphyrin level was deemed high at 208 nmol/mmol (<35 nmol/mmol) in the spot urine test.

Based on these results, the patient was diagnosed with AIP. Genetic analysis was also performed to determine the variant of concern. A variant was identified in the *HMBS* (hydroxymethylbilane synthase) gene. Consequently, following her diagnosis, she was followed up with both the genetic and metabolism departments.

DISCUSSION

Porphyrias are rare disorders of heme metabolism caused by a deficiency in the enzymes of the heme synthesis pathway. Heme synthesis involves eight enzymes and a deficiency in any of these enzymes leads to symptoms resulting from the accumulation of intermediate metabolites in either the liver or bone marrow[2]. In general, porphyrias are hereditary diseases with the three most common types, including acute intermittent porphyria (AIP), porphyria cutanea tarda (PCT), and erythropoietic porphyria (EPP)[3]. AIP is the most common porphyria, with an estimated prevalence of ~ 5 per 100,000 in the United States, including asymptomatic patients[2]. AIP is inherited in an autosomal dominant manner and is associated with porphobilinogen deaminase (PBGD) enzyme deficiency. Nonetheless, environmental factors can also affect the disease course.

Specifically, enzyme deficiency is caused by variants in the *HMBS* gene [4]. Most patients present after puberty in the third and fourth decades of life. Furthermore, AIP is a condition that impacts more females compared to males[5]. Individuals with an AIP genotype may remain asymptomatic for a long time. However, it can manifest following triggers such as porphyrogenic drugs, female hormones, alcohol, prolonged hunger and any life-threatening factors[6]. Attacks can be complicated, and patients can present with severe and/or life-threatening symptoms. These symptoms are distinctive, including many gastrointestinal, cardiovascular, neuropsychiatric, endocrine, and renal systems[3]. Neurological involvement includes the central, peripheral, and autonomic nervous systems. Neurological involvement is identified as the cause of abdominal pain, neuropsychiatric symptoms and neuropathies[7].

Approximately 80% of patients complain of abdominal pain and nonspecific symptoms, such as nausea, vomiting, and constipation[8]. In addition, tachycardia, hypertension, and arrhythmias can be observed with catecholamine release due to autonomic nervous system involvement[9]. We postulate that neuropsychiatric involvement may be due to the structural similarity between ALA and gamma-aminobutyric acid (GABA), which accumulates as part of the pathophysiology. Additionally, it is believed that heme metabolite accumulation and insufficient heme synthesis may be neurotoxic to nerve cells[10]. The neurological complications experienced tend to include peripheral, cranial, and autonomic neuropathy as well as epileptic seizures.

Acute motor axonal neuropathy is typically seen in porphyric neuropathy[11]. As in our patient, proximal involvement and the onset of upper limbs constitute some of the important features. Cranial neuropathy is observed in approximately 75% of patients with acute porphyric neuropathy. Generally, cranial neuropathy is observed following limb involvement and it is often accompanied by facial and vagal nerve involvement. Moreover, if it is not treated, involvement of the respiratory muscles is inevitable, as in our patient [7]. Dysphagia, dysarthria, and dysphonia may also manifest. If abdominal symptoms are unclear, neuropathy can be confused with other conditions such as Guillain-Barré Syndrome (GBS). Initial proximal and upper extremity involvement and recurrence of polyneuropathy are among the findings favoring porphyric neuropathy. Furthermore, given the possibility of differential diagnosis, heavy metal toxicity, vasculitis, poliomyelitis and certain infectious diseases like Lyme Disease, enteroviruses, and herpes-mediated polyradiculoneuropathies should also be considered[10,12].

In acute encephalopathy attacks, epileptic seizures may complicate the situation. Seizures may be born of ALA's and porphobilinogen (PBG) neurotoxigenic effects or due to hyponatremia[11]. Hyponatremia is also observed in approximately 90% of acute attacks. It may be associated with the syndrome of inappropriate anti-diuretic hormone (SIADH), as well as being secondary to gastrointestinal and renal losses[13]. A wide variety of psychiatric symptoms can also develop in AIP. Depression, hallucinations, and delirium are often noted, while psychosis, hypomania, and catatonia have also been described[14].

Clinicians should consider acute hepatic porphyrias in the presence of the following three symptoms: motor neuropathy, abdominal pain, and changes in consciousness[7]. Urine and feces porphyrin

precursors should be evaluated for the diagnosis of porphyria. In AIP, the first-line diagnostic tool is PBG levels measured using the spot urinary test[3]. Diagnostic PBG levels range from 20–200 mg/L (N:0-2mg/L). Moreover, although the ALA level is not required for a diagnosis, ALA levels between 25−100 mg/L support a diagnosis of AIP[13]. When suffering attacks, electrolyte abnormalities such as hyponatremia and increasing aminotransferases may help the diagnosis. Although genetic diagnosis is not necessary to confirm the disease, it is recommended to support the diagnosis, to provide genetic counseling to first-degree relatives and to identify asymptomatic carriers. Approximately 95% of individuals with disease-causing variants are asymptomatic throughout their lives. Consequently, there is a vital need to recognize these patients to ensure that the disease is not exacerbated with triggers[15].

In our patient, a history of severe abdominal pain, recurrent descending polyneuropathy, autonomic findings, epileptic seizures, accompanying electrolyte imbalance, and porphyria were considered in the preliminary diagnosis. Once increased urine D-ALA and PBG levels were established, we diagnosed our patient with AIP. The clinical diagnosis was further confirmed following the identification of an *HMBS* gene variant. Neurological involvements cause diagnostic difficulty in people who are yet to be diagnosed, as in our patient, since such symptoms may also be indicative of other diseases, such as Guillain-Barré syndrome, acute encephalitis, and ileus. In addition, it is also vital that patient follow-up is conducted in centers that can systemically evaluate and treat the patient following a diagnosis.

In conclusion, since the disease is extremely rare, highly complex, and life threatening, and its prognosis includes individual differences, there is a vital need to follow these patients in porphyria centers by porphyria experts.

Yazar Katkıları: Çalışma konsepti/Tasarımı: ST, AMK; Veri toplama: ST, OT; Veri analizi ve yorumlama: ÇE, ED; Yazı taslağı: ST, ÇE; İçeriğin eleştirel incelenmesi: ED, OT; Son onay ve sorumluluk: ST, AMK, ÇE, ED, OT; Teknik ve malzeme desteği: AMK; Süpervizyon: ED, ÇE; Fon sağlama (mevcut ise): yok.
Etik Onay: Olgudan aydınlatılmış onam alınmıştır.
Hakem Değerlendirmesi: Dış bağımsız.
Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.
Finansal Destek: Yazarlar bu çalışmanın finansal destek almadığını beyan etmişlerdir.
Author Contributions: Concept/Design : ST, AMK; Data acquisition: ST, OT; Data analysis and interpretation: ÇE, ED; Drafting manuscript: ST, ÇE; Critical revision of manuscript: ED, OT; Final approval and accountability: ST, AMK, ÇE, ED, OT; Technical or material support: AMK; Supervision: ED, ÇE; Securing funding (if available): n/a.
Ethical Approval: Informed consent has been received from the case.
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: The authors declared that this study has received no financial support.

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