ACTA FACULTATIS
MEDICAE NAISSENSIS

UDC: 616.8-008.9-07-08:615.065
DOI: 10.5937/afmnai41-47223

Case report

Successful Treatment Response in a Patient with Severe Neurological Manifestations of Drug-Induced Acute Intermittent Porphyria: A Case Report

Stefan Todorović[1], Gordana Đorđević[1,2], Andrija Rančić[3], Dejan Aleksić[4]

[1]*University Clinical Center Niš, Clinic of Neurology, Niš, Serbia*
[2]*University of Niš, Faculty of Medicine, Niš, Serbia*
[3]*University Clinical Center Niš, Clinic of Gastroenterology and Hepatology, Niš, Serbia*
[4]*University of Kragujevac, Faculty of Medical Sciences, Kragujevac, Serbia*

SUMMARY

Introduction. Acute intermittent porphyria is a rare metabolic disorder of the hem biosynthetic pathway that can cause severe neurological symptoms involving the central, autonomic and peripheral nervous system. Diagnosis may be delayed due to variable symptoms that can mimic other diseases.
Case report. A 23-year-old woman with abdominal pain, constipation, progressive development of quadriparesis and bulbar palsy was admitted to our intensive care unit two weeks after undergoing dental surgery. Preventive antibiotic therapy (erythromycin) and bromocriptine (due to cessation of breastfeeding) could represent precipitating factors for an acute attack of the disease. The diagnosis was confirmed by a high level of porphobilinogen and delta-aminolevulinic acid in urine. The patient was treated conservatively with high carbohydrate intake and human hemin, with a good treatment response. Two months after therapy, the patient was admitted to the Department of Physical Medicine and Rehabilitation and started physical therapy. There was a significant reduction of neurological manifestations at the follow-up examination after three months.
Conclusion. Early diagnosis of acute intermittent porphyria is important for the preventiing of serious consequences and applying of prompt therapy. Further monitoring of patients is also important to avoid potential risk factors that can trigger a porphyria attack.

Keywords: **diagnosis, neurologic manifestation, acute intermittent porphyria, porphobilinogen, delta-aminolevulinic acid, hemin**

Corresponding author:
Stefan Todorović
e-mail: todorovicstefan815@gmail.com

INTRODUCTION

Porphyria is a rare metabolic disorder of the hem biosynthetic pathway, a protein that is a part of hemoglobin (1). The accumulation of various metabolites, primarily delta-aminolevulinic acid (ALA) and porphobilinogen (PBG) can cause damage to the central, autonomic and peripheral nervous system (2). Acute intermittent porphyria (AIP), the most common form, is characterized by the most serious clinical manifestations. Other acute porphyrias are less common and include variegate porphyria (VP), hereditary coproporphyria (HCP), and 5-aminolevulinic acid (ALA) dehydratase deficiency porphyria (3). The prevalence of symptomatic AIP in Europe is about 5.9 per million people, affecting women more often than men (up to 2:1), with symptoms appearing most often between the ages of 18 and 40 (4). Considering the wide range of clinical manifestations, AIP is often associated with misdiagnosis or delayed diagnosis (5). Attacks of AIP are usually manifested by abdominal pain, neurological and psychiatric disorders. Neurological manifestations can cause symptoms involving the central, autonomic and peripheral system. The symptoms of porphyria can be serious and life-threatening (6). Attacks may be precipitated by medications, hormonal changes, physical and emotional stress, starvation, smoking, alcohol and other factors (7). Herein, we report a case of a young woman with severe neurological manifestations of AIP precipitated by drugs.

CASE REPORT

Herein we reported a case of a 23-year-old woman with the symptoms of severe abdominal pain accompanied by constipation, limb pain, and weakness. Her ultrasonography of the abdomen and abdominal X-ray, serum lipase, and amylase level were normal. The presence of chronic gastritis, anemia and hyponatremia was determined during the hospitalization at the local hospital. A few days after hospitalization, hyperthermia (up to 38 degrees), and leg weakness with the inability to walk independently appeared. The ward doctor consulted a neurologist who found flaccid paraparesis in her neurological status. Due to the complaints, the patient was referred to the University Clinical Center Niš under suspicion of acute inflammatory demyelinating polyneuropathy (AIDP). Two weeks before the onset of symptoms, the patient had dental surgery using local anesthesia (lidocaine), and then treated with antibiotic therapy (erythromycin 500 mg, taken 3 times a day, for 2 weeks). In addition, the patient started taking bromocriptine three months before the onset of symptoms due to cessation of breastfeeding. She was not a smoker and did not consume alcohol or drugs. No family history of similar complaints was present.

At the time of hospital admission to hospital, the patient was alert, communicative and oriented. No psychomotor agitation was registered. Neurological examination revealed a moderate degree of flaccid quadriparesis, with dominant weakness of the proximal muscle groups. The other part of the neurological examination was normal. During the diagnostic examination in laboratory analyses, persistent severe hyponatremia (rang 111 - 130 mmol/L) was registered (despite regular therapeutic correction), with an imbalance of other electrolytes (especially magnesium and chloride) (Table 1). The immunological markers ANA, ANCA, anti-DSA, anti-cardiolipin, anti-beta2-glycoprotein, anti-SSA, anti-SS, JO1 AB-B and anti-centromere-B were negative. Serological tests for syphilis, HIV infection, cytomegalovirus, HSV, HZV, borreliosis, hepatitis B and hepatitis C, and toxoplasmosis were also negative. The level of vitamins was also measured, which was within the reference range. Cerebrospinal fluid (CSF) analysis indicated a mild proteinorachia (0.62 g/L), with normal glycorrhachia and cellularity. Magnetic resonance imaging (MRI) of the brain and cervical spine was without pathological substrate. Such a finding and the clinical presentation at that time indicated the possibility of AIDP. Furthermore, she developed acute hypertension (150/100 mmHg) and tachycardia (up to 140 beats/min), with pulse oxygen at 92%. Despite conservative management of hypertension, tachycardia and electrolytes, unresolved electrolyte imbalance and exacerbating neurovisceral status required intensive care during the disease course. Her neurovisceral status rapidly deteriorated, leading to severe quadriparesis and bulbar palsy within 10 days. Administration of high doses of glucose (> 500 g/day), correction of electrolytes balance and stabilization of the cardiac status led to a slight improvement in the patient's neurovisceral status. At the time, arterial blood gas analysis revealed pH 7.35 (normal range 7.35 – 7.45); $PaCO_2$ 36 mmHg (normal range 38 – 42 mmHg); PaO_2 95 mmHg (normal range 75 – 100 mmHg); HCO_3 19.2

Table 1. *Electrolyte balance and values of PGB and delta-ALA during hospitalization*

Days of hospitalization	Na (135 - 145 mmol/L)	Mg (0.65 - 1.05 mmol/L)	Cl (97 - 108 mmol/L)	PBG (< 15 μmol/L) delta-ALA (11.4 – 57.2 μmol/L)
Hospital day 1	111	0.52	87	
Hospital day 3	114	0.54	89	
Hospital day 5	117	0.56	89	
Hospital day 7	119	0.52	87	
Hospital day 9	121	0.64	94	
Hospital day 12	126	0.86	96	
Hospital day 14	130	0.88	99	179.9 151.6

PBG – porphobilinogen; **delta-ALA** - delta-aminolevulinic acid

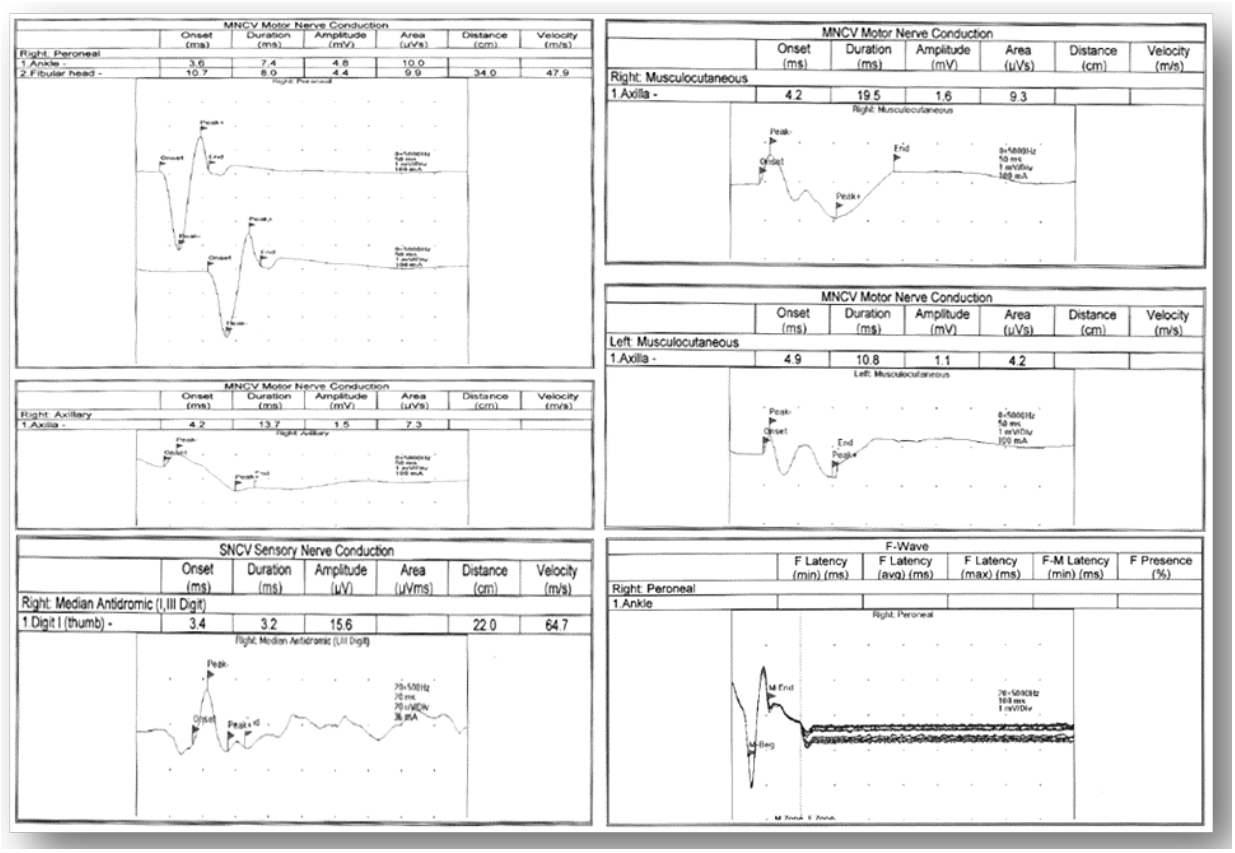

Figure 1. *EMNG indicates motor-predominant, axonal neuropathy*

mmol/L (normal range 23 – 29 mmol/L) and $SatO_2$ 99%. Other laboratory analyses revealed sodium 126 mmol/l (normal range 136 - 145 mmol/l), Hb 114 g/L (normal range 120 - 160 g/L), Ht 0.33 (normal range 41 - 50%), AST 89 U/L (normal range 10 - 36 U/L), ALT 81 U/L (normal range 4 - 36 U/L), LDH 373 U/L (normal range 105 - 233 U/L). Other analyses were normal (potasium 4.6 mmol/l, calcium, 2.33 mmol/l, magnesium 0.88 mmol/l, chloride 99 mmol/l, CRP 0.2 mg/L, RBC 3.79 x 1012, leukocytes 11.4 × 109/L, platelets 178.000, glucose 5.6 g/L, urea 6.6 mmol/l, creatinin 71.8 μmol/L, albumin 34 g/L, amylase 124 U/L).

In the further diagnostic course, electromyoneurography (EMNG) was performed and indicated the absence of conduction of both peroneal nerves, low amplitude M potential during stimulation of the

axillary nerve and musculocutaneous nerve on both sides, absence of F waves when stimulating both peroneus and reduced persistence when stimulating the right median nerve (3/10). Repetitive nerve stimulation (RNS) and single-fiber electromyography (SFEMG) for myasthenic syndrome or MG were negative. Thus, the patient had severe predominant axonal motor neuropathy (Figure 1).

Finally, due to the reddish color of her urine and further diagnostic examination, with the detection of a higher level of porphobilinogen (PBG) (179.9 μmol/l, normal values < 15 μmol/L) and delta-ALA in the urine (151.6 μmol/L, normal range 11.4 - 57.2 μmol/L), a diagnosis of porphyria was made. Molecular genetic testing is not essential to confirm a diagnosis when biochemical porphyrin findings are characteristic and it was not performed in this case.

She received heme (Normosang® 25 mg/mL), in the dose of 4 mg/kg/day, four days in a row, with a good treatment response. Two months after therapy, the patient was admitted to the Department of Physical Medicine and Rehabilitation. The follow-up examination was performed after three months. There was a significant reduction of neurological manifestations, with the detection of mild quadriparesis in her neurological status.

DISCUSSION

We presented a young woman with the first attack of AIP. The suspicion of GBS was rejected and the patient was correctly diagnosed as AIP (diagnosed based on clinical picture, reddish urine, enzyme level and EMNG) provoked most likely using erythromycin and/or bromocriptine. The patient was successfully treated with heme preparations and made a significant recovery.

AIP is a genetic and metabolic disorder of the hem biosynthetic pathway, caused by a deficiency of porphobilinogen deaminase (PBGD). Patients with AIP have acute attacks which can affect all parts of the nervous system, followed by a high level of PBG and ALA in urine. The first presentation of porphyria usually includes abdominal pain (in 85% - 95% of patients), while 45% of patients may have peripheral predominant motor neuropathy. The exact mechanism of neuronal damage remains unknown and one of the theories indicates the possible role of the crystallization of by-products that can cause damage in neural structures (3, 8).

The prevalence of symptomatic AIP is about 5.9/million in Europe, with a prevalence of pathogenetic HMBS mutations 1/1782 and a penetrance of less than 1% (9). This indicates that even in a patient with a negative family history, we should always consider this disease if the clinical status indicates it. Due to the heterogeneity of the clinical picture, AIP is a disease that is rarely easily diagnosed (10).

Many drugs are considered a provoking factor for attacks in AIP – porphyrinogenic drugs (Metamizole, Clindamycin, Erythromycin, Nitrofurantoin, Sulfonamides, Trimethoprim, Phenobarbital, Carbamazepine, Topiramate, etc.) (5). On the other hand, the UK Porphyria Association updates the list of safe drugs every year (available at: http://porphyria.org.uk/safe-drug-list/).

Bromocriptine and erythromycin are not included in this list of drugs. Bromocriptine is not considered a safe drug and may provoke an attack of AIP (11, 12), although the data is not consistent between the different bases, because it is unsafe in one (http://porphyriadrugs.com/) and most likely not unsafe in the other base (http://www.drugs-porphyria.org/sp1.php) (13). The erythromycin should be avoided because it is regarded as unsafe and has reportedly triggered attacks (5, 13 - 15)

In our patient, AIP presented as acute neuropathy (mainly motor, mainly axonal), which is a differential diagnosis and a potential finding in various conditions such as: GBS (AMAN), CIDP, MND, DM, toxicity with heavy metals (lead, arsenic, thallium), drugs, alcohol, polyneuropathy due to vitamin deficiency (B1, B6, B12) (5). AIP should be considered in all patients with a clinical picture of GBS due to the clinical heterogeneity in the manifestation of both diseases. In AIP, specific signs of autonomic dysfunction begin before developing neurological symptoms, whereas in GBS, autonomic dysfunction usually develops parallel to the paresis. AIP is usually not a gastrointestinal post-infectious complication or in association with CMV-reactivation. Albuminocytological dissociation in CSF seemed to support GBS diagnosis, but this is a common finding in AIP as well (5, 16). Mild hyperproteinorachia without cellular elements in the cerebrospinal fluid was noted in our patient. Likewise, mixed axonal-demyelinating polyneuropathy was noted in our patient, which was also reported in earlier studies (5).

The FDA and the EMA approved a new drug for patients with recurrent attacks of acute hepatic

porphyria. Among the 89 patients with AIP, the mean annualized attack rate was 3.2 in the Givosiran group and 12.5 in the placebo group ($p < 0.001$). Givosiran led to lower levels of urinary ALA and porphobilinogen, fewer days of hemin use, and better daily scores for pain. The observed adverse events were elevations in serum aminotransferase levels, changes in serum creatinine levels and the estimated glomerular filtration rate, as well as injection-site reactions (17, 18). The drug is still not available in Serbia.

CONCLUSION

Acute intermittent porphyria can cause severe neurological symptoms that can affect all parts of the nervous system, mimicking the clinical presentation of other diseases. A timely diagnosis of AIP, in addition to an adequate therapeutic approach, is also important in the further monitoring of patients to avoid potential risk factors that can provoke a new attack of the disease. Late and wrong diagnosis can lead to serious consequences and fatal outcome.

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Article info
Received: October 19, 2023
Revised: November 7, 2023
Accepted: November 20, 2023
Online first: September 26, 2024

Uspešan terapijski odgovor kod bolesnika sa teškim neurološkim manifestacijama akutne intermitentne porfirije izazvane lekovima: prikaz slučaja

Stefan Todorović[1], Gordana Đorđević[1,2], Andrija Rančić[3], Dejan Aleksić[4]

[1]*Univerzitetski klinički centar Niš, Klinika za neurologiju, Niš, Srbija*
[2]*Univerzitet u Nišu, Medicinski fakultet, Niš, Srbija*
[3]*Klinika za gastroenterologiju i hepatologiju, Univerzitetski klinički centar Niš, Niš, Srbija*
[4]*Univerzitet u Kragujevcu, Medicinski fakultet, Kragujevac, Srbija*

SAŽETAK

Uvod. Akutna intermitentna porfirija je redak metabolički poremećaj u čijoj je osnovi poremećaj biosinteze hema i može izazvati teške neurološke simptome, koji uključuju centralni, autonomni i periferni nervni sistem. Pravovremena dijagnoza bolesti često predstavlja veliki izazov zbog raznovrsnih simptoma koji mogu imitirati kliničku prezentaciju drugih bolesti.
Prikaz slučaja. Žena stara 23 godine sa bolovima u stomaku, konstipacijom, progresivnim razvojem kvadripareze i bulbarne paralize primljena je u jedinicu intenzivnog lečenja dve nedelje nakon stomatološke operacije. Prethodna upotreba preventivne antibiotske terapije (eritromicin) i bromokriptina (korišćen radi supresije laktacije) može da uslovi nastanak akutne bolesti. Dijagnoza je potvrđena detekcijom visokih nivoa porfobilinogena i delta-aminolevulinske kiseline u urinu. Bolesnica je lečena konzervativno visokim unosom ugljenih hidrata i humanim heminom. Postignut je dobar odgovor na lečenje. Dva meseca nakon terapije, bolesnica je primljena na Odeljenje fizikalne medicine i rehabilitacije i tada je započet fizikalni tretman. Na kontrolnom pregledu nakon tri meseca došlo je do značajnog poboljšanja u njenom neurološkom statusu.
Zaključak. Rana dijagnoza akutne intermitentne porfirije značajna je za pravovremeno ordiniranje terapije i prevenciju ozbiljnih posledica, kao i za dalji monitoring bolesnika u cilju izbegavanja potencijalnih faktora rizika koji mogu provocirati naredni atak porfirije.

Ključne reči: **dijagnoza, neurološka manifestacija, akutna intermitentna porfirija, porfobilinogen, delta-aminolevulinska kiselina, hemin**