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Title: Porphyria in pregnancy with exacerbation after delivery due to COVID-19

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Abstract

We present a case of acute intermittent porphyria (AIP) diagnosed in a pregnant woman with subsequent exacerbation after delivery due to COVID-19 infection. The patient's symptoms manifested with acute neurovisceral attacks - abdominal pain followed by flaccid quadriparesis, sensory disturbances, hypertension and disturbance in electrolyte levels. The blood plasma test and a 24-hour urine collection revealed increased levels of urine porphobilinogen, 5-aminolevulinic acid and uroporphyrins, which led to the diagnosis of AIP. The patient received i.v. human hemin with positive outcome. After delivery she was again admitted to the hospital due to abdominal pain and trunk hyperesthesia that occurred after a mild course of COVID-19 infection. The second administration of human hemin led to the improvement of the patient's condition. The aim of this case report is to indicate that even with severe risk factors of AIP such as infection and pregnancy, proper diagnostics can increase the chance of quick recovery.

Keywords: acute intermittent porphyria, porphyria in pregnancy, hemin treatment in pregnancy, acute neurovisceral attacks with coexisting COVID-19 infection, risk factors of acute intermittent porphyria

Introduction

Porphyrias are a heterogenous group of rare, metabolic diseases of genetic etiology. They are characterized by the deficiency of one or more of enzymes involved in heme biosynthesis. There are eight subtypes of porphyrias. Four that form the group of acute hepatic porphyrias (AHP) and can cause neurological symptoms are the following: acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP) and ALA-dehydratase porphyria (ALADP). The other subtypes focus mainly on skin and are categorized as photocutaneous porphyrias. These include: congenital erythropoietic porphyria (CEP), sporadic and familial porphyria cutanea (PC), erythropoietic protoporphyria (EPP) and X-linked protoporphyria (XLPP). [1] [Tab.1]

Table 1. Subtypes of porphyrias and their characteristics.
AD - autosomal dominant; AR- autosomal recessive

Subtype of porphyria	**Inheritance**	**Deficient enzyme**	**Clinical presentation**
Acute intermittent porphyria (AIP)	**AD**	**Porphobilinogen deaminase**	**Acute neurovisceral attacks**
Variegate porphyria (VP)	AD	Protoporphyrinogen oxidase	Acute neurovisceral attacks and photosensitivity
Hereditary coproporphyria (HCP)	AD	Coproporphyrinogen oxidase	Acute neurovisceral attacks and photosensitivity
ALA-dehydratase porphyria (ALADP)	AR	ALA dehydratase	Acute neurovisceral attacks
Congenital erythropoietic porphyria (CEP)	AR	Uroporphyrinogen III synthase	Photosensitivity, blistering, increased hemolysis
Sporadic and familial porphyria cutanea (PC)	AD	Uroporphyrinogen III decarboxylase	Photosensitivity, blistering
Erythropoietic protoporphyria (EPP)	AR	Ferrochelatase	Photosensitivity
X-linked protoporphyria (XLPP)	X-linked	5-aminolevulinate synthase 2	Photosensitivity

The most common acute hepatic porphyria is the acute intermittent porphyria, which is inherited, in most cases, in autosomal dominant manner, and is associated with a decreased activity of porphobilinogen deaminase.[2] Due to the multiple mechanisms in which

porphyrin precursors influence the body, there can be no clear group of symptoms which can be present in every patient affected by the disorder. The multitude of non-specific complaints from a patient might prove difficult for a clinician to establish an accurate diagnosis. One of the most prevalent systems affected by AIP include: gastrointestinal system (presenting with abdominal pain, diarrhea, nausea and vomiting, constipation), nervous system (presenting with epilepsy, polyneuropathy), cutaneous system, hematological system, psychiatric symptoms and so forth. [3] There are plenty of triggering factors that are known to worsen the course of AIP or even precipitate first onset of symptoms in patients with genetic predisposition. Among the most frequent ones one can list: hormonal imbalances, certain medications taken, infections, alcohol, smoking and poor dietary habits. [4] [Tab.2]The aim of this article is to present a case of a patient, whose first episode of AIP was precipitated by early pregnancy – thus being a mix of different risk factors.

Table 2. Factors precipitating porphyria attacks. Based on: *DeLoughery TG. Acute Intermittent Porphyria*

Female sex hormones	Fluctuations in estrogen/progesterone ratio Oral contraception Perinatal period
Diet	Extended fasting Diet poor in carbohydrates
Medications	Barbiturates Sulfonamides Nitrofurantoin Gryzeofulvin Diclofenac Carbamazepine Valproic acid Amitryptilin/Imipramine Dimenhydrynatte
Toxins	Alcohol Nicotine Organic solvents
Biological factors	Bacterial infections Viral infections
Physical factors	Stress Surgeries Dehydration Extended sunlight exposure

Case report

The case presents a 35-year-old female patient diagnosed with porphyria and axonal polyneuropathy while being in the first trimester of the pregnancy (6th week) in May 2021. The symptoms began on the 15th of May with acute lower abdomen ache that led the patient to the hospital emergency ward. Gynecological consultation and transvaginal ultrasound were performed - a gestational sac, 2.7 mm in diameter was visible in the uterine cavity. She received drotaverine both orally and intravenously and was discharged home. Two days later due to the continuous pain of the lower abdomen she was admitted to the Department of Obstetrics and Pathology of Pregnancy. During her hospitalization she developed flaccid quadriparesis which was progressing until the 23rd of May. Then the lumbar puncture and MRI of the head and cervical spine were performed with no pathologies in the results. However, the electromyography revealed sensory-motor axonal polyneuropathy. On the 26th of May the patient was transferred to the Department of Neurology. The detailed neurological examination revealed flaccid quadriparesis, more pronounced proximally and on the left side, sensory disturbances in the arms, thighs, trunk and in the area of innervation of the third branch of the trigeminal nerve on the right side, with decreased superficial touch sensation or hyperesthesia, lack of reflexes in the upper limbs, weak knee reflexes, normal Achilles tendon reflexes, no sphincter disorders, negative Babinski sign. Initially there was an assumption that the patient had Guillain-Barre syndrome, thus as a treatment she received intravenously (i.v.) immunoglobulin G for three days. Unfortunately, her condition did not improve. Hypokalemia and hyponatremia together with increased blood pressure and tachycardia were also observed. Correction of electrolyte disturbances and hypertension (with methyldopa and metoprolol) was applied. Based on the patient's symptoms, porphyria was suspected.

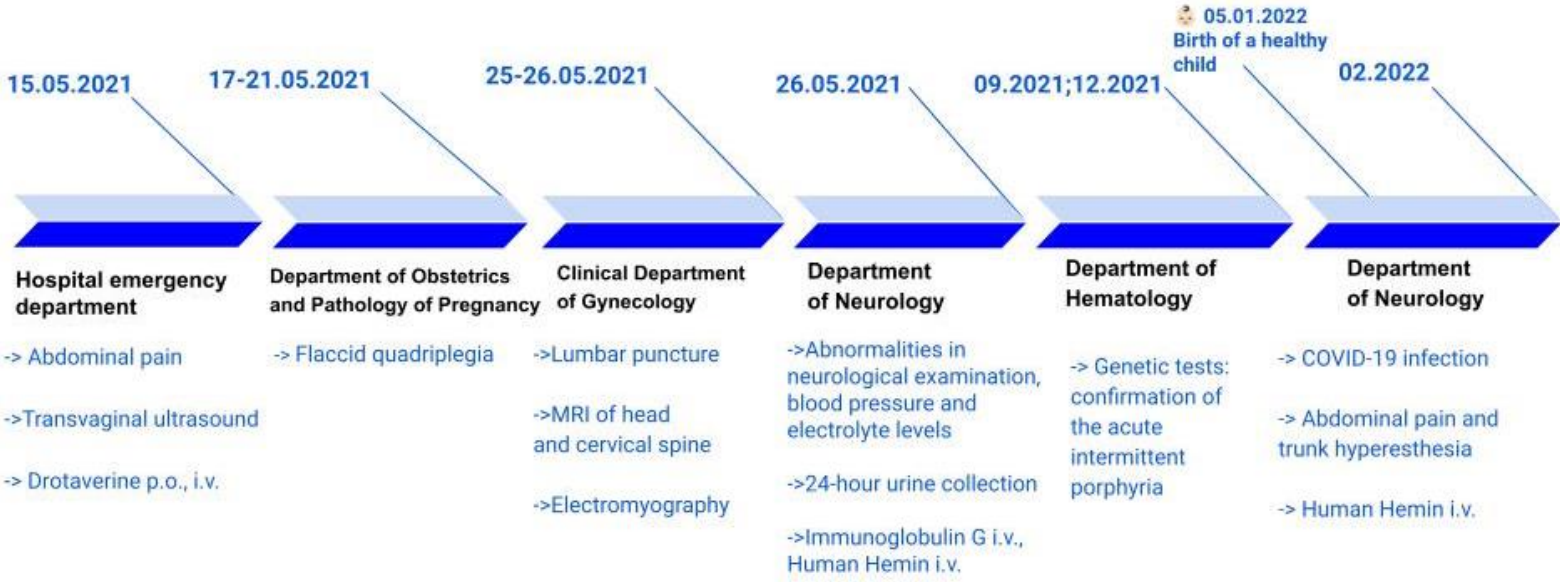
Blood plasma test and urine test from a 24-hour urine collection revealed significantly increased levels of urine porphobilinogen PBG = 465 umol/d (N: 0.4-7.5) 5-aminolevulinic acid ALA = 419 umol/d (N: 1.9-49) and uroporphyrins = 846.9 nmol/d (N: 3.6-30). This led to the diagnosis of acute intermittent porphyria. The patient received i.v. human hemin at the dose of 3 mg/kg per day for four days.

As a result of the treatment, abdominal pain disappeared and the severity of paresis and sensory disturbances decreased. During rehabilitation on the ward the patient was verticalized and was able to walk independently for short distances. On the 7th of June the patient was discharged home.

In September and December 2021 the patient was hospitalized in the Department of Hematology, where the genetic tests were made and acute intermittent porphyria was confirmed. On the 5th of January 2022 she gave birth to a healthy child via cesarean section.

In February 2022 the patient was again admitted to the Department of Neurology due to exacerbation of neurological symptoms. Abdominal pain and trunk hyperesthesia had been present for approximately one week.The patient was in isolation until February 10th, due to a positive test result for COVID-19 and suffered from a mild course of SARS-CoV-2 infection. During the neurological examination paresthesia in the area of thighs and perineum, hypoaesthesia in the area of the right scapula were found, but tendon reflexes were present. Human hemin was administered i.v. again at a dose of 3 mg/kg daily for 3 days, without complications. As a result the pain in the lower abdomen disappeared. The patient was discharged home in good general condition. [Fig.1.]

Figure 1. Timeline of the patient's hospitalization and treatment



Discussion

This case illustrates the typical onset of acute intermittent porphyria in a pregnant patient with a healthy child delivery. There have been few cases of concomitant AIP and pregnancy in the available literature. Nonetheless, the link should not be overseen as pregnancy in women with AIP has been associated with a higher risk of spontaneous abortions, low birth weight and significantly higher infant mortality (even up to 40%), especially when the onset of symptoms takes place during the first trimester.[5,6] Symptoms primarily reported by the patient – nausea, vomiting, stomach ache, dizziness – are quite non-specific and could easily be misdiagnosed as preeclampsia or hyperemesis gravidarum, which is a significantly more common condition. For this reason, introducing appropriate treatment is often delayed and the final outcome less favorable.[3] In our case, axonal polyneuropathy preceded by stomach ache and treatment with drotaverine, lack of cyto-albuminologic dissociation in the cerebrospinal fluid analysis, led the clinicians to the appropriate diagnosis through urinalysis, showing severely increased concentration of porphobilinogen and 5-aminolevulinic acid. Later, the patient also confirmed that she suffered from an episode of mild depression in the past that could have been the first sign of AIP.

Electrolyte disturbances (hypokalemia and hyponatremia) are characteristic for AIP, but could have also been caused by frequent vomiting. Severe hyponatremia might have resulted in epileptic attacks, which, luckily, did not occur in this particular case. What is also worth noting is that since the AIP episode occurred during the patient's first pregnancy, the clinicians should predict with a significant level of certainty that during following pregnancies there will be a relapse of symptoms that will require immediate intervention.

Pregnancy proves to be one of the essential factors associated with provoking episodes of AIP. Although the link is not yet fully explained, it is suspected that it involves changes in

hormonal activity. Some female patients experience cyclic AIP attacks during luteal phases of menstrual cycles, and there is an estimated 50% chance of a porphyric attack during pregnancies. Both estrogen and progesterone are claimed to take part in exacerbation of symptoms, and there have been cases in which an episode of porphyria has even been precipitated by oral contraceptives. The exact mechanism in which female sex hormones affect porphyrin metabolism is yet to be fully determined. [7,8]

The patient suffered from another exacerbation of neurological symptoms after a mild course of COVID-19 infection. SARS-CoV-2 infection has been reported to be a triggering factor of an attack of porphyria, however not many cases of such type exist. [9] Various viral and bacterial infections can be the cause of porphyria attack because inflammation disturbs protoporphyrin metabolism via impairment of hemoglobin and iron distribution throughout the body that is why it can be the cause of an exacerbation of AIP. [10]

In the treatment of AIP in pregnant women, the first step is to identify potential risk factors that are known to precipitate acute attacks, such as certain antibiotics and other medications, inflammation of any kind, dehydration, poor nutrition etc., and implement appropriate prophylaxis.[4] Once the episode starts, therapeutic options become significantly more limited. Appropriate analgesic choice is of utmost importance and patient-controlled analgesia might also be considered. Close monitoring of a patient's vital function and electrolyte levels (especially sodium, both in blood and in urine) also cannot be omitted.[6,11] In mild episodes, symptomatic treatment such as proper analgesia, diet rich in sodium and carbohydrates or i.v. glucose is enough to achieve remission in a satisfactory amount of patients.[8] Unfortunately, when there are severe neurological deficits, other clinically important symptoms or severe hyponatremia, human hemin is the drug of choice.[6,11] Due to the lack of randomized controlled trials that account for safety of human hemin's use in pregnancy, its use remains somewhat controversial. Even though there are no clear reports of its teratogenic properties,

clinicians should take into consideration its capability of inducing phlebitis or hepatic damage due to the iron overload.[12] Since each acute AIP episode is associated with substantially increased risk of spontaneous abortions and mother's mortality, the use of human hemin in life-endangering instances seems undoubtedly justified. Despite that, close monitoring of mother's liver functions are necessary for the early diagnosis of hemin-induced hepatic damage. In multigravidae mothers, who have already experienced acute porphyric attacks during previous pregnancies, prophylaxis use of human hemin could also be considered in correlation with severity of past episodes.

Conclusions

In conclusion, the presented case shows that acute intermittent porphyria still proves to be a relevant diagnostic problem, especially in pregnancy, because of its symptoms mimicking milder and more frequent conditions in pregnant patients. Nonetheless, in case of uncertain diagnosis early urinalysis focused on measuring levels of protoporphyrin and 5-aminolevulinic acid may significantly impact both patients’ and fetuses' survivability. Since human hemin remains a pillar among successful treatment options for severe episodes of AIP, more randomized controlled trials need to be performed to further assess its safety and efficacy in this indication. It should be also taken into consideration that COVID-19 infection, even of a mild course, can be a triggering factor of an attack of porphyria.

List of abbreviations:

AIP - acute intermittent porphyria

AHP - acute hepatic porphyrias

VP -variegate porphyria

HCP - hereditary coproporphyria

ALADP - ALA-dehydratase porphyria

CEP- congenital erythropoietic porphyria

PC - sporadic and familial porphyria cutanea

EPP - erythropoietic protoporphyria

XLPP - X-linked protoporphyria

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