REVIEW

Acute Hepatic Porphyria – Minireview

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Abstract

Acute Hepatic Porphyria (AHP) is an uncommon and hereditary illness that belongs to a group of disorders known as porphyries. This condition results from a deficiency of the porphobilinogen deaminase enzyme, which plays a role in heme production, a crucial component of haemoglobin in the bloodstream. This deficiency leads to the accumulation of substances called porphyrins in the body, which can trigger the appearance of severe and potentially life-threatening symptoms.

In the following, we will discuss classifications - with a focus on the similarities and differences between subtypes of porphyria, the pathophysiology of acute hepatic porphyria, risk factors – and their influence on the onset of the disease, clinical manifestations, diagnosis, and management – both curative and symptomatic, all of which play a very important role in understanding this rare condition.

Keywords: Porphyria, haemoglobin, Acute hepatic porphyria (AHP).

Rezumat

Porfiria acută hepatică este o boală rară și de origine ereditară, inclusă într-un grup de afecțiuni numite porfirii. Această afecțiune este cauzată de o deficiență a enzimei porfobilinogen deaminază, care este implicată în producerea hemului, o componentă esențială a hemoglobinei din sânge. Această deficiență duce la acumularea de substanțe numite porfirine în organism, ceea ce poate declanșa apariția unor simptome grave și potențial letale. În cele ce ce urmează vom discuta despre clasificări – cu accent pe asemănările și diferențele dintre subtipurile de porfirii, fiziopatologia porfiriei hepatice acute, factori de risc – cu influența lor asupra debutului maladiei, manifestări clinice, diagnostic și management – atât curativ, cât și simptomatic, toate având un rol foarte important în înțelegerea acestei afectiuni rare.

Cuvinte cheie: Pofirie, hemoglobina, Porfiria acută hepatică.

Porphyria is a collection of rare hereditary conditions that impact the synthesis of heme, a vital constituent of haemoglobin that is responsible for carrying oxygen throughout the bloodstream.

In principle, porphyria can be classified through two major ways, but there are also other subtypes that deviate from these two methods.

The classification can be made according to major physiological sites where the heme is being produced, or in reference to major clinical manifestations. That being said the classification consists of acute hepatic porphyria where the site is found in the liver and erythropoietic porphyria where the site can be found in the bone marrow. Regarding the symptomatic manifestations, percu-

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taneous porphyria and acute porphyria are included in the classifications of the specialized literature.

One difference between the two is that the first one refers strictly to the cutaneous manifestations resulting from phototoxicity, while the second category refers to neurovisceral manifestations such as severe abdominal pain.

Another distinction between the two of them stands in the cause of the symptomatology.

On the one hand, acute porphyria symptoms are caused by an accumulation of neurotoxic intermediates ALA and PBG resulting from inefficient biosynthesis of heme, leading to damage to the nervous system. In contrast, percutaneous porphyria symptoms are caused by increased concentrations of photosensitizing porphyrins.

Furthermore, we will discuss a specific type of porphyria called acute hepatic porphyria

Acute Hepatic Porphyria (AHP) is a rare genetic disorder that affects the production of heme, a vital component of haemoglobin, the protein in red blood cells that carries oxygen throughout the body. AHP is characterized by the accumulation of porphyrin precursors in the liver, which can cause acute attacks of severe abdominal pain, nausea, vomiting, and constipation. There are some more symptoms that may occur such as muscle weakness and pain (particularly in the arms, legs, and back), anxiety, confusion, seizures and hallucinations as well as urinary problem like urinary retention, incontinence, or dark urine.

It's important to note that not all patients with AHP will experience all of these symptoms, also the severity and frequency of symptoms can vary from person to person.

PATHOPHYSIOLOGY OF ACUTE HEPATIC PORPHYRIA

AHP is a genetic disorder caused by mutations in one of the enzymes involved in the heme biosynthesis pathway. Heme is a critical component of many proteins in the body, including haemoglobin in red blood cells, myoglobin in muscle cells, and various enzymes involved in energy production and detoxification. Heme biosynthesis occurs primarily in the liver and involves eight different enzymes that catalyse a series of reactions, ultimately leading to the production of heme.

In AHP, mutations in one of the enzymes in the heme biosynthesis pathway lead to a partial deficiency of that enzyme's activity. This results in the accumulation of precursor molecules, such as delta-aminolaevulinic acid (ALA) and porphobilinogen (PBG), in the liver and other organs. These molecules are thought to be neurotoxic and can cause acute attacks of AHP.

During an acute attack, the accumulation of these molecules in the liver causes a marked increase in their levels in the blood and urine. This leads to the characteristic symptoms of AHP, which include severe abdominal pain, nausea, vomiting, constipation, and in severe cases, seizures, confusion, and paralysis. The exact mechanism by which these molecules cause neurological symptoms is not entirely understood, but it is believed to involve the inhibition of the neurotransmitter gamma-aminobutyric acid (GABA), leading to overexcitation of the nervous system.

The most common types of AHP are Acute Intermittent Porphyria, Variegate Porphyria, and Hereditary Coproporphyria Acute Intermittent Porphyria is the most common type of AHP, accounting for approximately 80% of cases.

AHP is an autosomal dominant disorder, meaning that individuals with the defective gene have a 50% chance of passing it on to their children. AHP affects both men and women, although women are more likely to experience symptoms due to hormonal fluctuations during menstruation, pregnancy, and menopause. Being a rare genetic disorder, its prevalence varies depending on the specific subtype. In the United States, the estimated prevalence of AHP is approximately 1 in 75,000 individuals. However, this may be an underestimation due to the challenges in diagnosis and the lack of awareness of this condition among healthcare providers.

PREDISPOSING AND RISK FACTORS FOR ACUTE HEPATIC PORPHYRIA

Although this disease is a genetic, hereditary disorder, it also has other predisposing factors in addition to genetic ones, including:

- **Gender:** Women are more commonly affected by AHP than men, with a female to male ratio of about 4:1. Hormonal changes such as those that occur during menstruation, pregnancy, and menopause can trigger acute attacks of AHP. That being said women with AHP or at risk of it, should discuss their condition with a healthcare

provider, if they ever consider hormonal therapy.

- **Medications:** Certain medications can trigger acute attacks of AHP by altering the activity of enzymes involved in heme biosynthesis. Hormonal contraceptives, antiepileptic drugs, and some antibiotics are among the medications that have been reported to trigger attacks.
- **Fasting and dieting:** Prolonged fasting, crash dieting, and other stress factors that can lead to calorie restriction have the ability to trigger acute attacks of AHP. Therefore, maintaining a balanced diet and avoiding prolonged fasting is recommended for patients with AHP. In order to prevent episodes, certain patients may need to consume several small meals at regular intervals
- **Environmental factors**: Exposure to certain chemicals, such as pesticides and solvents, has been associated with an increased risk of developing AHP. However, the exact mechanisms by which environmental factors contribute to the development of AHP are not well understood.

It is important to emphasize that the existence of the risk factors mentioned earlier does not inevitably result in the occurrence of this disease in all patients.

DIAGNOSIS

Diagnosis of AHP can be challenging due to the rarity of the disease and the nonspecific nature of its symptoms. Diagnosis typically involves a combination of clinical evaluation, biochemical testing, genetic testing, and exclusion of other conditions that can cause similar symptoms. The following are some of the tests that are used to diagnose AHP:

1. Urine and blood tests: These tests measure the levels of porphyrins and their precursors in urine and blood. Elevated levels of porphyrins in urine and/or blood are a key diagnostic feature of AHP.
2. Stool tests: These tests measure the levels of porphyrins in stool. The presence of high levels of porphyrins in stool is a characteristic feature of AHP.
3. Genetic testing: Genetic testing can identify mutations in the genes responsible for AHP. This type of testing is useful for confirming a diagnosis and for identifying carriers of the condition.
4. Imaging tests: Imaging tests, such as an abdominal ultrasound or CT scan, may be used to look for signs of liver or spleen damage, which can occur in some cases of AHP.

Early diagnosis and management of AHP are crucial to prevent complications and improve long-term outcomes for individuals with the condition. Furthermore, it is important to note that AHP is a medical emergency, that being said, hospitalization is imperative for patients in which this disease is suspicioned

MANAGEMENT AND TREATMENT

The management of AHP involves several approaches, including symptomatic treatment, prevention of acute attacks, and genetic counselling. Symptomatic treatment includes the use of pain medications, antiemetics, and laxatives to alleviate symptoms during acute attacks. Prevention of acute attacks involves the identification and avoidance of triggers, such as certain medications, fasting, and alcohol consumption.

As for a more targeted treatment, a recent clinical trial evaluated the efficacy and safety of a small molecule drug called Givosiran in individuals with AHP. Givosiran is designed to reduce the production of porphyrin precursors in the liver and has shown promise in reducing the frequency and severity of acute attacks in individuals with AHP.

The trial found that Givosiran was well-tolerated and significantly reduced the rate of acute attacks in individuals with AHP, suggesting that it may be a promising treatment option for this condition.

Genetic counselling is also an essential component of AHP management, as it can help individuals and families understand the genetic basis of the condition and make informed decisions about family planning.

Genetic testing can identify carriers of the AHP gene and help prevent the development of AHP in future generations through pre-implantation genetic diagnosis (PGD) or prenatal testing.

In addition, ongoing research is examining the relationship between AHP and other conditions, such as chronic pain and mental health disorders, to better understand the impact of AHP on overall health and well-being.

One recent study published in the Journal of Hepatology aimed to determine the prevalence and clinical characteristics of AHP in a large cohort of patients with unexplained acute abdominal pain. The study found that AHP was present in approximately 4% of patients with unexplained acute abdominal pain, high-

lighting the importance of considering AHP in the differential diagnosis of this condition.

Another study published in the Journal of Clinical Endocrinology & Metabolism examined the relationship between AHP and thyroid function. The study found that individuals with AHP were more likely to have abnormalities in thyroid function, suggesting a potential link between the two conditions.

In conclusion, Acute Hepatic Porphyria is a rare genetic disorder that can cause severe and potentially life-threatening symptoms. Early diagnosis and management are crucial to prevent complications and improve long-term outcomes for individuals with the condition.

While there is currently no cure for AHP, ongoing research is examining new treatment approaches that show promise in reducing the frequency and severity of acute attacks and improving quality of life for individuals with the condition. With continued research and advancements in treatment, there is hope for a better understanding of AHP and improved outcomes for those affected by this condition and their families

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