Review Article

Acute intermittent porphyria in pregnancy: A common misdiagnosis

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Summary

Acute intermittent porphyria (AIP) is inherited in an autosomal dominant fashion. Only 10% to 15% of the gene carriers have the clinical syndrome. The prevalence of AIP in Europe is 1/20,000. Pregnancy represents an essential risk factor in patients suffering from AIP. The clinical syndrome in AIP presents mainly with acute attacks, especially during the first trimester. Misdiagnosis of AIP unfortunately is very common. Pregnancy in women with AIP is associated with higher rates of spontaneous abortion, hypertension, low birth weight infants and considerable mortality (2-42%). Pregnancy, despite the major hormonal alterations it causes, is seldom associated with porphyric symptoms. There are only limited reports supporting the use of hemin during pregnancy, but experience indicates that it can be safely administered in pregnant women. Until clinical improvement is achieved, symptomatic treatment is recommended. Despite the fact that pregnancy in women suffering from AIP is related to higher rates of morbidity and complications, close management throughout the pregnancy could ensure a good outcome.

Key words: Acute intermittent porphyria; Pregnancy; Hemin; Treatment; Acute attacks.

Introduction

Acute intermittent porphyria (AIP) is a rare metabolic disorder, inherited in an autosomal dominant fashion. Pregnancy represents an essential risk factor in patients suffering from AIP. There are only limited reports dealing with the incidence, the clinical presentation, the diagnosis, the differential diagnosis and the treatment of patients with AIP in pregnancy. It is this rarity that has resulted in the increasing number of misdiagnoses of AIP.

This review article tries to disentangle different modalities concerning the management of patients with AIP in pregnancy and to keep physicians alert.

Classification of porphyria

The term porphyria refers to a group of rare, heterogeneous, metabolic disorders arising from the reduced activity of any of the enzymes in the heme biosynthetic pathway. Porphyrias can be classified as hepatic or erythroid depending on the main site of the defect. They can also be classified as either clinically acute: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP), ALA-dehydratase deficient porphyria (ADP), or cutaneous: porphyria cutanea tarda (PCT), hepatoerythropoietic porphyria (HEP), erythropoietic protoporphyria (EPP), congenital erythropoietic porphyria (CEP) according to their major clinical manifestations [1-3]. With the exception of porphyria cutanea tarda, all porphyrias are attributed to inherited enzyme deficiencies and all hepatic porphyrias are acute. Some acute porphyrias may also display cutaneous manifestations; however, cutaneous porphyrias never present acute neurologic manifestations, with the exception of erythropoietic protoporphyria in crisis [4].

Inheritance of AIP

AIP is inherited in an autosomal dominant fashion, caused by a deficiency in the enzyme uroporphyrinogen I synthetase, often called porphinobillinogen deaminase (PBG). The gene responsible for encoding this enzyme is located on chromosome 11q24, and the coding sequences are spread over 15 exons. So far, 301 mutations in the PBGD gene have been described [5]. The mutations reported include single base substitutions, splicing defects, insertions, and deletions that lead to structural impairment or loss of function of PBGD. As a consequence, the defect is unable to convert PBG to uroporphyrinogen I [6-10].

The outcome of a mutation is a 50% decrease in enzyme activity. This explains the rarity of homozygotes, as a failure to produce hemin in this condition is incompatible with life [1-11]. The remaining activity of the enzyme is usually sufficient. This could possibly justify why only 10% to 15% of the gene carriers have the clinical syndrome. Moreover, almost 33% of patients are reported with a family history of the disorder [12, 13].

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Incidence of AIP

The prevalence of AIP in Europe is estimated to be one in 20,000 people. However, the frequency rates between different populations, ranging from 1.5 per 100,000 Swedish people living in the USA and 3 per 100,000 people in Finland and Western Australia, to 1 per 1,000 people in Lapland Sweden, with clinical disease manifesting in approximately 10% of these carriers. Peak age of presentation is in the third decade [14-19]. Pregnancy represents an essential risk factor in patients suffering from AIP. Acute attacks have been reported as being more common during pregnancy (24-95%), especially during the first trimester [20, 21].

Clinical presentation of AIP in pregnancy

The clinical syndrome in AIP presents mainly with acute attacks. Acute attacks are expected in cases where there is an increased demand for hepatic heme; commonly when a precipitating factor occurs. In response, there is an induced synthesis of -aminolaevulinic acid (ALA) and overproduction of porphyrin precursors following the synthetic pathway to the point at which the partial enzyme deficiency becomes restrictive. Intermediates, which have no known useful physiologic function, accumulate in the body. Precipitating factors that can induce symptoms can be categorized as drugs, starvation, infection, and hormonal factors.

Endogenous hormones have been described as a vital factor in the induction and severity of acute attacks in patients with AIP [22]. During pregnancy, there is a major increase in sex hormone levels and on that basis, pregnancy has been thought to represent an essential risk factor in patients suffering from AIP.

In fact, acute attacks have been reported as being more common during pregnancy (24-95%), especially during the first trimester, but pregnancy is generally well tolerated. However, pregnancy in women with AIP is associated with higher rates of spontaneous abortion, hypertension and low birth weight infants [20, 21]. Furthermore, it is associated with considerable mortality (2-42%) [20]. Additionally, it has been reported that smoking may be related to a worse outcome of pregnancy in women with AIP. Smoking, which increases hepatic cytochrome P450 enzymes and presumably heme synthesis, has also been shown to be associated with a higher frequency of attacks [23].

On the other hand, it has been reported that pregnancy, despite the major hormonal alterations it causes, is seldom associated with porphyric symptoms and that with appropriate and close management, a good outcome could be achieved [24-27].

At the hormonal level, progesterone variability may partially explain why attacks are more common in women and during the luteal phase of the menstrual cycle [28, 29]. Moreover, oral estrogen intake is linked with a higher incidence of acute attacks in women with AIP [30]. In addition, despite the fact that there is no difference in AIP prevalence between genders, women seem to suffer more often than men. The onset of menses is correlated with a 10% to 20% higher incidence of acute attacks in women with AIP [31, 32]. Furthermore, attacks are more frequent during childbearing years, with only a few cases having been described in women before puberty. Similarly, attacks are limited after menopause [33, 34]. The use of gonadotropin-releasing hormone analogue (GnRH) has been shown to protect women with AIP from cyclical attacks. GnRH use, after an initial period of stimulating gonadotrophin secretion, leads to down-regulation of pituitary function, reduced secretion of gonadotropins and, as a consequence, a drop in the endogenous sex-hormone levels [32, 33, 35, 36].

AIP is characterized by acute attacks of abdominal pain, which is present in 85% to 95% of patients. Abdominal pain is severe, diffuse and unremitting but typically presents without rebound tenderness or guarding. However, pain is frequently accompanied by nausea/vomiting (43%-88%), constipation (48%-84%), tachycardia (80%) and occasionally by diarrhea (5%-12%). Less often, fever or leukocytosis may present, raising suspicion of acute surgical abdomen. However, despite the severity of symptoms, clinical examination of the abdomen is normal in most cases, probably because there is no peritonism [37]. Pain in the abdomen is believed to be related to autonomic neuropathy, as is pain in the extremities, back, chest, neck or head that present in 50% to 70% of cases. Extremity pain indicates involvement of the sensory nerves, with objective sensory loss being reported in 10% to 40% of patients [38-43].

Peripheral, motor neuropathy manifests early during an acute attack as muscle weakness (42%-68%). This weakness is usually symmetric, affecting the upper extremities more often than lower and involving the proximal muscles of the extremities. Fasciculation is absent and deep tendon reflexes are lost in severe attacks. Weakness may progress to respiratory paralysis (8%-20%) Moreover, seldom, the cranial nerves may be involved resembling Guillain Barre' syndrome. Mental symptoms occur in 40% to 58% of patients, ranging from minor changes in behavior to agitation, confusion, hallucinations, depression, or even psychosis and schizophrenia [44-46]. Psychiatric symptoms may present as the only manifestation of AIP [47] and this is probably the explanation for the higher prevalence of AIP in patients with psychiatric illness than in the general population [48-50].

Electrolyte disturbances are commonly found in AIP; hypokalemia, hyponatremia, hypomagnesemia, hypochloremia, azotemia and dehydration may become severe [51]. Seizures may present in up to 15% of patients, due to hyponatremia, which is often the result of a syndrome of inappropriate antidiuretic hormone secretion (SIADH) or sodium depletion [52].

AIP is also related to chronic hypertension (36%-55%), despite the fact that hypotension may occur during acute attacks. Renal impairment has also been described as a long- term complication [53]. Furthermore, patients suffering from AIP are at higher risk of developing hepatocellular carcinoma [54-60].

Risk factors of acute attacks

An acute attack of AIP may be precipitated by many factors during surgery and anesthesia, including fasting, dehydration, stress, infection, and drugs. Drugs used in anesthesia, many of which have high lipid solubility, and cytochrome metabolism have been implicated in the development of severe reactions in patients with AIP. In emergency cases, without knowledge of the problem and full biochemical examinations, the situation could well become serious. Knowledge of the situation poses a hard-to-solve puzzle, in selection of the appropriate drugs and operating management. Summaries of anesthetic drugs, known for their safety, have been published; however, there are also numerous conflicting reports [32]. Furthermore, other factors such as stress or infections may precipitate a porphyric crisis. On the other hand, availability of very short-acting anesthetic agents has led to the increased safety of anesthetic techniques. However, it would be fair to say that most analgesic agents may be used safely, despite the fact that some isolated case reports have implicated these drugs in porphyric attacks. Provided that reasonable precautions are adopted and sensible guidelines are followed, anesthesia may be considered safe. Postoperative close monitoring should continue for five days, to delay the onset of a porphyric crisis [61-74].

Diagnosis - differential diagnosis

Misdiagnosis of AIP unfortunately is very common, probably because of the rarity of the disease. When an acute attack of AIP is suspected, increased urinary porphobilinogen levels are expected. However, due to the low sensivity (40%-69%) and speciality (28%-53%) of the method, measurement of the 24-hour urinary excretion of porphobilinogen has become the first-line examination. However, further evaluation is needed, in order to differentiate between AIP, variegate porphyria and hereditary coproporphyria. Erythrocyte porphobilinogen deaminase activity is decreased up to 50% in almost 90% of patients. Additionally, urine porphyrin levels are markedly increased, while plasma and fecal porphyrin levels remain normal or slightly elevated [75-81].

Due to its dominant mode of inheritance, it is prudent to screen relatives for acute porphyrins and to offer proper genetic counselling to family members at risk. When possible, diagnosis should be confirmed in childhood to avoid the precipitating factors which may induce acute attacks after puberty. However, given the fact that approximately 50% of patients remain symptom-free throughout their lives, 30-40% experience mild symptoms and that the measuring of porphyrins and porphyrin precursors in these individuals may give variable results, DNA analysis is the only reliable means to screen symptom-free patients. Despite the large number of possible mutations, those reported are usually family specific. Those members who are unaffected experience great psychological relief as it is unnecessary for them to follow the restrictions required to prevent attacks. Moreover, screening of future generations of that particular family branch is not necessary [10, 13, 82].

Treatment of acute attacks of AIP

Hospitalization is required for treatment of acute attacks of AIP. The primary objective is to identify and limit any potential precipitating factors. Careful examination for underlying infections must be performed. Initial treatment comprises high glucose or intravenous hemin intake. Glucose is clearly less effective and is recommended only for attacks with mild pain and without signs of paresis. Hemin acts by repressing hepatic ALA synthase activity, thus reducing the overproduction of ALA and porphobilinogen [83-90]. A response to heme therapy is usually observed within one to four days after the start of infusion, but early initiation of intravenous hemin is associated with an earlier response and improved outcome [91-94]. There are only limited reports supporting the use of hemin during pregnancy, but experience indicates that it can be safely administered in pregnant women [35].

Until clinical improvement is achieved, symptomatic treatment is recommended. One of the main objectives should be that of pain control. However, careful selection of drugs allowed in pregnancy is paramount. Oral contraceptives have been shown to act as precipitating factors [34]. It is recommended that the use of sex hormones in women suffering from AIP is restricted. Notwithstanding, contraception is encouraged when adopting barrier methods.

Prevention of future attacks

Prevention of future attacks requires identification and avoidance of precipitating factors, preferably followed by changes in habits. Prevention comprises adequate carbohydrate and high calorie diets, avoidance of exacerbating drugs, alcohol consumption, smoking, dehydration, psychological stress, sex hormone treatment and sensitivity to treatment of any infection. Moreover, the patient should be forewarned that high estrogen concentrations may provoke attacks during pregnancy. Despite the fact that pregnancy in women suffering from AIP is related to higher rates of morbidity and complications, close management throughout the pregnancy could ensure a good outcome.

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