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Review Article

Acute Hepatic Porphyria: Epidemiology, Etiology, Pathogenesis, Classification, Clinic. Review

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Abstract

Porphyria is a group of hereditary diseases, which are based on the insufficiency of any one enzyme for the synthesis of the organic part of heme-protoporphyrin. The review presents up-to-date data on epidemiology, etiology, pathogenesis, classification, and clinic, the possibility of differential diagnosis and treatment of acute porphyria.

Keywords: *Acute Porphyria; Acute Intermittent (Hepatic) Porphyria; Epidemiology; Etiology; Pathogenesis; Classification; Clinic*

Abbreviations

AIP: Acute Intermittent Porphyria; AP: Acute Porphyria; ALA: Aminolevulinic Acid; ADP: Aminolevulinic Acid Dehydratase Porphyria; ADH: Antidiuretic Hormone; BP: Base Pairs; BBB: Blood-Brain Barrier; CNS: Central Nervous System; CI: Confidence Interval; CEP: Congenital Erythropoietic Porphyria; CMV: Cytomegalovirus Infection; dALA: Delta-Amino-Levulinic Acid; DGGE: Denaturing Gradient Gel Electrophoresis; DM: Diabetes Mellitus; EPP: Erythropoietic Porphyria; GABA: Gamma Aminobutyric Acid; SSC: Hematological Research Center; HCC: Hepatocellular Carcinoma; HEP: Hepatoerythropoietic Porphyria; HCP: Hereditary Coproporphyria; HMBS: Hydroxymethylbilane Synthase; LT: Liver Transplantation; LDL: Low-Density Lipoprotein; mRNA: Messenger Ribonucleic Acid; PBG: Porphobilinogen; PBGD: Porphobilinogen Deaminase; PCT: Porphyria Cutanea Tarda; PRES: Posterior Reversible Encephalopathy Syndrome; SSCP: Single-Strand Conformation Polymorphism Analysis; T4: Tetraiodothyronine; VP: Variegate Porphyria; HBV: Viral Hepatitis B; HCV: Viral Hepatitis c; XLP: X-Linked Protoporphyria

Background

Porphyrias (porphyriae; Greek porphyra - purple dye) are a group of hereditary diseases, which are based on the insufficiency of any one enzyme for the synthesis of the organic part of heme - protoporphyrin [26]. The beginning of the study of disorders of porphyrin metabolism dates back to 1841, when Scherer proved that the red color of the urine of patients is due to the presence of certain pigments in it, and not the presence of hemoglobin molecules. Fisher in 1930 received the Nobel Prize for his work on heme intermediates and, in 1934, published the book The Chemistry of Pyrroles [28]. Porphyria as a terminological category was introduced into clinical practice by J. Waldensrom in 1937, instead of the term "hematoporphyria" proposed earlier by H. Gunter [5]. In Russia, the first works on this problem appeared in the late 1960s and early 1970s, but their number was and remains small to this day. Since 1996 in the Hematological Research Center (SSC) of the Russian Academy of Medical Sciences, scientific and organizational work has begun on complex diagnostics,

observation, treatment and the creation of a database of patients with various forms of porphyria. In total, 100 patients suffering from acute forms of porphyria were registered as outpatients (among them 12 patients identified by L.I. Idelson in the 60 - 80s of the XX century). The number of newly registered patients from different regions of Russia is gradually growing. So, in the period from 1996 to 1998. Only 15 patients with acute intermittent porphyria (API) were identified, then in the next 3 years their number increased by 2 times, and in the period from 2002 to 2005 it increased by another third [9].

Epidemiology

Federal Law of November 21, 2011 No. No 323-FZ "On the basics of protecting the health of citizens in the Russian Federation" defines rare diseases associated with prevalence: no more than 10 cases per 100,000 population. It currently includes 24 diseases [6].

The European Health Commission defines rare diseases as life-threatening or chronic diseases that have a low prevalence (less than 1 in 2000 people) and require special combined efforts to diagnose and treat them. In Japan, a rare disease is one that has fewer than 50,000 patients, or about 1 in 2,500 people. In the US, the Rare Diseases Act (2002), like the earlier Rarely Used Drugs Act (1983), defines a rare disease strictly by prevalence: any disease or condition that affects fewer than 200,000 people in the US, or about 1 in 1,500 person [6].

Porphyrias are not endemic diseases and occur with the same frequency among the population of all continents [3,15]. The prevalence of acute porphyrias (AP) in Western Europe is 1-10:100,000 of the population, while the carriage of the mutant gene can be significantly higher (1 - 2 per 10,000 people), because the penetrance of the disease varies from 1 to 60% [4,43]. The prevalence of OP in Northern Europe is 1 case per 100,000 [39].

The most common of the acute porphyrias, acute intermittent porphyria (AIP), accounts for more than 85% of all cases of acute porphyria. The prevalence of variegated porphyria (VP) is 2-3:100,000. The prevalence of hereditary coproporphyria (HCP) is about 1:100,000 of the population. The disease gene was found on the long arm of the 3rd chromosome (3q12) [25] - less than 10 cases of this disease have been described [35].

At the State Scientific Center of the Russian Academy of Medical Sciences for 2007 provides information on patients suffering from acute porphyria in such regions as: the Republic of Tatarstan, Chuvashia, Yaroslavl, Samara, Sverdlovsk and Tver regions. In St. Petersburg and the northern regions of Russia, for 1995 - 2002. 12 people were identified [9]. In 2012 - 2013 47 subjects, in which 69.7% of the population of the Russian Federation live, 28 patients with a diagnosis of AIP were registered (children - 2 people (7.1%), which amounted to only 0.4% of all patients in the regional segments of the disease register from the "group of 24 -x" in these regions. The official prevalence of AIP at the end of 2013 is 0.03:100,000 of the population. The publications of the State Scientific Center contain information on 125 patients with AIP, 7 with variegated porphyria, and 4 with congenital coproporphyria [27]. According to the data on the prevalence of rare diseases, according to the regional segments of the Federal Register (80 subjects of the Russian Federation, 92.9% of the country's population), the number of patients with AIP as of 01.01.2014 amounted to 38 people, 0.4% of all patients in the register, respectively, 0.03 per 100,000 population; as of 01.01.2015 - 50, 0.4%, 0.03 per 100,000 population, respectively [14]. In 2017 the absolute number of patients was 92 people or 0.06% per 100,000 population, in 2018 - 100, 0.07% per 100,000 population, respectively [30]. The increase in the number of patients was 163%. It can be concluded, that the growth rate of patients with acute intermittent porphyria is maintained. Perhaps, this is due to the better detection of this disease.

The incidence of AIP was similar in all countries (0.13 per million per year; 95% CI: 0.10 - 0.14) except in Sweden (0.51; 95% CI: 0.28 - 0.86). The prevalence of erythropoietic protoporphyria (EPP) was less uniform across countries and, in some, higher than previous estimates. Fourteen new cases of hepatocellular carcinoma (HCC) (11 from Sweden) have been reported in patients with acute porphyria. With recurrent attacks of acute porphyria, 67 patients were identified. The estimated percentage of patients with AIP, who will develop recurrent acute attacks was 3 - 5%. The prevalence of AP, may be declining, possibly due to improved treatment, while the prevalence of

porphyria cutaneous tardio (PCT) may be increasing due to improved diagnosis (because photosensitivity is the trigger). The prevalence of EPP was less homogeneous across countries and in some countries exceeded previous estimates [35].

Etiology and pathogenesis

Porphyrins are cyclic tetrapyrroles with different end groups, which are heme precursors [20]. Basically, heme biosynthesis is a step in the metabolism of porphyrins, starting with the reaction of glycine with succinyl-coenzyme A and ending with the formation of protoporphyrin. This chain of synthesis involves not the porphyrins themselves, but their reduced form, the porphyrinogens. In air, colorless porphyrinogens are rapidly oxidized to porphyrins, giving red fluorescence [20]. Heme is predominantly synthesized in the bone marrow (80%) and liver (20%). Porphyrias are violations of heme biosynthesis [47].

The menstrual cycle acts as a trigger in the development of AIP, since even in healthy women, the level and activity of 5-ALA dehydratase changes during the menstrual cycle, and therefore the level of heme and porphyrin synthesis fluctuates significantly, reaching a maximum value in the second phase of the menstrual cycle [13]. The same happens during pregnancy [10]. Barbiturates and surgical interventions provoke acute attacks in both manifest and latent patients [17]. Sometimes there is an increase in serum T4 (tetraiodothyronine) and thyroxine-binding globulin in the absence of hyperthyroidism. They also have increased levels of serum cholesterol and low-density lipoprotein (LDL) [43]. Since the menstrual cycle is the main endogenous provoking factor, more than 80% of patients with AP are women aged 11 - 20 to 45 years. The disease rarely manifests itself before puberty, as well as menopause [35,36]. Attacks of acute porphyria in men are possible, but are much less common than in women [12,41].

A number of drugs provoke seizures, often causing acute intermittent porphyria [40,46]. More than 100 of them are known and this list is constantly growing [18]. Also, AIP can provoke ethanol, which inhibits the activity of the main enzymes of the heme biosynthesis system. As a result, according to the feedback principle, a threefold increase in activity occurs in the liver, the key enzyme - ALA synthase, which sharply stimulates the formation of porphyrins. The development of acute intermittent porphyria is also affected by insolation [8,35], hypocaloric low-carbohydrate diet [18], bacterial and viral infections (especially viral hepatitis C (HCV), viral hepatitis B (HBV), cytomegalovirus infection (CMV) [18].

These factors lead to an increased consumption of the end product of the biosynthesis cycle - heme (for example, activation of the cytochrome P-450 system), or have a direct stimulating effect on the activity of the first enzyme of the biosynthesis cycle - 5-aminolevulinate synthase, which leads to an increase in its activity (for example, the action progesterone), as a result of which the synthesis of all intermediate products of the metabolism of porphyrins is accelerated. In AIP, there is an excessive accumulation of ALA and porphobilinogen (PBG) in tissues, leading to segmental demyelination of nerve fibers with impaired nerve conduction [23,28]. AIP is associated with a deficiency of the third enzyme of heme biosynthesis, hydroxymethyl bilane synthase (HMBS), or another name, porphobilinogen deaminase (PBGD) [25].

When a 50% porphobilinogen deaminase (PBGD) deficiency occurs, then by itself it is insufficient to cause symptoms of acute intermittent porphyria [43,47]. Asymptomatic carriage is more common: 1 case per 2 - 3 thousand of the population for AIP. In order for the latent carriage of a gene to be realized in the clinical stage of the disease, not only the presence of a gene mutation is necessary, but also the impact of exogenous or endogenous inducing factors [13]. During an episode of AP, the hepatic heme regulatory pool is depleted and there is a marked induction of an accessory form of dALA synthase, an enzyme that limits the rate of heme synthesis, leading to accumulation of ALA and PBG, two intermediates located closer to the deficient enzyme [34,43]. The most common and severe type of this type of disease is considered to be AIP associated with reduced PBGD activity, which catalyzes the third stage of heme biosynthesis, during which the sequential deamination and condensation of four porphobilinogen molecules occur to form unstable linear tetrapyrrole 1-hydroxymethylbilane [25,37]. Almost all carriers of AIP, with rare exceptions, are heterozygous for the defective PBGD gene and most of them, do not have obvious symptoms of the disease [10]. This is an autosomal dominant pathology caused by a partial deficiency of

porphobilinogen deaminase [2]. Currently, over 400 mutations in the PBGD gene have been recorded in different countries [25]. The defective form, exon 1 and exons 3 - 15 (NCBI reference sequence NM_000190.4) often leads to a decrease in enzyme activity, causing AIP, having a dominant inheritance pattern, is characterized by low penetrance (according to maximum estimates up to 10 - 15%), indicating that that a mutation in the PBGD gene is a necessary but not sufficient condition for the clinical manifestation of the disease, the main severity of which is associated not with the deficiency of the product of the enzymatic reaction catalyzed by PBGD, but with the accumulation of an excess of the toxic substrate precursor 5-ALA, which is synthesized as a result of the intermediate product of the citrate cycle from succinyl-CoA with condensation with glycine [54]. As a result of the transition from mitochondria to the cytoplasm, 5-ALA is synthesized into PBG, which is also a toxic precursor substrate in AIP [19].

There are data from clinical studies of porphyrin metabolism in the metabolic syndrome in women, allowing to draw conclusions about the triggers of acute intermittent porphyria [16].

Disorders of porphyrin metabolism are observed in the majority of patients - in 29 (61.7%), they are manifested by qualitative (change in the ratio of porphyrin fractions) and quantitative (increase in the content of precursors and fractions of porphyrins) changes. Violation of porphyrin metabolism is more often recorded in women against the background of physiological menopause. There is evidence that suggests a close relationship between carbohydrate metabolism disorders and porphyrin metabolism disorders. M. Pisanets and P. Pavlov in patients with type 2 diabetes mellitus (DM) revealed changes in the biosynthesis of porphyrins at its initial stages (at the stage of conversion of ALA into PBG) and believe that dysmetabolism of porphyrins in DM is due to a change in the function of hepatocytes in the mitochondrial system which biosynthesis of porphyrins and gemma is carried out [16].

Classification

Depending on where the heme synthesis is predominantly impaired - in the bone marrow or in the liver - erythropoietic and hepatic forms of porphyria are distinguished [4,26]. Erythropoietic porphyrias are accompanied by the accumulation of porphyrins in normoblasts and erythrocytes, and hepatic porphyrias - in hepatocytes [41,43]. Pathological deviations of porphyrin metabolism in porphyrias are predominantly concentrated either in the cells of the bone marrow (erythropoietic type) or in hepatocytes of the liver (liver type) and are associated with a defect in one or less often two enzymes of heme biosynthesis [17,44]. Porphyria is not a single disease, but a group of nine disorders: acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP), porphyria cutanea tarda (PCT), dALK dehydratase- deficient porphyria (ADP), hepatoerythropoietic porphyria (HEP), congenital erythropoietic porphyria (CEP), erythropoietic porphyria (EPP) and X-linked protoporphyria (XLP) [43]. Defects in any of the eight steps of heme biosynthesis can lead to a porphyrin disorder [42]. It is generally accepted, albeit conditional, to divide porphyrias according to the site of the predominant disturbance in the metabolism of porphyrins [24] into hepatic and erythropoietic (Table 1), in accordance with the organ in which excessive production of heme precursors (dALA, PBG, and porphyrins) occurs predominantly [29]. In the liver, heme synthesis is regulated by negative feedback due to the intracellular free heme pool [33].

According to clinical manifestations, hepatic porphyrias are further subdivided into acute forms, occurring with a predominant lesion of the nervous system, and chronic, occurring with skin lesions (Table 1) [24].

Classification of porphyrias	
Forms of porphyria	Porphyria
Erythropoietic forms of porphyria	Congenital erythropoietic porphyria
	Erythropoietic porphyria
Hepatic porphyrias	X-linked protoporphyria
	Aminolevulinic acid dehydratase porphyria
	Acute intermittent porphyria
	Variegate porphyria
	Porphyria cutanea tarda
Acute forms of porphyria	X-linked protoporphyria
	Aminolevulinic acid dehydratase porphyria
	Acute intermittent porphyria
	Hereditary coproporphyria
	Variegate porphyria
Forms flowing with skin integument	X-linked protoporphyria
	Porphyria cutanea tarda
	Porphyria cutanea tarda
	Variegate porphyria
	Congenital erythropoietic porphyria
	Erythropoietic porphyria

Table 1: *Source [55].*

Clinic

Acute intermittent porphyria is a hereditary metabolic disease with an autosomal dominant mode of inheritance [1,8]. Fermentopathy leads to excessive accumulation in the body of protoporphyrin precursors - PBG and ALA. The toxic effect of these metabolites on the body determines the characteristic clinical symptoms of porphyria [26,32]. Most heterozygotes remain asymptomatic throughout life. Symptoms very rarely appear before puberty and are 4 - 5 times more common in women [2] than in men [2,43]. The first attack of acute porphyrias can develop at the age of 14 - 16 years. The onset of the disease is acute, rarely subacute [11]. Acute attacks, with rare exceptions, do not have a spontaneous regression and can quickly lead to severe complications and death [23]. The classic clinical manifestations of AIP are:

1) Pain syndrome of various localization, most often abdominal, difficult to anesthetize:
2) Autonomic dysfunction with a predominance of sympathicotonia;
3) Psychopathological disorders, in severe cases in the form of a delirious syndrome with hallucinations and perceptual delusions;
4) Polyneuropathic syndrome involving, in untreated cases, cranial nerves (VII, IX, X, XII) [7].

The symptoms of AIP are due to effects on the visceral, peripheral, autonomic, and central nervous systems [43]. In the clinical picture of acute hepatic porphyrias, symptoms of damage to the autonomic part of the central nervous system (CNS) are most pronounced, such as acute colicky pains in the lower abdomen with nausea and vomiting, constipation, but without peritoneal symptoms, lasting from several hours to several days (90%), physical examination reveals stagnation of intestinal contents [2,50]; cardiopalmus [11] up to 160 beats per minute (30 - 80%); arterial hypertension, nausea, vomiting [2,21]. Severe recurrent abdominal pain in these patients may exceed headache [38,54]. One of the most common manifestations that dominates the clinical picture of acute attacks of porphyria is peripheral polyneuropathy [10,39]. Rhabdomyolysis, which develops in parallel with polyneuropathy during an attack, explains why proximal muscle weakness in the legs often predominates over distal muscle weakness in patients with acute porphyria [22]. Severe pain in the muscles of the back, chest, neck, as well as progressive muscle weakness, reaching the depth of paralysis (96.9% of cases), are the main signs of peripheral sensory and motor polyneuropathy. Encephalopathy, epileptiform seizures, intellectual impairment, inappropriate behavior, hallucinations, and psychosis are symptoms of damage to higher centers of nervous activity [11]. Psychiatric features encompass behavioral changes such as mood disturbances, anxiety and insomnia, depression and psychotic symptoms [44,52]. The pathogenesis of seizures may be related to metabolic imbalances such as hyponatremia or to the intrinsic epileptogenic role of certain porphyrins such as delta-aminolevulinic acid (dALA). ALA has been shown to interact with gamma-aminobutyric acid and glutamate receptors [31,54]. ALA also acts as a direct neurotoxin and can promote free radical formation and inhibit the sodium and potassium pump (Na-K-ATPase), thereby promoting uncontrolled release of glutamate [32]. The leading neurological manifestation of AIP (polyneuropathy) is based on axonal degeneration, which may be accompanied by secondary segmental demyelination [18]. Urinary retention or incontinence, pain during urination are often observed [2]. The most frequent, especially in acute forms of porphyria, are the phenomena of hypersensitivity of the skin to exposure to sunlight. It is caused by photochemical reactions that occur under the action of the ultraviolet spectrum of solar radiation (400 - 410 nm) with an excess amount of porphyrins deposited in the dermis, which leads to the formation of reactive particles, for example, superoxide anion, which activates xanthine oxidase, and other metabolites that damage basement membrane cells [11]. The skin is usually not affected in AIP. However, concomitant progressive kidney disease can limit porphyrin excretion and increase plasma porphyrin levels sufficiently to cause blistering of sun-exposed skin [43,45,51].

The onset of the disease in the vast majority of cases is acute and is associated with exposure to provoking factors [11]. In most cases, the symptoms reach their maximum development within 1 - 4 weeks, but sometimes the progression phase lasts up to 2 - 3 months. Progression occurs continuously or stepwise [18]. At the onset of AIP, malaise, dysphoria and palpitations appear. Frequent symptoms of

this period are also emotional lability, depression, tearfulness, irritability. Macromanifestation of the disease often begins with abdominal pain, rapidly increasing in intensity. Pain is not localized and can migrate. It is necessary to pay attention to the absence of signs of inflammation in AIP (leukocytosis, increased ESR, sharply positive symptoms of peritoneal irritation). Starting from the second week of the disease, a clinic of polyneuropathy appears in the form of muscle weakness in the proximal limbs with a gradual transition to the distal parts. Without treatment, the depth of paresis reaches the degree of plegia. At the peak of the attack, patients may experience mental lability, inadequacy, hallucinations, convulsions. Seizures can occur both in the type of epileptiform, accompanied by loss of consciousness, and in the type of peripheral convulsions of the extremities. In the later stages of AIP, symptoms of damage to the VII, IX-XII pairs of cranial nerves appear [11]. The relative stability of the central structures is explained by the poor permeability of the blood-brain barrier for ALA and PBG [18]. During an exacerbation, there is often an increase in the content of catecholamines in the blood. AIP is one of the common causes of the syndrome of inappropriate ADH (antidiuretic hormone) secretion, which is associated with damage to the hypothalamus and leads to hyponatremia and plasma hypo-osmolarity and as a result, to severe cerebral manifestations (depression or clouding of consciousness, epileptic seizures) [18,49]. Also, hyponatremia can develop as a result of sodium loss with vomiting and through the kidneys due to their damage [31,49]. Against the background of various disorders of the central nervous system, the syndrome of posterior reversible encephalopathy - Posterior Reversible Encephalopathy Syndrome (PRES) can develop - this is an acute condition leading to the development of vasogenic cerebral edema. Currently, there are two generally accepted hypotheses regarding the pathogenesis of PRES: 1) excessive cerebral perfusion caused by an increase in blood pressure that violates the threshold for autoregulation of cerebral blood flow; 2) violation of the blood-brain barrier (BBB) due to vascular endothelial dysfunction due to toxic substances. The first theory is the main mechanism leading to PRES, since the hindbrain has no sympathetic innervation and is sensitive to fluctuations in blood pressure [52]. Clinically, PRES is expressed by: 1) a change in consciousness (a decrease in the level of wakefulness with periods of psychomotor agitation), 2) epileptic seizures, 3) headache, 4) visual disturbances, 5) an increase in blood pressure (BP). The syndrome reflects the severity of the condition, its presence requires urgent elimination of the process that provoked the PRES [7]. Neurovisceral symptoms are one of the typical manifestations of AIP. Considering the absence of sympathetic innervation in the posterior regions of the brain, it was concluded that sympathetic dysfunction in AIP is the pathological basis for PRES initiation. Parasympathetic as well as sympathetic dysfunction makes arteries in the posterior region more susceptible to vasodilation and hyperperfusion, resulting in homeostatic dysregulation of cerebral blood flow. Abnormal accumulation of ALA and PBG is the underlying pathological process in AIP and a potential mechanism for PRES. ALA is neurotoxic and affects the binding affinity of gamma-aminobutyric acid (GABA) to its receptors, but not the binding of serotonin or dopamine. It can be assumed that the underlying mechanism affects the permeability of the BBB and causes vasogenic edema in the brain tissue, which leads to PRES. At the same time, changes in BBB permeability also lead to changes in the intracranial ALA concentration, causing ALA neurotoxicity [4,52]. Since many antiepileptic drugs are porphyrinogenic and aggravate the course and prognosis of acute porphyria in these patients, in this regard, the development of the epileptic syndrome introduces additional problems in treatment [7].

A bright marker of acute porphyria is the allocation of different shades of red or brown urine “color of port” [11]. Acute porphyria is referred to as a small imitator, with most patients presenting with clinical symptoms suspicious of acute porphyria, and therefore, other diseases are exposed on examination [21,56].

Summary

Thus, acute porphyrias are serious diseases that bring suffering to patients and have high mortality and mortality. Many aspects of this disease require resolution. There is insufficient data on the epidemiology of AIP, in particular in Russia. Not studied, in many regions, mutations and other causes leading to this disease, complicating its course. Due to the rarity of AIP, the features of her clinic are not sufficiently presented, there are no clear criteria for an attack precursor.

Conflict of Interest

There is no financial interest or conflict of interest.

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