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Case Report

Porphyria: Clinical Manifestations at the Junction of Gastroenterology and Neurology. Case Report

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Abstract

Porphyrias belong to groups of metabolic diseases that develop as a result of genetic defects in enzyme systems of heme biosynthesis. However, some variants of porphyria are acquired due to possible intoxications and liver diseases. Disruption of porphyrin metabolism is unique to all types of this disease, as a result of which the content of porphyrins and their precursors increases in various organs and systems [1].The course of these diseases is characterized by a common triad: abdominal pain, neuropsychiatric disorders and neuropathy [6].

Etiology and pathophysiology

Porphyrins are intermediate products on the path of biosynthesis of biochemical substrates. In the human body, they are the chemical precursors of heme, which are iron-deprived. To understand the pathogenesis of the disease, it is necessary to indicate the path of heme biosynthesis. It is a cascade of eight biochemical reactions, each of which is provided by a specific enzyme [2]. When the biochemical synthesis of heme is enzymatically disrupted at one of the stages, there is an excessive accumulation of intermediate products - porphyrinogens, which is the pathogenetic basis for the formation of the porphyria disease [3]. It depends on the level at which there is an enzymatic violation of this synthesis, this type of porphyria will be determined.

Modern classification divides porphyrias into two large classes, such as erythropoietic porphyrias, which include

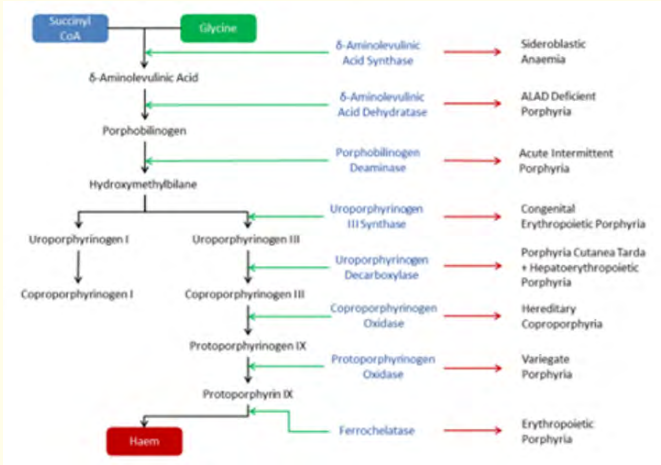

Figure 1: Heme biosynthesis pathway. The green arrow is a metabolic pathway provided by the corresponding enzyme; red arrow – corresponding subtype of porphyria.

- Congenital erythropoietic porphyria
- Erythropoietic protoporphyria
- X-linked protoporphyria.

and hepatic porphyrias, which include

- Acute intermittent porphyria
- Hereditary coprophorphyria
- Porphyria associated with delta-aminolevulinic acid dehydrolase
- Skin porphyria
- Hepatoerythropoietic porphyria [4].

The four types of hepatic porphyrias, such as acute intermittent porphyria, hereditary coproporphyria, variant porphyria, and porphyria associated with delta-aminolevulinic acid dehydrolase to the greatest extent in their clinical manifestations, cause disturbances from the nervous system. Acute attacks of these diseases occur due to an increase in the production of delta-aminolevulinic acid by the liver in order to increase the production of heme against the background of its insufficiency due to an enzymatic violation of its synthesis.

Risk factors that contribute to the manifestation are such conditions as alcohol, starvation, excessive insolation, the use of medical drugs such as barbiturates, sulfonamides, analgin, combined oral contraceptives, etc. Regarding drugs that affect the nervous system, carbamazepine and phenytoin should be used with caution [5].

The pathophysiological mechanism through which delta-aminolevulinic acid causes neurological disorders is complex and consists in the spread of free radicals by the nervous system, their competitive binding to sites for GABA, mitochondrial dysfunction, which secondarily causes the inability to maintain the integrity of axons. There is also a violation of the function of Na/K-ATPase, which compromises the axonal membrane to electrical instability.

Clinical manifestations

The course of these diseases is characterized by a common triad: abdominal pain, neuropsychiatric disorders and neuropathy [6]. Gastroenterological manifestations of the disease are caused by disorders of the autonomic nervous system in the absence of organic pathology from the gastrointestinal tract.

Disorders of the autonomic nervous system

In 90% of cases, the exacerbation of the disease is manifested by pronounced non-localized acute abdominal pain. Complaints of nausea, vomiting and constipation are also noted. Very often, these complaints come to the fore, with which patients seek medical help, and are mistakenly directed to immediate surgical treatment in the form of laparoscopy or laparotomy. There was no surgical pathology during the operation. According to our observations, such patients during each new exacerbation may receive repeated surgical treatment in the scope of relaparoscopy or relaparotomy. Any surgical intervention associated with anesthetic support, which is contraindicated in patients with porphyria. General anesthesia is an objective factor that compromises the manifestation of exacerbation of porphyria [7]. Arterial hypertension, tachycardia, and hyperhidrosis are also typical disorders of the autonomic nervous system during an attack of porphyria.

Porphyric neuropathy

At the maximum degree of severity, it can cause tetraparesis or tetraplegia, respiratory failure, which necessitates the useage of artificial lung ventilation [7]. The neuropathy is of the axonal type, which is pathognomonic for porphyria. But it can be difficult to differentiate with Guillain-Barré syndrome. What should be paid attention to: with porphyria motor deficits are affected by distal groups of muscles or with rapid rates of development a characteristic generalized lesion. Regarding reflexes, general hyporeflexia/areflexia is noted. In 60% of cases, there are sensory disturbances, usually paresthesias, the development of myalgic pain is possible [8]. Cervical nerves lesions accompany porphyric neuropathy in 75% in the form of impaired functioning of the facial, vagus, less often trigeminal, hypoglossal, accessory and oculomotor nerves.

According to ENMG data, axonal motor neuropathy (demyelizing neuropathy is almost absent) is determined (Figure 2) [9].

Disorders of the central nervous system

They appear in

- **Convulsions:** the most common are partial convulsions without secondary generalization. However, some patients have myoclonic convulsions, tonic-clonic convulsions, absences [10]

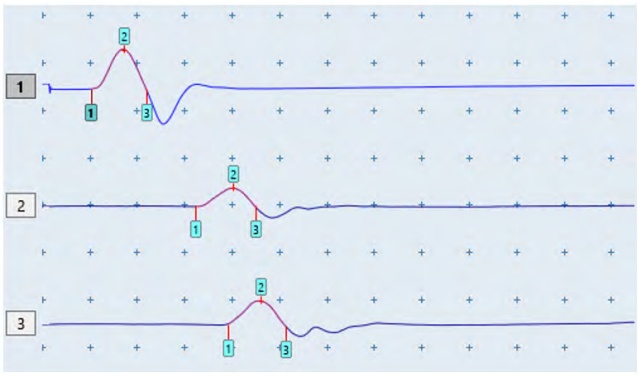

Figure 2: Stimulation ENMG in axonal motor neuropathy. Decrease in amplitude to 40% of normal (1 - from the area of the metatarsal; 2- from the head of the fibula; 3 - from the popliteal fossa).

- **Neuropsychiatric disorders:** manifest from minor changes in behavior to severe anxiety, severe depression, hallucinations and delusions [11]
- Progressive decline of cognitive functions
- Disturbance of consciousness.

One of the complications of porphyria, which leads to death, is cerebral edema, which can develop in a short time from the onset of the manifestation. The mechanism of development of both cerebral edema and central nervous system disorders consists in the release of porphyrinogens along the concentration gradient from the blood plasma to the intercellular fluid of the brain substance. In the future, cell swelling, neuron dysfunction and its subsequent death occur. As a result of cerebral edema, a life-threatening state of wedging of the brain stem into the large occipital foramen occurs with rapid suppression of vital functions.

Diagnostics

A screening method of diagnosis during an acute attack is a study for the presence of urinary porphobilinogen using Ehrlich's reagent. When porphyria is aggravated, urine usually has a burgundy color. When conducting a study with Ehrlich's reagent, a characteristic change in the color of urine from maroon to light yellow when illuminated by sunlight is a qualitative reaction of urine to porphyrinogens. The advantage of this method lies in the availability and speed of its implementation. Diagnostics of daily urine with its analysis for aminolevulinic acid, porphobilinogen, general and differentiated porphyrins provides a clear definition of the type of porphyria but is not screening due to the considerable time it takes. During the period of remission, the indicators of fecal and plasma porphyrins are within the normal range. After treatment of an attack of porphyria, it is necessary to carry out genetic testing (for PPOX, HMDS, etc. genes) of the patient and his first-line relatives to verify the heredity of the disease [12].

Treatment

There is no etiotropic treatment.

Pathogenetic treatment of porphyria is available only during exacerbation of the disease and consists in the introduction of hemin, which eliminates heme deficiency by a feedback mechanism, thereby reducing the synthesis of porphyrins and toxic metabolic precursors of heme [13]. After gemin treatment, long-term and intensive therapy is necessary for the treatment and recovery of the central, peripheral and autonomic nervous system. Observation by a hematologist and minimization of the presence of the provoking factors that mentioned above, which manifest an attack of porphyria, are indicated.

Case Report

Woman I., 23 years old, sought medical help with complaints of acute abdominal pain. After the surgeon's examination, she was hospitalized in the surgical department with suspicion of an acute abdomen.

- **Life anamnesis:** Information about the illness of relatives is unknown. She denied chronic diseases.

She was operated on for an acute abdomen. No surgical pathology was found during the operation. The condition was interpreted as dynamic intestinal obstruction. After 3 days from the onset of the disease, a pattern of intestinal obstruction appeared, an urgent relaparotomy was performed. The condition is interpreted as early adhesion disease. Four days after the second operation, tetraparesis developed. The patient was hospitalized in the regional clinical hospital.

- **Examinination indicated:** stitches from the operation on the front abdominal wall, the stomach is slightly swollen.
- **In the neurological status:** gross tetraparesis of the peripheral type, muscle hypotonia, areflexia, pronounced neuropathic pain in the limbs.

Urination through a catheter, urine of a saturated color closer to burgundy. A positive urine test with Ehrlich's reagent. Positive tests for active porphyrinogens in urine and blood.

- **The diagnosis was established:** Porphyria, acute intermittent form (urocoproporphyria).

Normosang (hemin) was prescribed to the patient in therapeutic doses.

Against the background of therapy, the urine became straw-yellow in color, but there were signs of a CNS disorder in the form of a decrease in cognitive functions, anxiety, depression, apathy, and a generalized attack of tonic-clonic convulsions. Computed tomography of the brain was performed. According to the results of the CT scan, signs of pronounced cerebral edema were revealed in the form of a lack of differentiation of the ventricles of the brain and the subarachnoid space. At the end of the first week from the start of gemini therapy, the patient's somatic condition stabilized. But there was a violation of the degree of consciousness to the chronic vegetative state, with which the patient remained after the end of the porphyria crisis.

Conclusion

This information is provided with the aim of drawing the attention of specialists of various specialties to the clinical manifestation of porphyria, namely gastroenterological disorders, the necessity for rapid diagnosis and treatment, knowledge of the provoking factors of the development of a porphyria crisis and its prevention in the future.

Conflict of Interest

None.

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