PORPHYRIA

Guidelines for the discipline "Medical Genetics"
for the training of interns, 5th year students
and cadet doctors of postgraduate education cycles

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
Харківський національний медичний університет

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ПОРФІРІЯ

Методичні вказівки
з дисципліни "Медична генетика"
для підготовки лікарів-інтернів,
студентів 5-го курсу та лікарів-курсантів
циклів післядипломної освіти

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I. Passport

1.1 Porphyria

1.2 Code ICD-10:

Impaired porphyrin and bilirubin metabolism (E80)

Included: catalase and peroxidase defects

E80.0 Hereditary erythropoietic porphyria

Congenital erythropoietic porphyria. Erythropoietic protoporphyria

E80.1 Dermal porphyria

E80.2 Other porphyria

Hereditary coproporphyria. Porphyria acute intermittent (hepatic). If necessary, identify the cause using an additional code of external causes (class XX).

E80.3 Defects of catalase and peroxidase acatalasia

E80.4 Gilbert's syndrome

E80.5 Krigler-Nayyar syndrome

E80.6 Other disorders of bilirubin metabolism

Dubin-Johnson syndrome. Rotor syndrome

E80.7 Impaired bilirubin metabolism, unspecified

1.3 For whom the protocol is intended (potential users)

Doctors-interns, 5th year students, doctor cadets of postgraduate education cycles, doctors and nurses of the KhISMGC-CR(O)D

1.4 Purpose of the protocol:

Identification and correction of metabolic disorders in porphyria

1.4 Date of compilation: February 2017

1.5 Date of revision:

1.6 Order of the KhISMGC-CR(O)D on the development of local protocols

1.7. The composition of the working group on the development of the local protocol "Porphyria"

FULL NAME	position
Grechanina Yelena Yakovlevna	General Director of the KhISMGC-CR(O)D, Corr. NAMSU, MD, professor
Grechanina Yulia Borisovna	Head of the Department of Medical Genetics, KNMU, MD, professor
Molodan Lyudmila Vladimirovna	Director KhISMGC-CR(O)D, candidate of medical sciences, associate professor
Nagieva Camilla Feliksovna	Geneticist KhISMGC-CR(O)D

1.8 Medical and technological documentation at the industry level, on the basis of which a local protocol has been developed:

– Order of the Ministry of Health of Ukraine No. 751 dated September 28, 2012 "On the creation and implementation of medical and technological documents for standardizing medical care in the system of the Ministry of Health of Ukraine";

– Order of the Ministry of Health of Ukraine No. 641/84 of 12/31/2003 "On the improvement of medical and genetic care in Ukraine";

List of abbreviations:

KhISMGC-CR(O)D	Kharkov Interregional Specialized Medical Genetic Center – Center for Rare (Orphan) Diseases
LHCP	Local Health Care Protocol
RMGC	Regional Medical Genetics Center
IMGO	Interdistrict Medical Genetic Office / consultation
AP	Acute porphyria
AIP	Acute intermittent porphyria
HC	Hereditary coproporphyria
VP	Variegative porphyria
PPB	Porphobilinogen
AC	Aminolevulinic acid
HCV	Viral hepatitis C
HBV	Viral hepatitis B
GIT	Gastrointestinal tract
AH	Arterial hypertension
HD	Hemodialysis
NSAID	Nonsteroidal anti-inflammatory drugs
CMV	Cytomegalovirus infection
PP	Plasmapheresis
GRH	Gonadotropin releasing hormone
ARF	Acute respiratory failure
TBT	Tracheobronchial tree

II. The common part

2.1 Medical services provided

The center is a unique functional association of the Kharkov Interregional Specialized Medical Genetics Center – the Center for Rare (Orphan) Diseases, the Ukrainian Institute of Clinical Genetics, the Department of Medical Genetics of Kharkov National Medical University, and the association of specialists and families with a hereditary pathology:

• Ukrainian Association of Ultrasound Diagnostic Physicians in Perinatology, Genetics and Gynecology;

• Association of geneticists and families with children with phenylketonuria;

• Kharkov charity foundation "Cystic fibrosis" (an association of parents of disabled children with cystic fibrosis);
• The Future Generations Fund;
• Association of families with children with chromosome characteristics.

The main tasks of the KhISMGC-CR(O)D:

– organization of the provision of care specialized in the areas of genetics;
– carrying out three-level prophylaxis of congenital and hereditary pathology;
– the introduction of modern means of prevention, diagnosis and treatment of congenital and hereditary pathologies;
– analysis of the causes of perinatal and infant mortality from diseases in accordance with the direction of specialization and the development of preventive measures (genetic monitoring);
– statistical reporting on generalized regional indicators for established patterns, a systematic analysis of activities;
– ensuring continuity in work with health facilities on the prevention, diagnosis and treatment of congenital and hereditary pathologies;
– development of issues of social rehabilitation of patients;
– Providing feedback with LHCP and RMGC on issues of timely detection, quality of follow-up and treatment of patients with congenital and hereditary pathology;
– definition of a strategy and development of a set of measures for the functioning and further development of a certain area of medical genetics based on modern achievements of medical science and practice;
– providing advisory assistance, scientific, practical and organizational and methodological support to medical and genetic services institutions of various levels;
– development of basic regulatory documentation in a certain area: modern quality standards for conducting clinical and laboratory genetic examinations, criteria for assessing pathology;
– quality control of clinical and laboratory genetic examinations in areas of activity;
– submission of proposals to health authorities to improve the relevant activities of the medical genetic services;
– advanced training of employees of healthcare institutions at various levels in the areas of specialization of the center.

When conducting genetic counseling, the geneticist abides the rules of bioethics and deontology. According to the current legislation, information on the hereditary nature of the disease in the proband or in the family is confidential and is provided to the person who was consulted. Medical specialists ensure the right of the patient about the need to inform other family members about the detected pathology.

In the case when a child or a person with reduced mental development acts as a proband, the results of genetic studies in the form of a conclusion are issued to parents or persons replacing them, in accordance with applicable law.

Operating procedure:

1. Patients with suspected metabolic disturbances are referred to the KhISMGC-CR(O)D for consultation.

2. The examination is carried out after collecting complaints, an anamnesis of the disease and life, building a family tree and conducting a clinical genealogical analysis, describing the phenotype by a geneticist and conducting a syndromological analysis, drawing up a genetic map.

3. The duration of the initial family consultation is 1.5 hours.

4. Regulatory documentation is drawn up in accordance with the requirements of the orders of the Ministry of Health of Ukraine.

Geneticist KhISMGC-CR(O)D:

Grechanina Ye. Ya. – General Director of the KhISMGC-CR(O)D, Corr. NAMSU, MD, professor, geneticist of the highest category

Grechanina Yu. B. – Head Department of Medical Genetics, KNMU, MD, associate professor, geneticist of the highest category

Molodan L. V. – Director of KhISMGC-CR(O)D, candidate of medical sciences, associate professor, geneticist of the highest category

Zdybskaya E. P. – Head of the metabolic center, candidate of medical sciences, associate professor, geneticist of the highest category

Bugaeva E. V. – Head of the connective tissue center, candidate of medical sciences, associate professor, geneticist of the highest category

Gulenko I. I. – Head of the Department of Genetic Monitoring, geneticist of the highest category

Biletskaya S. V. – deputy Director of the KhISMGC-CR(O)D for the medical part, geneticist of the second category

Krasov A. V. – Deputy Director for organizational and methodological work, geneticist

Adamyan L. M. – geneticist

Vernigora Oh. Yu. – geneticist

Grinyuk A. V. – geneticist of the first category

Grinchenko Yu. N. – geneticist

Evstigneeva O. V. – geneticist

Eliseev V. M. – geneticist

Elkova A. A. – geneticist

Zabelina A. A. – geneticist

Hmil O. B. – geneticist

Yanovskaya G. A. – geneticist of the first category

• has a valid local protocol

• obtains patient information consent for conducting genetic counseling and examination

• conducts qualified genetic counseling

• provides effective consultation on the results of the examination, provides information to the patient about his health status with recommendations for non-drug and drug treatment, behavior tactics in case of a sudden worsening of the course of the disease orally and in the form of an opinion

• maintains a list of patients with porphyria for dispensary observation; the list includes the following information: name, date of birth (in the format dd.mm.yy), address of registration and residence, contact phone number, diagnosis according to the latest wording, notes (additional information).

Nurse KhISMGC-CR(O)D:

• invites a family to an office for conducting genetic counseling

• treats the surface of the couch with a disinfectant

• prescribes referral for medical genetic counseling in accordance with the instructions of the geneticist

• fills in a statistical coupon for each patient

• calls for examination of patients from the dispensary group as directed by the doctor.

2.2 Diagnostics:

Geneticist:

– collects complaints, medical history;

– conducts a clinical genealogical analysis;

– assesses the phenotype;

– conducts syndromological analysis;

– directs to laboratory research, conducts an assessment (interpretation) of laboratory research;

– directs to instrumental methods of examination, evaluates (interprets) the data;

– conducts differential diagnostics;

– gives a diagnosis.

Nurse:

• writes out a referral for examination in accordance with the doctor's prescriptions;

• At 9.00 hours takes the test results daily

• informs the doctor about changes (if any) in the work of key points of medical care daily.

III. Clinical position

3.1 Definition:

Porphyria is a group of hereditary diseases that are based on a violation of heme biosynthesis, which leads to excessive accumulation of porphyrins and their precursors in the body, namely, porphobilinogen (PBG) and δ-amino-levulinic acid (ALA). Excess of these substances has a toxic effect on the body and causes characteristic clinical symptoms. The reason for this violation is the

mutation of the gene responsible for the activity of one of the enzymes involved in multistage heme synthesis.

Heme biosynthesis or porphyrin metabolism. At first, the term "porphyros" was not a disease, but shiny purple-red crystalline porphyrins, which got their name from the Greek "porphyros" (purple). Porphyrins are cyclic tetrapyrroles with different terminal groups. The main feature of this complex ring group is the ability to bind metals, the most important of which are iron and magnesium (the most famous metalloporphyrin is heme and chlorophyll). Basically, heme biosynthesis is the metabolism of porphyrins, starting with the reaction of glycine with succinyl coenzyme A and ending with the formation of protoporphyrin.

3.2 Classification:

Porphyria are subdivided into erythropoietic and hepatic forms, depending on the tissue, where the predominant metabolic disorder of porphyrins occurs.

Hepatic forms of porphyria:– Porphyria, due to deficiency of δ-aminolevulinic acid dehydratase – Acute intermittent porphyria;

– hereditary coproporphyria;
– variegated porphyria;
– Late cutaneous porphyria.

Erythropoietic forms of porphyria:

– congenital erythropoietic porphyria (Gunther disease)
– erythropoietic protoporphyria.

According to the clinical course of the disease, porphyria is divided into acute forms and forms that occur with a clinic of predominant damage to the skin.

In the clinic of acute porphyria, severe neurological disorders dominate, affecting all parts of the nervous system. As the name implies, they are characterized by an acute, less often subacute onset of the disease.

This group consists of:

– Porphyria, due to a deficiency of δ-aminolevulinic acid dehydratase
– Acute intermittent porphyria;
– hereditary coproporphyria;
– variegated porphyria.

The group of porphyria occurring with the effects of skin lesions include:

– congenital erythropoietic porphyria;
– erythropoietic protoporphyria;
– Late cutaneous porphyria.

3.3 Epidemiology

Acute porphyria is not endemic and occurs with approximately the same frequency in all regions of the globe. The frequency of the porphyria that occurs has the following ratio:

Late cutaneous porphyria: 15–20 : 100 000

Acute intermittent porphyria: 5–10 : 100 000

Hereditary coproporphyria: 3–5 : 100 000
Variegatna porphyria 2–3 : 100 000

The statistics given are true for cases that appeared at the clinical stage. Speaking about the endemicity of Porphyry, it is necessary to take into account possible features characteristic of this geographical region.

3.4 Etiopathogenesis

The development of various forms of porphyria is associated with abnormalities in the heme biosynthesis cycle and has common features. The development of each form of porphyria is based on a genetically determined decrease or lack of activity of a particular enzyme in the heme biosynthesis chain, resulting in excessive accumulation of porphyry products of a new exchange before the degree where the defective enzyme is located. At toxic concentrations, the clinic of the disease appears. Enzyme genes are located on different chromosomes and do not have group linkage. A decrease in enzyme activity up to 50 % of the norm may not have clinical manifestations.

3.5 Induction factors and their role

In AP, factors (porphyrinogenny) can induce genetic carriage and provoke a clinical manifestation of the disease. These include:

– alcohol
– drugs (NSAIDs, barbiturates, cephalosporins, sulfonamides, etc.)
– menstrual cycle, pregnancy (in women)
– insolation
– bacterial and viral infections (especially HCV, HBV, CMV)
– hypoglycemia

These factors lead to increased consumption of the final product of the bio-synthesis cycle – heme (for example, activation of the cytochrome P-450 system), or directly stimulate the activity of the first enzyme of the biosynthesis cycle of δ-ALA synthetase, which leads to an increase in its activity (for example, the action of progesterone) As a result, the synthesis of all intermediate products of porphyrin metabolism is accelerated. At the stage of participation of the defective enzyme, excessive accumulation of metabolites in toxic concentrations begins, which leads to exacerbation. In AP, excessive accumulation of δ-ALA and PPG in the tissues leads to segmental demyelination of nerve fibers with impaired nerve conduction. All parts of the human nervous system are subject to toxic effects.

3.6 Clinical manifestations

Porphyria form	Signs	Type of inheritance	Enzyme defect
Erythropoietic uroporphyria (congenital	Skin lesions, hemolytic anemia with intracellular hemolysis, deposition in the skin, red blood cells and excretion	Autosomal recessive	An increase in the activity of the δ-aminolevulinic acid synthase enzyme and a slight decrease in

Porphyria form	Signs	Type of inheritance	Enzyme defect
porphyria, or Gunther porphyria)	of uroporphyrin isomer with urine I. The disease can occur in newborns (the urine in them is red). A few weeks or months after birth, bubbles appear on different parts of the baby's body, which often ulcerate. Ulcers do not heal well, secondary infection joins. Significantly darkening of the teeth in the child, their red glow under UV irradiation. In patients, an increase in the size of the spleen is observed. Typical signs of hemolytic anemia occurring with intracellular hemolysis are noted		the activity of the cosintase enzyme uroporphyrinogen III
Erythropoietin Protoporphyria	Characterized by increased sensitivity to solar radiation. On the open parts of the body after a few minutes of exposure to the sun, edema, redness, and itching appear, often the body temperature rises. With prolonged exposure to the sun, hemorrhagic rashes are observed. Occasionally, vesicles form, which ulcerate and leave small scars in the future	Autosomal dominant	Violation of heme synthesis in erythrokaryocytes, as well as an increase in the synthesis of δ-aminolevulinic acid in them
Erythropoietin Coproporphyria	Similar to erythropoietic protopor-phyria		The content of protoporphyrin in red blood cells increases by 30–80 times compared with the norm. The content of porphyrins in urine increases slightly, mainly due to coproporphyrin
Acute intermittent porphyria	Abdominal pain, which can be localized in various parts of it. Damage to the nervous system is manifested by severe polyneuritis; tetraparesis may develop, later paralysis of the respiratory muscles is possible. Sometimes epileptiform seizures, as well as hallucinations, delusions are noted. The exacerba-tion of the disease is provoked by pregnancy, childbirth, taking a number of medications (for example, barbi-turates, tranquilizers, sulfonamides, estrogens). Severe exacerbations occur after surgery, when thiopental sodium is used for sedation. After the development of severe exacer-bations, spontaneous remission may occur with a complete restoration of all functions	Autosomal dominant gene mapped at 11q 23.3	Violation of the activity of the synthase enzyme uroporphyrinogen-i and an increase in the activity of the δ-aminolevulinic acid synthase enzyme. Clinical manifestations are due to the accumulation of δ-aminolevulinic acid in nerve cells, which leads to inhibition of the activity of sodium, potas-sium-adenosine phosphatases and impaired ion transport through membranes, that is, to a violation of the function of the nerve fiber. Its demyelination, axonal neuropathy develops

Porphyria form	Signs	Type of inheritance	Enzyme defect
Hereditary hepatic coproporphyria	In clinical manifestations it resembles acute intermittent porphyria, but neurological symptoms are less pronounced. The most common symptom is abdominal pain, sometimes there are mental disorders, paresis, not as pronounced as with acute intermittent porphyria. Blood pressure may increase, tachycardia is possible. Some patients have signs of bullous photodermatitis		
Coproprotoporphyria (variegate porphyria)	Characterized by signs of acute intermittent porphyria, and skin manifestations, which are more common in men. Neurological disorders are very severe; in contrast to acute intermittent porphyria, renal failure sometimes develops	Autosomal dominant	Violation of the activity of the enzyme protoporphyrinogen oxidase. In addition, by increasing the activity of δ-aminolevulinic acid synthase, increased synthesis of δ-aminolevulinic acid
Chester's form of porphyria	Resembles acute intermittent porphyria with a severe course. Renal failure is sometimes observed		
Urocoproporphyria (late cutaneous porphyria)	It is characterized by severe skin symptoms, which appears more often in people over 40 years old. Its main signs: hypersensitivity to slight mechanical trauma and sun exposure, hypotrichosis, pigmentation disorder. Bubbles resulting from exposure to sunlight are usually localized on the rear of the hands and face. An increase in the size of the liver, often with functional impairments, is characteristic		The activity of the enzyme uroporphyrinogen decarboxylase of the liver is reduced

Clinical variants for the course

The course of AP can be divided into:

• classic, step

• atypical

• monosymptomatic

In most cases (up to 85 %), the symptoms of AP develop in stages. The development of symptoms in this case is tied to specific time stages, determining some "stepwise" evolution of the disease. You can talk about the early and late stages. Assessing the somatic status of the patient, one can imagine the degree of progression of the disease, evaluating the totality of symptoms and the time of their appearance and offering an adequate amount of medical care. Up to 10 % of patients, the so-called atypical development (usually rapidly developing), when the symptoms of the advanced stages of the

disease can occur in the debut and there is no continuity described above. It is even more difficult to verify AP in monosymptomatic course, for example, manifested by changes in behavioral reactions (~1–5 %).

The selection algorithm for patients with suspected AP:

- emotional lability
- tachycardia, arterial hypertension
- hyponatremia
- abdominal syndrome
- discoloration of urine
- vomiting, constipation
- diarrhea, paresis

Suspecting acute porphyria in a patient, until the diagnosis is excluded, the doctor should refrain from prescribing drugs and performing procedures (including operations) that could damage him. In most cases, the diagnosis of porphyria has not been verified, but certain tests need to be worked out.

Polyneuropathies with porphyria have a number of features:

– The predominance of the vegetative component at the beginning of the attack in the form of severe burning pains in the abdomen, lower back, extremities, cardiovascular and gastrointestinal disorders, dysuria, gallbladder sphincter dysfunction.

– In severe attacks, symmetric motor polyneuropathy joins, often with a primary lesion of the proximal extremities, and further and respiratory muscles with the development of respiratory failure. Less common is asymmetric or focal polyneuropathy. Cranial nerve involvement is possible.

– Sensory disorders can accompany motor neuropathy, manifested in areas of paresthesia, dysesthesia, anesthesia, often do not fit into any anatomical framework. The prevalence of subjective sensitivity disorders over objective and qualitative over quantitative is characteristic.

– According to electroneuromyography (ENMG), there is axonopathy or a combination of axonopathy with myelinopathy.

– According to pathomorphology, short motor axons are primarily affected (unlike other dysmetabolic axonopathies, if long motor nerves are affected earlier).

– Polyneuropathy is usually combined with pigmentation.

– Against the background of polyneuropathy, signs of central disorders may appear.

– There is an incomprehensible leukocytosis, a moderate increase in the levels of ALT, AST, LDH, and electrolyte disturbances are possible.

– In the cerebrospinal fluid, changes are not detected.

In addition, chronic neuropsychiatric symptoms in the form of depression, anxiety, dissomnia, illusions, apato-abulichny disorders, dementia, etc. are possible. These symptoms can also occur with other mental illnesses, however, with porphyria drug refractoriness, cycloid exacerbations with menses or after drinking are more common.

Repeated epileptic seizures may be a symptom of acute porphyria, but they do not necessarily indicate an attack of porphyria. If epileptic seizures are symptoms of porphyria attack, they are combined or preceded by one or more of the following symptoms: pain or discomfort in the abdomen, lower back, limbs, less often vomiting, etc.

3.7 Diagnostics

Porphyria form	Laboratory diagnostics
Erythropoietic uroporphyria (congenital porphyria, or Gunther porphyria)	A biochemical study reveals a large amount of I isomer of uroporphyrin and, to a much lesser extent, I isomers of coproporphyrin in urine, a large amount of I isomer of uroporphyrin in red blood cells
Erythropoietin Protoporphyria	Increased protoporphyrin in red blood cells; significantly increased the amount of protoporphyrin and coproporphyrin in the feces
Erythropoietin Coproporphyria	Erythropoietin-like protoporphyria
Acute intermittent porphyria	detection in urine of an increased content of precursors for the synthesis of porphyrins - porphobilinogen and δ-aminolevulinic acid
Hereditary hepatic coproporphyria	During an exacerbation in the urine, an increased amount of δ-aminolevulinic acid and porphobilinogen is found, which is lower than in acute intermittent porphyria. In urine and feces, the amount of coproporphyrin is sharply increased. The content of uroporphyrin in urine and protoporphyrin in feces is within normal limits. During remission, the content of porphobilinogen and δ-aminolevulinic acid may be normal with an increased content of coproporphyrin in urine and feces.
Coproproto Porphyria (variegated porphyria).	A constant significant increase in the amount of protoporphyrin in feces is characteristic. The content of δ-aminolevulinic acid and porphobilinogen in the urine increases during the period of exacerbation and becomes normal during remission
Chester's form of porphyria	
Urocoproporphyria (late cutaneous porphyria)	Throughout life, in patients the number of porphyrins in feces is increased. When the functional state of the liver changes under the influence of alcohol, hepatotoxic poisons, the process of excreting excess porphyrins with bile is disrupted, they are deposited in the skin and excreted in the urine. In urine, the content of uroporphyrin and to a lesser extent coproporphyrin is sharply increased

If an attack of acute porphyria is suspected, it is necessary to perform a qualitative reaction with Ehrlich's reagent, sensitive to an increase in urine porphobilinogen (PPB) more than 5 times higher than normal, which meets the criteria for an attack of acute porphyria, and quantify the level of each porphyrin in urine. The increased content of porphyrins makes it possible to diagnose acute porphyria.

The final step in the diagnosis of porphyria in patients and, in particular, in asymptomatic carriers is DNA analysis.

3.8 Complications and acute conditions

3.8.1. Acute respiratory failure (ARF).

One of the most formidable complications of porphyria polyneuritis is a violation of the innervation of the diaphragm and skeletal respiratory muscles.

In the development of the respiratory failure clinic, paresis of the diaphragm appears earlier than paresis of the intercostal skeletal muscles. Three components play an important role in the formation of respiratory failure:

– paresis of the respiratory muscles
– airway obstruction
– alveolar insufficiency

The development of paresis of the respiratory muscles is a manifestation of polyneuropathy in AP and can begin at the end of the first month of the disease. The following can accelerate the progression of this ARF mechanism:

• continued exposure of the patient to the porphyrinogenic agent (for example, pregnancy or the menstrual cycle, porphyrinogenic drugs).
• surgery (tissue trauma) in combination with the use of prohibited general anesthesia can lead to fulminant development of ARF.

In the development of the obstructive mechanism of ARF, an important role is played by infections of the tracheobronchial tree (TBT) and weakening of the cough. The following elements play a role in the pathogenesis of obstructive pulmonary obstruction:

• paresis of the diaphragm
• paresis of skeletal muscles
• paresis of the muscles of the abdominal wall
• non-closure of the vocal cords (due to bulbar syndrome)
• paresis of the ciliary epithelium of the bronchi.

Alveolar insufficiency develops with pneumonia, atelectasis of the parenchyma, leads to a significant reduction in the respiratory surface of the lungs, characterized by a decrease in the indicator of functional residual capacity, appears with spirometry.

3.8.2. Bulbar syndrome.

Boulevard syndrome occurs with damage to the sublingual (XII pair), additional (XI pair), vagus (X pair) and glossopharyngeal (IX pair) cranial nerves and is characteristic of advanced cases of AP. The clinical symptoms of the development of bulbar syndrome are: nasal tone of the voice - rhinolalia, slurred speech - dysarthria, dysphagia, as well as overhang of the soft palate and lack of mobility during phonation.

3.8.3. Infectious complications.

In most patients, by the end of the second, beginning of the third week from the debut of the AP, a neurological deficit in the form of paresis and plegia begins to form. The condition of patients is also worsened by a violation of the function of visceral organs. Such patients are paralyzed and lie in bed. After 1–2 months, as a result of increased catabolism of muscle proteins, weight loss of 6–15 kilograms or more occurs. In addition, there are always dysfunctions of the pelvic organs, weakening of the excursion of the chest and pronounced paresis of the gastrointestinal tract. The presence of these complications and the

need for prolonged prosthetics of the functions of various organs create the prerequisites for the development of infectious complications characteristic of AP, which can be divided into 5 categories:

- respiratory tract infections
- urinary tract infections
- maxillofacial sinus infections
- gastrointestinal infections
- central venous catheter infections (CVC).

Functional insufficiency of the respiratory muscles (diaphragm and intercostal muscles) leads to incomplete chest excursion with the development of hypoventilation of mainly the basal segments and the lower part of the lungs, which creates the prerequisites for the development of pneumonia. Paresis of the ciliary epithelium of the bronchi, together with incomplete closure of the vocal cords of the larynx, are manifested by pronounced violations of the evacuation function of the TBT. There are stasis of sputum with obstruction of the small bronchi. This is especially often observed in patients who already have mechanical ventilation.

Dysfunction of the pelvic organs due to reverse denervation of the bladder. This leads to an overstretching of its walls, an increase in hydrostatic pressure of urine. In the future, urine is thrown into the ureters, bowls, and Pielmovenous reflux develops.

Infections of the maxillofacial sinuses are often observed in patients with plegia, who are for a long time in a forced lying position. This disrupts the natural aeration of the cavities and the outflow of their contents. The situation is aggravated by the installed naso-tracheal and nasogastric ventilation tubes and probes.

In patients with paresis of the gastrointestinal tract, the evacuation of the gastrointestinal contents is impaired, causing a disturbance in the processes of physiological cavity and parietal digestion in the intestinal tube, followed by the formation of pathogenic microbial flora. Paresis of the sphincters of the stomach threatens the development of aspiration. There is a need to install a naso-enteral or naso-gastric probe for artificial feeding. With parenteral nutrition, the lack of stimulation of the major duodenal papilla with food worsens the evacuation of bile from the gallbladder, provokes overstretching of its walls.

Inpatient treatment of patients with AP requires the installation of a CVC for the patient. Poor hygiene of the patient, inadequate care of the catheter, lead to infection of the CVC.

3.8.4. Chronic renal failure.

Clinical and laboratory signs of the development of renal failure are more characteristic for patients suffering from repeated attacks of AP for a long time (several years). The pathogenesis of kidney damage during repeated attacks of

AP is not completely clear. However, the most likely effect of several etiological factors:

• cytotoxic and vasospastic effects on the nephron of excess porphyrins and their precursors;

• transient arterial hypertension with very high numbers of blood pressure in attacks of AP, accompanied by pathological involvement of the renal arteries, followed by the formation of arteriolo-nephrosclerosis;

• nephrotoxicity of tissue catabolism products (myoglobin, etc.), due to polyneuropathy, occurs with severe attacks of AP.

3.8.5. Sensory-motor polyneuropathy.

The result of excessive secretion of porphyrin and their precursors (PPB and δ-ALA) is their accumulation in all organs and tissues. Porphyry precursors, especially δ-ALA, have a neurotoxic effect and lead to axonal segmental demyelination of the nerve trunks with impaired conduction and thereby the development of paresis, which have specific features in patients with AP.

The differential diagnostic criteria for paresis in AP include:

• paresis is always symmetrical and equally extends all limbs;

• first of all, the proximal and then the distal parts of the extremities are affected;

• paresis is always sluggish;

• paresis progresses rapidly without specific therapy aimed at suppressing the synthesis of porphyrin.

In the later stages of the disease, in the absence of adequate therapy in patients, paresis progresses to the degree of plegium. The following complications are typical for such patients:

– thrombosis of the venous vascular bed due to slowing blood flow in the non-working extremities, along with the use of drugs that promote hypercoagulation (contraceptives, heme preparations)

– the formation of musculocutaneous defects (pressure sores) with their subsequent infection in places of increased contact of the skin with a hard surface due to microcirculation disorders;

– the formation of stiffness of the ligamentous apparatus of the limbs with ankylosis of mainly small joints

– hyperesthesia and hyposthesia as a manifestation of sensory polyneuropathy;

– the development of erirocytopenia and anemia (worse impaired heme biosynthesis)

– rapid loss of muscle mass caused by the predominance of catabolism in the metabolism.

3.8.6. Syndrome of inadequate secretion of antidiuretic hormone (ADH, vasopressin).

Quite rare and very specific for AP is the inadequate secretion syndrome appears due to excessive accumulation of porphyrin metabolism products in the pituitary gland. The syndrome develops with an excess release of ADH and an

increase in its concentration above 4.0 ng/L in serum and is manifested by a decrease in serum sodium. With a decrease in serum sodium levels below 120 mmol/L, a clinic of general cerebral symptoms appears. With an increase in hyponatremia, a brain coma may develop with a risk of death.

3.8.7. Gastrointestinal paresis. Abdominal syndrome.

The vast majority of patients suffering from attacks of AP have abdominal pain caused by paresis of the gastrointestinal tract (observed in 80 % of patients with AP) and constipation. In the pathogenesis of paresis of the gastrointestinal tract, an important link is the development of spasm of mesenteric vessels, accompanied by impaired motility of the loops of the small intestine.

3.9 Pregnancy and porphyria

The metabolites of endogenous sex steroids increase the activity of synthetase, δ-ALA, in the liver. Progesterone induces the activity of synthetase – δ-ALA, both directly and indirectly through the activation of cytochrome P-450 in the liver, which leads to the activation of the first enzyme in the biosynthesis cycle. Compared with other sex hormones, progesterone has a more pronounced effect in provoking attacks of AP. Healthy women showed significant fluctuations in the level of δ-ALA synthetase in leukocytes during the menstrual cycle, with a peak during menstruation. In women with a latent course of AP, this lability of the activity of this enzyme often leads to excessive accumulation of intermediate products of porphyrin metabolism and the onset of an attack of AP. Especially often, seizures occur in the early stages of pregnancy and in the labor period, which is explained by significant hormonal changes at this time. That is, pregnancy is a high risk factor for developing an attack of the disease for patients with AP.

The following criteria play an important role in determining pregnancy management strategies:

– in patients with AP after a seizure, followed by full recovery before pregnancy, at least two years of the unobstructed course of AP should pass for a steady decrease in porphyrin metabolism;

– before the onset of a planned pregnancy, it is necessary to reorganize all foci of infection, including the oral cavity;

– after pregnancy, dynamic monitoring is necessary in the hospital, where delivery will be planned;

– All drug therapy should be coordinated between geneticists, obstetricians, hematologists and nephrologists;

– heme arginate should be the drug of choice for the relief of an attack during pregnancy;

– an indication for the appointment of heme arginate is not only a significant increase in the concentration of total porphyrin and PPB (compared with previous indicators), but also the appearance of characteristic clinical symptoms of AP;

– assessment of the stability of porphyrin metabolism must be carried out throughout pregnancy using regular quantitative analyzes of the excretion of porphyrins and their precursors in urine at least once every two months;

– the risk of an attack from exposure to any porphyrinogenic factor is significantly higher in patients with AP who have recently suffered an "attack" of the disease than in patients with latent course of AP for several years

– It is necessary to focus on the nature of the course of AP before pregnancy. In women with repeated menstrual-associated seizures, the risk of having another seizure during pregnancy is much higher;

– In the first and last trimesters of pregnancy, hormonal changes are more pronounced and the risk of developing an attack is more likely.

3.10 Differential Diagnostics

Acute porphyria should be differentiated with all diseases accompanied by:

– abdominal pains;

– the development of symmetrical limb polyneuritis;

– bulbar disorders;

– the release of colored urine;

– encephalopathy;

– mental disorders: psychosis, resistant to the treatment of schizoaffective disorder;

– cycloid psychosis;

– conversion disorders; somatization and chronic fatigue syndrome.

3.11 Treatment

Geneticist:

– explains to the patient the features of the further development of the disease;

– gives recommendations for nutrition correction according to the results of the survey;

– prescribes drug therapy with proven effectiveness;

– draws up a plan of treatment and preventive measures for the patient;

– coordinate with the patient the scheme and regimen of medication;

– appoints planned visits of the patient to the doctor with an interval of 2 to 3 weeks to monitor the condition of the patient and conduct a follow-up examination (control of metabolic parameters that have been changed)

– issues an opinion with the results of the examination, a final diagnosis (if installed) and recommendations;

– planning consultations of related specialists (infectious disease specialist, immunologist, endocrinologist, allergist, gastroenterologist, nephrologist, vascular surgeon, etc.).

Treatment measures:

Porphyria form	Measures
Erythropoietin uroporphyria (congenital porphyria, or Gunther porphyria)	Splenectomy has a definite effect.
Erythropoietin Protoporphyria	Sun protection (wearing hats, gloves, using sunscreens) is recommended. The forecast is favorable
Erythropoietin Coproporphyria	No treatment developed
Acute intermittent porphyria	It is recommended to exclude drugs that lead to an exacerbation of the disease. With severe pain, narcotic analgesics, chlorpromazine can be used. With a sharp tachycardia and an increase in blood pressure (BP), β-blockers are used. To reduce the production of porphyrins, glucose is administered up to 200 g per day or phosphaden (Aden) up to 250 mg per day intramuscularly. In severe cases, hematin is prescribed; plasmapheresis has a certain effect. When improving the condition to restore movement using massage, therapeutic exercises. The prognosis is serious with severe damage to the nervous system. Prevention is the elimination of factors causing exacerbation during the course of the disease
Hereditary hepatic coproporphyria	Treatment of exacerbations is similar to treatment for acute intermittent porphyria
Coproproto Porphyria (variegated porphyria)	Treatment, prognosis and prevention are the same as with hereditary hepatic coproporphyria
Chester's form of porphyria	
Urocoproporphyria (late cutaneous porphyria)	Treatment of urocoproporphyria is ineffective when the patient continues to consume alcoholic beverages. An effective remedy is delagil, which forms a complex with porphyrins of the skin and removes them with urine. The drug is prescribed in small doses of 0.125 g 2 times a week for 2 weeks, then 0.125 g every other day for 2 weeks, with good tolerance of 0.125 g daily for 3 months. By the end of the course of such therapy in most patients, the clinical manifestations of the disease are completely stopped, the level of proporphyrin in the urine is normalized or significantly reduced. A faster therapeutic effect is observed with a combination of delagil with inosine (riboxin) 0.2 g 3–4 times a day for 2–3 months

3.12 Acute Attack Treatment Algorithm

When ascertaining an attack, it is necessary to begin pathogenetic treatment, involves the use of the following methods:

- replacement therapy for arginate heme;
- carbohydrate load;
- elimination of porphyrin metabolites by a series of plasmapheresis (PP), sometimes hemodiafiltration.

The method of choice, of course, is replacement therapy for arginate heme. More long-term prospects for obtaining a clinical effect have a carbohydrate load, which can be seen both with parenteral solutions and enteral mixtures in the form of artificial nutrition. PA give the greatest effect in the treatment of UPC and AP, where the main metabolites are porphyrin isomers. With GLP and porphyria, due to a deficiency of δ-ALA dehydratase, which differ in the predominance of porphyrin precursors, the effect of PP is much less pronounced. Extremely useful PP can become in the debut of the AP, if there is evidence of previous alcoholism or medication. In such cases, it is necessary to conduct 2–3 sessions of PP in order to eliminate pores of the phyrinogenic factor A. If menstrual cycles often (three or more times a year) provoke attacks of AP, reproductive function must be suppressed. Treatment is started if there are several symptoms of AP and an increase in porphyrin metabolism (compared with previous dynamics). With the development of an acute attack, immediate initiation of pathogenetic therapy is necessary to suppress excessive porphyrin biosynthesis:

1. Purpose: heme arginate (Normosang *) 3 mg/kg IV drip 1 time per day. 4–7 days in a row.
2. Ensuring excess intake of carbohydrates in the body (200–600 g of glucose dry matter). 40 % – 1 000 ml iv in the drip per day, daily, 2–4 weeks.
3. Sandostatin in a dose of 100–500 mcg/day., Subcutaneously, daily for from 4 weeks to 6 months in combination with plasmapheresis, 6–10 sessions.
4. Riboxin 2 % 10 ml in a dilution of 100–200 ml of a 0.9 % NaCl solution, in/drip 1–2 times a day, daily 2–4 weeks.

IV. Dispensary observation

Clinical observation is carried out in all patients with porphyria.

Geneticist:

– carries out regular medical supervision:

– appoints planned visits of the patient to the doctor to assess the tolerability, effectiveness and safety of treatment;

– monitoring the patient's compliance with the recommendations received is carried out with an interval of 2 to 4 weeks;

– after achieving improvement in clinical manifestations and normalization of biochemical parameters, the interval between scheduled visits is no more than 3 months

– monitors the implementation of recommendations, motivates and adjusts recommendations and appointments;

Nurse:

– in accordance with the prescriptions of the doctor invites patients to receive;

– invites three days before the recommended inspection;

– prescribes a referral for examination in accordance with the doctor's prescriptions.

Навчальне видання

ПОРФІРІЇ

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