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Clinical cases of toxic hepatitis: aspects of differential diagnosis with viral hepatitis

In modern conditions of environmental problems, practicing doctors increasingly have to provide assistance to patients with hepatitis, the cause of which is not only known viral agents, but also chemical poisons. General information about toxic, primarily drug-induced, and viral hepatitis is given. The main hepatotoxic drugs are listed. Their classification, mechanism of action, clinical symptoms, biochemical and morphological changes in various toxic liver lesions are highlighted. Information on drugs with high hepatic extraction, for which there is a high risk of overdose, is highlighted. For patients from risk groups, it is advisable to at least halve the dose of such drugs in accordance with the decrease in hepatic blood flow. Drugs with low hepatic extraction have a minimal risk of overdose, although metabolic insufficiency with long-term administration of such drugs may cause their accumulation. Finally, drugs that are excreted by the kidneys are practically devoid of the risk of hepatotoxicity. Other professional and household toxic substances that have a direct hepatotoxic effect are discussed (carbon tetrachloride, dichlorodiphenyltrichloromethylmethane, yellow phosphorus, amanito- and phallotoxins of the pale toadstool, various pesticides, etc.).

Clinical cases of own clinical observations of various toxic hepatitis are included. The general characteristics of viral hepatitis are given, primarily with an emphasis on their differential diagnosis with hepatotoxic lesions. The main signs of viral and toxic hepatitis are grouped in the table. For a successful differential diagnosis of toxic and viral hepatitis, it is necessary to apply a modern complex of anamnestic, clinical, biochemical, virological, instrumental and morphological examination methods as fully as possible.

Keywords: toxic hepatitis, drug-induced hepatitis, viral hepatitis, differential diagnosis.

The liver is a vital organ in the human body that plays a major role in the detoxification of poisons and metabolites. In today's environment, practitioners increasingly have to provide care to patients with chronic hepatitis caused not only by known viral agents but also by food and chemical poisons. Biochemical reactions (oxidation, reduction, methylation, condensation, phosphorylation, glycogenesis, lipogenesis, water and electrolyte balance, synthesis of essential amino acids and fat-soluble vitamins) take place in hepatocytes. The number of deaths from cardiovascular disease with comorbidity of obesity, diabetes, and cancer

has increased worldwide. Autoimmune and infectious diseases have taken the third place among the causes of death. It is the liver cells that neutralize toxins, metabolites and other waste products of microorganisms in the body of a sick person. Toxins actively affect hepatocytes directly, disrupting their function and blood circulation, which leads to impaired protein synthesis, lack of oxygen and vitamins. In this case, liver dysfunction develops — toxic hepatitis. Given the particular importance of timely recognition of this disease and the need for emergency care, the authors, being clinicians with 30–40 years of experience, decided to summarize

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the differentiation of toxic, primarily drug-induced, hepatitis with common viral hepatitis.

Toxic hepatitis (ICD-10: K71.0-K71.8) is a liver damage caused by a toxic agent: drugs, household chemicals, pesticides, occupational hazards, etc.

Drug-induced hepatitis plays an important role among toxic liver diseases. They occur more often with enteral administration of medications, which is associated with the peculiarities of blood supply to the liver and metabolism of drugs in it. The spectrum of hepatotoxic drugs is constantly expanding: in 1991, there was information about 748 such agents, in 1992 – 808, in 2000 – 1,121, in 2009 – about 1,412 [18]. The mechanisms of liver tissue damage are different and are realized through the direct toxic effect of drugs or their metabolites on hepatocytes. In addition, there are liver lesions caused by idiosyncrasy to drugs, which occur regardless of the dose of drugs taken.

Most often, drug-induced hepatitis can be caused by the following medications:

- halothane;
- methyldopa (dopegit);
- isoniazid, rifampicin, pyrazinamide, fluoroquinolones and most anti-tuberculosis drugs;
- tetracyclines, monobactams, carbapenems, penicillins and other antibiotics;
- antifungal chemotherapeutic agents (ketoconazole, fluconazole, itraconazole);
- sulfonamides;
- phenytoin, sodium valproate;
- zidovudine;
- nifedipine;
- acetylsalicylic acid, paracetamol, ibuprofen, indomethacin;
- amiodarone;
- hormonal contraceptives;
- allopurinol;
- azathioprine;
- tranquilizers and antidepressants [4].

Drug metabolism is carried out in two stages:

- *Stage I* is the hepatic biotransformation. Drug metabolites are more hepatotoxic than pharmaceuticals themselves. Their biotransformation is carried out, in particular, due to oxidative processes associated with the microsomal fraction, cytochrome P450, and mitochondrial enzymes. With the use of moderate amounts of drugs, all the compensatory systems involved increase their activity, but in liver disease, their activity is reduced and thus the ability of the hepatocyte to metabolize pharmaceuticals is impaired;

- *Stage II* is the stage of binding of first-phase drug metabolites to various substrates (glutathione, sulfate, glucuronides), which neutralize them. The

formed compounds are excreted in bile and urine. Ethanol (alcohol) reduces the activity of the microsomal oxidase system that metabolizes drugs. The activity of cytochrome P450 is largely genetically dependent, which explains the hepatotoxic selective effect in patients with a deficiency of this protein involved in redox processes [9]. A number of hormones (testosterone, aldosterone, estradiol, progesterone, hydrocortisone) inhibit the drug metabolic activity of the hepatocyte, since their breakdown and utilization occur only due to the cytochrome P450 enzyme. The enzymatic activity of the hepatocyte neutralizing systems depends on the preload of pharmaceuticals, their interaction, and pre-existing chronic diffuse liver disease [4].

Damage to the liver parenchyma in alcoholic disease, chronic active hepatitis of viral etiology, and liver cirrhosis, accompanied by a significant decrease in protein synthesis function, significantly affect the metabolism of pharmaceuticals. Drug utilization is less impaired in cholestatic hepatitis and primary biliary cirrhosis, but intrahepatic cholestasis slows the excretion of drugs and their harmful metabolites in the bile.

There are three groups of pharmaceuticals. The first group includes drugs with high hepatic extraction. They have a high risk of overdose, and normal doses can cause severe toxic effects in liver cirrhosis and right ventricular heart failure. In such patients, it is advisable to reduce the dose of drugs by at least half in accordance with the decrease in hepatic blood flow.

The second group of substances includes drugs with low hepatic extraction. Only with a decrease in the metabolic capacity of hepatocytes to 70% does the content of drugs in this group increase in the blood, so the risk of overdose is low, but metabolic failure with prolonged use of such drugs can cause their cumulation.

The third group of substances includes drugs that are excreted by the kidneys, so the risk of drug overdose in patients with liver disease in the absence of liver failure is low [2, 21, 27].

Risk factors in the treatment of patients with liver disease include hypoalbuminemia, prolonged prothrombin time, renal dysfunction, pleurisy of unknown origin, ascites, and chronic shunt and parenchymal hepatic encephalopathy. Many drugs can directly lead to acute and chronic toxic liver damage, hepatovascular disorders, and tumors of this organ. Drugs that cause toxic liver damage are divided into true (obligate) and facultative, idiosyncrasy-dependent.

Medications can act as indirect hepatotoxins. Among them are cytotoxic, cholestatic, and carcinogenic.

Cytotoxic substances include puromycin, tetracycline, etc.; cholestatic substances include anabolic steroids, lithocholic acid. These substances affect the liver through selective disruption of bile secretion [1].

An optional group of hepatotoxins includes substances that affect the liver due to hypersensitive allergic reactions (with the development of granulomatous liver damage with foci of eosinophilia, fever, rash, and an increase in the number of eosinophils in the blood), as well as hepatotoxins, which cause drug-induced liver damage due to toxic drug metabolites with a decrease in the activity of the hepatocyte glutathione system, cytochrome P450 activity, and oxidase activity of the microsomal fraction of hepatocytes. This disrupts the detoxification and protein synthesis function of the liver, damages cellular and subcellular membranes, due to a decrease in their resistance against the background of depletion of the antioxidant system, especially its glutathione-dependent link [11].

The mechanism of action of hepatotoxins that can cause idiosyncrasy (chlorpromazine, etc.), in addition to hypersensitivity reactions, is also associated with the formation of hepatotoxic metabolites.

Toxic drug metabolites can act as haptens and semi-haptens that bind to specific cell membrane molecules, resulting in the formation of antigens tropic to hepatocytes. The latter are destroyed with the formation of autoantigens, which, according to the laws of immunology, form antibodies to the hepatocytes' own antigens, destroying them. Thus, the process can become autoimmune [13].

Salicylates in a dose of 2 g/day can cause focal hepatocellular necrosis, and large doses of tetracycline cause liver damage similar to acute fatty degeneration of the organ with central and intermediate necrosis and fatty deposits in hepatocytes [25].

Drugs such as 6-mercaptopurine, methotrexate lead to an increase in the activity of alkaline phosphatase and serum aminotransferases, sometimes to hyperbilirubinemia. Paracetamol and methyl dopa can cause liver necrosis, acute or chronic hepatitis. Phenobarbital causes hepatomegaly, and cortisone and its derivatives cause fatty liver [4, 25].

Another group of drugs that are often hepatotoxic is the ubiquitously advertised so-called «fat burners». Sometimes advertisements claim that dietary supplements, or herbal remedies, have such properties: plants that supposedly break down fat, diuretic tea, pieces of lichen, unpeeled beans, etc. Who hasn't heard that pineapple melts fat? Yes, bromelain or bromelain is widely known, and it is found in the pineapple trunk, not in the fruit itself. Bromelain has in no way earned its reputation as

a fat burner for weight loss. And it has no effect on insulin metabolism, as previously thought. Other plants that seemed harmless turned out to be toxic and disappeared from the market. The same thing happened with some Chinese weight loss plants (the more exotic they were, the more people liked them), which caused serious toxic hepatitis [8, 15].

Very often, so-called slimming products contain laxatives such as anthraquinones or bisacodyl. They are cheap and available in pharmacies without a prescription. However, if they are used for a long time or simply exceed the dose, it can cause toxic damage to the liver, kidneys, colon mucosa, etc. [14].

Clinical and morphological features distinguish between cytolytic (with liver necrosis and steatosis), cholestatic, mixed (cholestatic-cytolytic) acute drug-induced hepatitis and less common chronic liver damage.

Only 10% of all adverse drug reactions involve liver damage, but the number of severe reactions among them is so high that drugs and chemical poisons are the main cause of acute liver failure. Cytolytic hepatitis accounts for 2/3 of all toxic (drug, chemical, organic poisons) hepatitis with a mortality rate of 60%, while in cholestatic hepatitis the mortality rate reaches 3%. Cholestatic lesions are caused by more than 100 drugs [20].

Cholestatic-cytolytic liver damage has been described in the setting of aminazin, rifampicin, tubazide, misclerone, sulfonamides, papaverine, cimetidine, nicotinic acid, leukeran, amitriptyline, elenium, seduxen, oxacillin, penicillin, mercazolil, and many others [3].

Nonspecific reactive hepatitis caused by dopegit, hydralazine, butadione, penicillin, which cause granulomatous hepatitis, sometimes in combination with cholestasis, is subclinical. Acute toxic (drug, chemical) hepatitis is more common in a jaundiced form and can occur both during the period of drug administration (or exposure to a chemical agent) and 3–4 weeks later [4, 18].

The main symptom in toxic hepatitis is jaundice, which was called salvarsan jaundice because it occurred in patients treated with salvarsan containing arsenic (salvarsan was used to treat syphilis, malaria, and typhoid fever). The disease developed most often in 2–3 months after the start of treatment and was mainly manifested as hepatitis A [18].

The clinical picture is dominated by signs of dyspepsia: nausea, vomiting, loss of appetite, abdominal pain, diarrhea, asthenic, allergic syndrome, often hepatoliver syndrome, palpable sharp liver tenderness. The increase in aminotransferase activity and bilirubin levels in the blood is directly related to cytolysis and the spread of liver necrosis.

In other cases, the same drugs cause allergic liver damage. In such cases, the appearance of jaundice is preceded by itching, urticaria, abdominal pain, nausea, vomiting, arthralgia, vasculitis, eosinophilia, and leukopenia. Hepatitis often occurs even after very small doses of the drug, for example, after taking only one tablet of aminazin. The disease usually occurs with cholestasis, which is sometimes mistaken for mechanical jaundice. Aminazin acute hepatitis can progress to primary biliary cirrhosis [18].

Differential diagnosis. Toxic and viral hepatitis have a very similar clinical picture. At the same time, their differentiation is of great importance due to completely different treatment, which can significantly affect the outcome of the disease.

The differential diagnosis of toxic hepatitis from viral hepatitis is primarily based on anamnesis (Table). Questioning the patient allows you to find out that before the onset of jaundice, he or she took one of the listed drugs or came into contact with a hepatotropic poison (carbon tetrachloride, dichloroethane, vinyl chloride). The onset of viral hepatitis is not associated with the use of these drugs.

To illustrate drug-induced toxic hepatitis, we present our own observation.

Patient A. V., 41 years old (medical record of an inpatient No. 03/07422), a resident of Ternopil, was admitted to the anesthesiology and intensive care unit of the regional clinical hospital on July 26, 2016, with complaints of general malaise, fever to 38.5–39.0 °C with chills, constant shortness of

Table. Comparison of the main signs of viral and drug-induced hepatitis

Index	Viral hepatitis	Toxic hepatitis
History	Possible disease outbreaks in children's groups (HA), parenteral infection (HB, HC)	Information about taking medications or contact with hepatotropic poisons
Course	Cyclic with the presence of a pre-jaundic period	Torpid, without a pre-jaundic period
Objective examination	Jaundice, hepatolienal syndrome; possible catarrh of the upper respiratory tract, diarrhea, arthralgia	Jaundice, hepatolienal syndrome, possible rash on the skin
Extrahepatic manifestations are possible	Vasculitis, dermatosis, arthralgia (HB), hyperthyroidism, hypothyroidism, hashimoto's thyroiditis, diabetes, intralobular pneumonia, cryoglobulinemia, lymphocytic sialoadenitis, mooren corneal ulcers, uveitis, glomerulonephritis, etc. (HC)	Fever, rash, arthralgia, myalgia, damage to kidneys, lungs, bone marrow
Cholestasis	Only with cholestatic form	A frequent occurrence
Laboratory examination of blood		
General analysis	Possible leukopenia	Leukocytosis, eosinophilia, sometimes agranulocytosis, increased ESR
Protein fractions	A sharp increase in the level of γ -globulins	Increase in the level of α_2 , γ -globulins
Bilirubin and its fractions	An increase in the level of mainly direct bilirubin	A slight increase in the level of mostly indirect bilirubin
ALT, AST	Increasing activity	Increasing activity
Thymol test	Rises	Normal
Sulem test	Decreases	Normal
Alkaline phosphatase	Increased activity – with cholestatic form	A sharp increase in activity
Creatinine	Normal	Rises
Urea	Normal	Rises
Prothrombin index	Decreases in severe cases	Decreases
Serum markers	Present	Not present (only with toxic hepatitis)
Liver biopsy with histological examination of liver	Inflammatory infiltration of the stroma, possible development of fibrosis and cirrhosis	Inflammatory infiltration of the stroma, necrosis of hepatocytes III or I zone of the acini

breath, frequent unproductive cough, severe pain in the right leg and its swelling.

Anamnesis: the disease began after thrombophlebitis of the right lower leg due to foot abrasion with new shoes.

Objective status. The patient's condition is serious. The patient is restless, periodic psychomotor agitation. The skin is pale. The oral mucosa is dry, the tongue is covered with a white coating. Heart sounds are weakened, pulse 126 per 1 min, tachyarrhythmia, mild tension and filling. Blood pressure 110/60 mm Hg. Over all lobes of the lungs — a mass of moist medium and small bubble rales, percussion sound is shortened, more on the left. The abdomen is soft; the liver is palpable 1 cm below the costal arch, densely elastic. On the medial surface of the right foot — large purulent erosions, the right tibia and thigh are sharply swollen, purple-cyanotic, active bending of the leg at the knee joint is impossible due to pain.

Complete blood count: hemoglobin 104 g/L; erythrocytes $3.1 \cdot 10^{12}$ /L; leukocytes $15.5 \cdot 10^9$ /L, myelocytes 3%, rod-shaped neutrophils 10%, eosinophilic neutrophils 4%, segmented neutrophils 58%, lymphocytes 23%, monocytes 2%; erythrocyte sedimentation rate (ESR) 70 mm/h. Coagulogram: prothrombin 77.5%, fibrinogen 3.3 g/L, thrombotest VI, fibrinogen B++.

General urinalysis and biochemical blood test were without significant abnormalities.

X-ray — bilateral *pneumonia* with lesions of all lung compartments.

Blood cultures — repeated growth of *Staphylococcus epidermidis*.

Diagnosis: acute staphylococcal (*S. epidermidis*) sepsis, septicemia (bilateral total pneumonia, deep vein thrombophlebitis of the right leg and thigh). Toxic encephalopathy with reactive neurotic manifestations.

Treatment: targeted antibiotics were prescribed — meropenem intravenously 500 mg three times a day, later — cephalosporins and IV-generation fluoroquinolones intravenously in maximum daily doses; immunorestorative, detoxification agents. Symptomatically, the patient received painkillers, and after the psychiatrist's recommendation, in order to calm psychomotor agitation, she was administered intramuscularly for 4 days with aminazine at a daily dose of up to 600 mg.

Despite clear signs of regression of respiratory failure, reduction of pain and swelling of the right leg, on the 7th day of treatment, jaundice of the mucous membranes and skin and itching appeared, fever persisted, and the liver increased by 4 cm along the midclavicular line.

The complete blood count showed the development of agranulocytosis (leukocyte count $0.6 \cdot 10^9$ /L), and

a biochemical blood test showed cholestatic-cytolytic liver damage: total bilirubin 318.4 $\mu\text{mol/L}$ (direct 229.5, indirect 88.9 $\mu\text{mol/L}$), alanine aminotransferase (ALT) 4.56 mmol/(L·h), aspartate aminotransferase (AST) 2.88 mmol/(L·h), alkaline phosphatase 30 mmol/(L·h), cholesterol 7.8 mmol/L, urea 7.12 mmol/L, creatinine 0.143 mmol/L, total protein 64.18 g/L. The urine was beer-colored, foamy, and the feces were hypocholic.

In connection with the appearance of signs of hepatitis, the blood was tested for the presence of HBV and HCV markers: HBsAg and anti-HCV were not detected.

After discontinuation of potentially hepatotoxic meropenem and symptomatic therapy (including aminazine), as well as supplementation with a hepatoprotective agent, the jaundice began to subside. Soon after, his body temperature and liver function tests normalized. After spending 43 days in the hospital, she was discharged home in satisfactory condition.

Conclusion from the given example, the patient developed drug-induced agranulocytosis and cholestatic hepatitis induced by the side effects of meropenem and/or aminazine while treating the underlying disease. After the root cause of the disease was eliminated (discontinuation of meropenem and aminazine), the manifestations of toxic hepatitis disappeared on their own. The rapid positive dynamics of liver tests allowed us to finally exclude viral hepatitis and confirm the preliminary diagnosis.

Androgens, anabolic steroids, and hormonal contraceptives can also sometimes cause cholestatic jaundice when used for a long time. Morphologically, it differs from viral hepatitis in the absence of cellular infiltrates in the portal zone. Jaundice usually develops on the 10–15th day of treatment, and sometimes 1–2 months after drug discontinuation. It is often intense, accompanied by itching of the skin and discoloration of the feces. The course of jaundice is usually favorable, although it can be prolonged.

Here is another observation of ours.

Patient V.O., 29 years old (medical record of an inpatient No. 1-3119), a resident of Ternopil, was admitted to the infectious diseases department of the Ternopil City Clinical Hospital on June 12, 2023, with complaints of general malaise, yellowing of the skin and sclerae, intense itching of the skin, especially in the evening and at night, and decreased appetite.

Epidemiology. 2 weeks ago, she returned from Mexico, where she had lived for a long time in a provincial town with unsatisfactory sanitary conditions.

Past medical history. She fell ill on 03/28/23, when she felt generalized weakness, nausea, vomiting, and body temperature rose to 38.7 °C. Within

a week, she noticed yellowness of the sclerae, darkened urine, and lightened stool color. She consulted a doctor at her place of temporary residence (Mexico), who, based on marker diagnostics of viral hepatitis (IgM to HAV was detected), diagnosed her with hepatitis A and prescribed outpatient treatment (she took ursodeoxycholic acid 250 mg three times a day). After 2 months, after arriving in Ukraine, she sought medical care and was referred to the infectious diseases department of the «Ternopil Municipal Emergency Hospital» for additional examination and treatment.

She has a history of psoriasis (periodically treated on an outpatient basis). There is no information about past childhood infectious diseases.

Objective status. Body temperature is 36.6 °C. The general condition is close to severe. Hyposthenic physique. The skin and visible mucous membranes are yellow. The jaundice is intense. Traces of scratching on the skin of the legs and trunk (Figure). There are single psoriatic plaques on the skin of the ankle joints.

Vesicular breath sounds over the lungs, no rales. SpO₂ 99 %, heart rate 19 per minute. Heart activity is rhythmic, loud, clear tones. Pulse 68 per 1 min, blood pressure 110 and 80 mm Hg. Abdomen is soft on palpation; liver and spleen are not enlarged.

Complete blood count: hemoglobin 115 g/L; erythrocyte $3.78 \cdot 10^{12}/L$; color indicator 0.8; leukocytes $5.76 \cdot 10^9/L$, rod-shaped neutrophils 1 %, eosinophilic neutrophils 2 %, segmented neutrophils 58 %, lymphocytes 34 %, monocytes 5 %; platelets $257 \cdot 10^9/L$; ESR 20 mm/h. Coagulogram: APTT 36.4 s; prothrombin activity 94.1 %, fibrinogen 5.99 g/L.

Biochemical blood test: total bilirubin 101.1 μmol/L (direct 63.1, indirect 38.0 μmol/L), ALT 136.5 mmol/(L·h), AST 156.9 mmol/(L·h), alkaline phosphatase 259 mmol/(L·h), urea 3.9 mmol/L, creatinine 76 μmol/L, total protein 61.6 g/L.

The urine was beer-colored, foamy. General urinalysis – without significant abnormalities. Feces is hypocholic.

By chemiluminescent immunoassay, IgM to HAV 2.21 S/CO (< 1 S/CO is negative), IgG to HAV < 20 mod/ml (negative).

HBsAg and anti-HCV were not detected. The results of the analysis for antinuclear and antimitochondrial antibodies were negative.

Ultrasonography of the liver dated 06/13/23. The liver is not enlarged, medium-grained. The right lobe's CVR is 110 mm (normal – up to 150 mm), the left lobe's thickness is 45 mm (normal – up to 60 mm). The contour is clear, even. The structure is

homogeneous. Tissue echogenicity is increased. The intrahepatic ducts are not dilated.

The portal vein is 9 mm (normal – up to 15 mm), choledochus is 4 mm (normal – up to 6 mm).

The gallbladder is reduced, 35 × 9 mm in size, 2 mm wall, no calculi are visible.

The pancreas is not enlarged, the structure is homogeneous. Echogenicity is normal. 16 mm head, 11 mm body, 15 mm tail. The ductus arteriosus is not dilated.

The spleen is 105 × 36 mm. The structure is homogeneous. Echogenicity is normal. The splenic vein is not dilated.

The right kidney measures 118 × 45 mm (normal – up to 120 × 60 mm). The contour is clear. Parenchyma 22 mm, thickened (normal – up to 20 mm). The pelvis is not dilated.

The left kidney is 98 × 36 mm. The contour is clear. The parenchyma is 16 mm. The corpuscles are not dilated.



Figure. Patient V. O., 29 years old, traces of scratching on the skin of the lower legs

Small amounts of salt crystals in both kidneys.

The ratio of parenchyma to BMP is 2:1, preserved. There are no signs of hydronephrosis. The bladder is not filled. There is no free fluid in the abdominal cavity.

Due to the absence of objective data in favor of hepatitis A, B, C, as well as autoimmune hepatitis, the patient was interviewed in detail once again and, in addition to the anamnesis, it was found that she had been taking «Yaryna» (drospirenone-ethinylestradiol) for a long time for oral contraception.

Diagnosis: acute drug-induced liver damage.

After discontinuation of the drug and supplementation with hepatoprotective agents, the jaundice began to subside. Soon, the itching disappeared and liver tests were normalized. After spending 16 bed-days in the hospital, she was discharged home in satisfactory condition.

Conclusion from the above example, given the epidemiology and objective data, the patient was initially suspected of jaundiced form of hepatitis A. However, given the very long course of jaundice (more than 2 months) without signs of positive dynamics, as well as the extremely unreliable single laboratory criterion – IgM to HAV, especially in the form of chronic detection without signs of seroconversion) with no signs of positive dynamics, as well as the extremely unreliable single laboratory criterion – IgM to HAV, primarily in the form of its chronic detection in the absence of signs of seroconversion or seroreversion, this diagnosis was changed in favor of acute drug-induced liver injury (toxic hepatitis). An additional diagnostic criterion was ex juvantibus therapy.

It is believed that drug-induced liver injury has no direct morphologic markers, but characteristic changes in the liver on Ultrasound examination that occur under the influence of various drugs have been described.

These changes include:

- fatty degeneration of hepatocytes;
- foci of collateral necrosis around the central veins;
- inflammatory infiltrate with a significant number of eosinophilic leukocytes;
- granulomas with no specific structure;
- lesions of the bile ducts with dystrophy of their epithelium;
- cholestasis in the periportal parts of the lobules;
- restructuring of the liver structure with the formation of false lobules of predominantly monolobular type, separated by fibrous septa [18, 20, 25].

The effects of medications, in particular hormonal drugs, are considered the main cause of liver peliosis and toxic sinusoidal enlargement.

Medications that induce microsomal enzymes (phenobarbital, rifampicin, diazepam) are characterized by significant proliferation and vacuolization of the smooth network of the hepatocyte cytoplasm. Drugs that cause impaired protein synthesis in hepatocytes (tetracycline, oleandomycin, cortisone, methotrexate) cause mitochondrial swelling, nuclear destruction, rapid development of fatty degeneration, and hepatocyte death [10].

Not only drugs have a direct hepatotoxic effect, but also various toxic substances (carbon tetrachloride, dichlorodiphenyltrichloromethylmethane (DDT), yellow phosphorus, amanito- and phallotoxins of the pale toadstool, various pesticides, etc.). According to the mechanism of development, acute and chronic liver lesions of this etiology are identical to drug-induced damage.

According to the conditions of action, hepatotoxic substances are divided into two groups: professional and household.

The action of factors of the 1st group can take place in the chemical, military, pharmaceutical industry, in the production of rubber, plastics, paints, cosmetics, as well as in agriculture. A large number of hepatotoxic agents of the 2nd group are some poisons (carbotetrachloride, yellow phosphorus, rodenticides, insecticides, pesticides, fungicides), mycotoxins (for example, aflatoxin-contaminated food products, poisonous mushrooms), toxins of plant origin (pyrrolizidine alkaloids), food products containing toxic preservatives, dyes, as well as many other household chemicals [5, 16, 22, 23, 28].

In order to illustrate a deliberate acute food poisoning accompanied by toxic hepatitis with jaundice, we present our own observation.

Patient G.Y., 30 years old (inpatient medical card No. 04/01358), a resident of the Ternopil region, an employee of a disinfection station, was taken to the anesthesiology and intensive care department of the regional clinical hospital on January 29, 2011, accompanied by her husband, with impaired consciousness.

From the anamnesis: the husband found his wife at home on the morning of January 29, 2011, lying in bed in an unconscious state. Based on the presence of vomiting near the patient and contamination of underwear with fecal masses, he suspected poisoning with vomiting and diarrhea. It is not known when she became ill, since no one has seen the patient for the past 3 days. The husband independently tried to bring his wife to consciousness, wash her stomach. However, despite the fact that the woman became unconscious for a short time, the disease still progressed: bleeding, convulsive syndrome, and jaundice developed. This prompted the man to seek medical attention.

Objective status. The condition of the patient is serious. The patient is disoriented in space and time, the answers are adequate only to the simplest questions, she follows instructions late. Pupils are dilated, their reaction to light is sluggish. The skin and visible mucous membranes are pale yellowish. There are numerous petechiae and large hemorrhages on the skin of the chest, abdomen, back, and limbs. Periodically, nasal and uterine bleeding (menstruation?) is restored. There is fresh blood in the gastric lavage.

Heart sounds are weakened, pulse 96 per 1 min, tachyarrhythmia, weak tension and filling. Blood pressure 90 and 60 mm Hg. Art. Breathing is vesicular, there are no wheezing. The stomach is soft. The liver is palpable 2 cm below the costal arch, elastic. The spleen is not palpable. The stools are liquid, light yellow with streaks of blood. Urine is dark brown.

General blood analysis: hemoglobin 96 g/L; erythrocytes $2.9 \cdot 10^{12}/L$; KP 0.9; leukocytes $11.8 \cdot 10^9/L$, rod-shaped neutrophils 8%, eosinophilic neutrophils 6%, segmented neutrophils 60%, lymphocytes 22%, monocytes 4%; platelets 50,000 in 1 mm^3 ; ESR 18 mm/h. Coagulogram: prothrombin 60.8%, prothrombin time more than 2 min (normal 8–10 s), activated partial thromboplastin time 1 min 40 s (norm 24–35 s), fibrinogen 0.5 g/L, level 5 thrombotest, fibrinogen «B» +. General analysis of urine – macrohematuria.

Biochemical blood analysis – total bilirubin 89.6 $\mu\text{mol}/L$ (direct 75.6, indirect 14.0 $\mu\text{mol}/L$), ALT 1.88 mmol/(L·h), AST 0.98 mmol/(L·h), thymol test 6 units, urea 7.4 mmol/L, creatinine 0.01 mmol/L. Extensive hemorrhages appeared at the injection sites.

Diagnosis at hospitalization: Acute poisoning with a coumarin-like substance? Thrombocytopenic purpura? Viral hepatitis, fulminant form? Nasal, intestinal and uterine bleeding.

12 hours after washing the stomach and intestines, infusion detoxification, enterosorption and hemostatic therapy, the patient became available for productive contact. It was found that on January 26, 2011, the patient with suicidal intent (husband's adultery) consumed about 80–100 g of Ratindan 0.5 powder dissolved in water, containing 0.5% of the active substance (0.4–0.5 g of ratindan powder concentrate).

In connection with the appearance of signs of hepatitis, the blood was examined for the presence of HBV and HCV markers: HBsAg and anti-HCV were not detected.

After the vital danger was eliminated (after 4 days of stay in department of anesthesiology and intensive care), she was transferred to the hematology department, where she spent another 12 bed

days, after which she was discharged home in a satisfactory condition.

Here is an excerpt from the instructions for ratindan: the active substance of the drug is diphenacin, which belongs to the I class of extremely dangerous substances according to DEST 12.1.007-76. According to the parameters of acute toxicity when injected into the stomach of rats and mice, ratindan belongs to the III class of moderately dangerous substances according to the classification of toxicity and danger of rodenticides (chemical substances for the destruction of rodents – author's note).

Diphenacin is an anticoagulant with pronounced cumulative properties. When it gets into the animal's body, it inhibits the synthesis of prothrombin in the liver, as a result of which blood clotting slows down, the permeability of the walls of blood vessels increases, which leads to hemorrhages and the death of rodents not only in the case of a one-time consumption of an absolutely lethal dose (LD) of poisoned bait, but also in the case of periodic ingestion of much smaller concentrations of poison due to its cumulative effect. Diphenacin is highly toxic for warm-blooded animals (LD50 for gray rats after a single injection is 4–6 mg/kg) [6, 24]. A person with a body weight of about 60 kg dies from a dose of the drug of 400–1000 mg [24].

Conclusion from the given example, the patient deliberately consumed the anticoagulant ratindan, which is used for rodenticidal purposes, with the intention of committing suicide. She had professional access to the powdered concentrate of this poison (an employee of a gas station). However, even before the circumstances of the poisoning were clarified, symptoms of liver damage similar to the manifestations of viral hepatitis appeared (nausea, vomiting, jaundice, dark urine, abdominal pain, liver enlargement, cytolytic syndrome). This became the basis for additional research on markers of hepatitis viruses. The negative result of such an examination, a very serious general condition despite moderate jaundice, clarification of anamnestic information and positive dynamics under the influence of a complex of emergency therapeutic measures used in acute poisoning with coumarin-like substances, made it possible to finally exclude viral hepatitis and confirm the presence of toxic hepatitis as one of the manifestations of ratindan poisoning.

The sensitivity of people to this or that pharmaceutical drug varies. In general, almost any drug can cause liver damage and the development of hepatitis of varying degrees of severity. Especially severe forms of hepatitis develop in case of poisoning by pale toadstool, white phosphorus, paracetamol, carbon tetrachloride, industrial poisons, etc.

As already mentioned, toxic hepatitis can be caused by the accidental use of toxic substances of industrial (for example, agricultural poisons) and plant (poisonous mushrooms) origin, as well as under the influence of certain medicines. Depending on the amount of substance or medication taken, symptoms of liver damage usually appear no later than 48 hours later and are similar to symptoms of viral hepatitis (loss of appetite, nausea, vomiting, dark urine, possible abdominal pain, clay-colored stools).

Poisoning by wild mushrooms in conditions of high urbanization is one of the important etiological factors in the development of toxic liver damage [7, 17]. The lethality of poisoning with inedible mushrooms reaches 12–35 %, in particular with pale toadstool – up to 80 % [26].

Mushrooms with a hepatotropic effect (pale toadstool) contain very strong toxins belonging to the group of cyclopeptides – amanitins and phalloidins, which have a selective effect on liver tissue and proximal parts of the renal tubules, which leads to the development of hepatonecrosis and acute hepatorenal failure. LD of phalloidin is 0.1 ml per 1 kg of body weight. For adults, this is equivalent to consuming 30–50 g of fresh mushrooms [26]. After the Chernobyl disaster, the danger of mushroom poisoning increased, as these plants are able to accumulate radioactive elements.

Depending on the clinical symptoms caused by the type and amount of mushroom toxin that entered the body, mushroom poisoning can be divided into three phases

- 1) latent phase: duration from 5 to 24 hours;
- 2) gastrointestinal phase: from 24 to 48 hours;
- 3) hepatic-renal phase: from 48 to 240 hours.

In order to illustrate poisoning by mushroom toxins with a hepatonephrotropic effect, we cite our own observation.

Patient P. T., 39 years old (inpatient medical card No. 02/04228), a resident of Ternopil, was admitted to the anesthesiology and intensive care department of the regional clinical hospital on 09/29/2006 with complaints of nausea, repeated vomiting, diffuse abdominal pain, loose stools up to 6 times a day, an increase in body temperature up to 37.3 °C.

From the anamnesis: on the eve of hospitalization, she and her husband were on vacation in the forest, where the couple consumed mushroom soup, prepared with the addition of freshly collected «champignons». She fell ill acutely at night, 6 hours after eating mushrooms: nausea, repeated vomiting, which did not bring relief. At the time of examining the patient, the husband felt satisfactory, but 12 hours later he was also hospitalized with similar symptoms.

Objective status. The condition of the patient is moderate. The skin is pale. The tongue is coated with a gray coating. Heart sounds are loud, pulse is 80 per 1 minute, blood pressure is 120 and 70 mm Hg Art. Breathing is vesicular, there are no wheezing. The abdomen is soft, moderately painful in the epigastrium. The liver is palpable 2 cm below the costal arch, elastic. Faeces are light yellow, semi-liquid, foamy.

General blood analysis: hemoglobin 122 g/L; erythrocytes $3.9 \cdot 10^{12}$ /L; color indicator 1.0; leukocytes $12.3 \cdot 10^9$ /L, rod-shaped neutrophils 8 %, eosinophilic neutrophils 3 %, segmented neutrophils 53 %, lymphocytes 32 %, monocytes 4 %; ESR 18 mm/h; hematocrit 53 %. General analysis of urine: protein 0.33 g/L, accumulation of leukocytes up to 10–15 in the field of vision. Biochemical analysis of blood: Blood α -amylase is 245 Units/ml, the rest of the parameters are without significant deviations from the norm.

Diagnosis: acute mushroom poisoning, gastrointestinal period?

Treatment: gastric and intestinal lavage, benzylpenicillin (as a means of antidote therapy), berliothion, detoxification and enterosorption treatment.

During the next 2 days, the patient felt quite satisfactory, there were no complaints. However, 3 days after the consumption of mushrooms, when the patient was feeling normal, negative dynamics of biochemical blood parameters were noted: total bilirubin 39.6 $\mu\text{mol/L}$ (direct 18.4, indirect 21.2 $\mu\text{mol/L}$), ALT 2.28 mmol/(L·h), AST 1.43 mmol/(L·h), thymol test 8 units, urea 9.8 mmol/L, creatinine 0.22 mmol/L, total protein 62.44 g/L.

Later, jaundice of the mucous membranes and skin became visible, the lower edge of the liver protruded from under the costal arch by 4 cm along the midclavicular line. 8 days after the consumption of mushrooms, the dynamics of biochemical changes remained unfavorable: total bilirubin 286.5 $\mu\text{mol/L}$ (direct 210.6, indirect 75.9 $\mu\text{mol/L}$), ALT 3.47 mmol/(L·h), AST 2.33 mmol/(L·h), thymol test 6 units, urea 10.4 mmol/L, creatinine 0.31 mmol/L. In the places of injections – numerous, sometimes extensive hemorrhages, in the general analysis of urine – fresh erythrocytes up to 20–30 in the field of vision.

In connection with the appearance of signs of hepatitis, the blood was examined for the presence of HBV and HCV markers: HBsAg and anti-HCV were not detected.

She received 2 sessions of hemodialysis («artificial kidney»). Prednisolone (80 mg/day), transfusions of fresh frozen plasma, contrical, aminocaproic acid, dicinon were added to the treatment.

During 20 days of treatment, manifestations of liver and kidney failure regressed. After spending

28 bed-days in a hospital, she was discharged home in a satisfactory condition.

Conclusion from the given example, the patient apparently accidentally consumed poisonous mushrooms with hepatonephrotropic toxins, and also ignored the need to boil them several times before consumption. After a latent period (6 hours after consuming mushrooms), a gastrointestinal syndrome developed, and after another 3 days of apparent well-being — a period of phalloid hepatitis and nephritis. In favor of mushroom poisoning, seasonality, anamnestic indication of mushroom consumption testified; the duration of the latent period (at least 6 hours); dyspepsia and subfebrile background; gradual disappearance of gastrointestinal disorders and sudden manifestation of hepatitis against the background of «full health»; appearance of jaundice after the end of gastrointestinal disturbances, enlargement of the liver, development of hemorrhagic syndrome; as well as the occurrence of symptoms of poisoning in a man who consumed the same mushrooms. Laboratory changes as a result of poisoning were also quite typical: leukocytosis with a shift of the leukocyte formula to the left, moderate proteinuria with leukocyturia in the general urinalysis, increased blood α -amylase activity; and in the period of phalloid hepatitis — cytolytic syndrome, development of hyperbilirubinemia, increase in the level of «renal tests», decrease in the prothrombin index. Positive dynamics under the influence of a generally accepted set of measures used in mushroom poisoning made it possible to finally rule out viral hepatitis and confirm the diagnosis of phalloid hepatitis.

Viral hepatitis (ICD-10: B15-B19) — A large group of mostly anthropogenic diseases that have a similar clinical picture, manifested by intoxication and predominant liver damage, often with jaundice, but differ in etiology, epidemiology, pathogenesis, course and outcome.

The following main hepatitis types are distinguished: A (GA), B (HB), C (HC), D (GD), E (GE), G (GG), each of which has its own causative agent.

The incubation period of HF lasts from 7 to 45 days. The onset of the disease is acute, most often with fever, symptoms of intoxication, catarrhal and dyspeptic manifestations. With the onset of jaundice, the body temperature normalizes, and the patient's health improves. Physical examination reveals enlargement of the liver, and in 1/3 of patients — spleen.

The disease is more often mild or moderate, jaundice increases rapidly, is not intense and disappears quickly. Only 5–10% of convalescents have exacerbations (increased signs of the disease characteristic of the acute period) or relapses (return of clinical

and/or biochemical signs of the disease) of hepatitis. GA mostly ends in recovery, with a prolonged course in only 3–5% of cases, no chronicity, and a very low mortality rate.

In HBV, the incubation period lasts from 6 weeks to 6 months. The disease starts gradually. The initial period can last up to 1 month or longer. Dyspeptic and asthenovegetative syndromes are more common. One third of patients have an arthralgic variant of the initial period, which is characterized by pain in large joints. In 10–15% of patients, erythema urticariale appears on the skin, accompanied by eosinophilia. The appearance of rashes is a prognostically unfavorable sign, as it is often an indication of a possible severe and prolonged course of hepatitis. In 5–7% of patients, there are no initial symptoms, and the appearance of jaundice is the first clinical manifestation of the disease. The fulminant form of hepatitis occurs more often in HBV than in other VHs.

The jaundiced period is longer than in GA, the jaundice is more intense, and one in five is accompanied by itchy skin (cholestasis syndrome). The manifestations of intoxication are mostly vivid. The liver is always enlarged. As a rule, the spleen is also enlarged. Often there are signs of cholecystitis, less often — pancreatitis. In HB, severe and very severe course is more often noted, which can be complicated by the development of hepatic coma, the mortality rate from which still exceeds 90%. Hepatitis also has more frequent exacerbations, relapses and complications (caused by the addition of HD), a bright asthenic syndrome in all clinical periods of the disease, and prolonged post-hepatitis asthenia, sometimes up to a year or longer.

In acute HBV, the duration of HBs antigenemia does not exceed 1–3 months. Detection of HBsAg in the blood for more than 3 months indicates a prolonged course of the disease. The presence of this antigen for 6 months or more after acute HB, even with normal clinical and laboratory parameters, indicates chronicity of the process and is an indication for a liver biopsy for final verification of the diagnosis. In 5–10% of cases, HBV progresses to chronic hepatitis and can further lead to liver cirrhosis and even hepatocellular carcinoma. Chronification of the process mostly occurs in people with a mild or moderate course of hepatitis. It is facilitated by unreasonable prescription of glucocorticoids and hepatoprotectors in the acute period.

In HS, the incubation period lasts from 2 to 12 weeks. The onset of the disease is gradual, the initial period lasts 1–2 weeks. The manifestations of asthenovegetative and dyspeptic syndrome prevail, and arthralgias are common. In 20–25% of

patients there is no prodrome, hepatitis is manifested by jaundice. With the onset of jaundice, the patient's health does not improve — continues to be disturbed by generalized weakness, dizziness, poor appetite, and heaviness in the epigastrium. The liver is moderately enlarged, and splenomegaly is noted in half of the patients.

Most often, acute hepatitis is subclinical, with manifest forms characterized by mild (up to 80 %) or moderate course, but occasionally a fulminant form is also possible. However, in 85–90 % of patients, acute hepatitis turns into chronic hepatitis, and some of them later develop liver cirrhosis and hepatocellular carcinoma. Chronic HCV develops on average 10 years after HCV infection, and cirrhosis — in another 10–15 years. However, these periods are significantly reduced if patients drink alcohol, abuse drugs, or are infected with other *viruses*. Due to the mild or asymptomatic course of acute HCV infection in most patients, it is extremely difficult to establish the time of infection and the duration of the disease, as patients often first seek medical attention with chronic HCV or even with established cirrhosis.

Acute HD occurs as a coinfection or superinfection of HBV. The onset is often acute, with a mixed variant: with asthenovegetative and dyspeptic phenomena, most patients have a fever, sometimes up to febrile figures, which also persists during the jaundice period. The pre-jaundice period lasts 5–7 days.

With the onset of jaundice, most patients feel worse, symptoms of intoxication increase, fever and arthralgia persist, and pain in the liver area persists. Cholestasis with significant itching of the skin and erythematous rashes is often noted.

A two-wave course of the disease with clinical signs of exacerbation in combination with hyperfermentemia is characteristic, which is explained by the presence of two *viruses* with different biological properties in the patient's body.

In general, acute HD in the form of coinfection is characterized by a cyclic, mostly moderate course and in most patients ends in recovery. The development of chronic hepatitis is rare. The disappearance of HBsAg also indicates the completion of delta infection. However, the use of glucocorticoids or other immunosuppressive drugs in the treatment of patients, which contribute to the long-term persistence of HBV, can lead to the expression of HDV.

In case of tuberculosis superinfection with HDV, chronic hepatitis develops in 70–80 % of patients and quickly leads to liver cirrhosis. Fulminant hepatitis is fatal in 20 % of patients.

The incubation period for GE lasts from 15 to 45 days, with an average of 40 days. Clinical

manifestations are similar to those of GA. The onset of GE is most often acute. The initial period lasts from 1 to 10 days and is dyspeptic. Jaundice-free and subclinical forms prevail. In contrast to GA, with GE, the patient's health does not improve with the appearance of jaundice. All patients have an enlarged liver and spleen, — only in some. The duration of clinical manifestations usually does not exceed 2–3 weeks. In 10–15 % of patients, the disease develops a prolonged course. There is no chronization of the process.

A significant proportion of adults, especially in the third trimester of pregnancy, have severe HE (lightning hepatitis), which often leads to death due to the development of acute renal failure. In lightning hepatitis, there is significant intoxication and liver dysfunction against the background of acute hepatic encephalopathy, hemorrhagic syndrome, renal disorders; pregnancy is terminated by miscarriage, and the mother often dies. With severe HE in pregnant women, the likelihood of fetal survival is low; most newborns die within the first month of life.

The mortality rate in GE ranges from 0.04 to 3 %, among pregnant women — it reaches 25 %.

HG very rarely occurs as a mono-infection, mostly — in the setting of HS or HBV. The disease begins gradually, with moderate manifestations of dyspeptic and asthenovegetative syndromes, and possible arthralgias. In 20 % of cases, there is no prodrome. The appearance of jaundice does not alleviate the patient's condition. The liver is enlarged in almost all patients, the spleen — in only one third. Serum ALT activity is slightly increased compared to other hepatitis. HG occurs mainly in subclinical or jaundice-free forms, and jaundice — is mostly mild. However, a fulminant form may occur.

In chronic hepatitis, mainly caused by viruses C, B, D, extrahepatic manifestations of the disease are often detected (in 35–45 %), which can dominate the clinical picture of the disease, hiding the classic signs of chronic HBV, and determine the prognosis of the disease. Arthritis or arthralgia, nodular periarteritis, glomerulonephritis, Raynaud's syndrome, cryoglobulinemia, etc. may develop. Mixed cryoglobulinemia is almost always associated with chronic HCV infection, even when there are no visible signs of liver damage. It occurs mainly in middle-aged and older women and is characterized by skin and joint damage, the appearance of purple skin ulcers, peripheral polyneuropathy, Meltzer's triad, Raynaud's syndrome, hypertension, and kidney damage. The role of HCV infection in the development of cryoglobulinemia is confirmed by the disappearance of its clinical manifestations after treatment with α -interferon.

Patients with chronic viral hepatitis who abuse alcohol most often develop extrahepatic manifestations such as pancreatitis, purine metabolism disorders, and cardiomyopathy.

Diagnosis of viral hepatitis is based on epidemiological, clinical and laboratory data. A complete blood count reveals a normal or decreased number of leukocytes, lymphocytosis, a decrease in ESR, a biochemical blood test – hyperbilirubinemia due to the direct fraction, increased ALT activity, less – ALT, and protein metabolism disorders. The ratio of AST/ALT (de Ritis coefficient) is usually less than 1. In the initial period of hepatitis, the activity of the 4th and 5th fractions of lactate dehydrogenase, sorbitol dehydrogenase, ornithine carbomoyl transferase, fructose-1-phosphatase, which are normally found in hepatocytes and enter the bloodstream in very small amounts, also increases significantly. An early and sensitive indicator of pigment metabolism disorders is urobilinuria. Bilirubin in the urine appears at the end of the prejaundice period. The thymol test increases and the sulemic titer decreases.

The value of the de Ritis coefficient in chronic hepatitis has a certain prognostic value. An increase in the coefficient to 1 and above – is an unfavorable sign that may indicate the progression of the process and the possibility of liver cirrhosis.

The necessary methods for examining the abdominal organs, including the liver, are hardware methods, in particular, – ultrasound, computed tomography, magnetic nuclear resonance, radioisotope scanning. Morphological examination of liver biopsies is an important method of diagnosis, especially for chronic hepatitis. It not only complements the data of biochemical, immunological and hardware studies, but also often indicates pathological processes and their features, which other methods do not reveal.

For the etiologic interpretation of hepatitis, it is necessary to detect markers of its *virus* in the blood serum or in the patient's liver biopsy. With the help of solid-phase or enzyme-linked immunosorbent assays, which are characterized by high sensitivity and specificity, pathogen antigens and antibodies to them can be detected, in particular HBsAg, HBeAg, HBcAg, antibodies to hepatitis A, B, C, D, E, G. It is necessary to differentiate antibodies by immunoglobulin classes. The presence of IgM antibodies indicates acute hepatitis or exacerbation of chronic hepatitis. A specific indicator of the period

of convalescence and chronic hepatitis is IgG antiviral antibodies, but they can also be detected in healthy individuals who have had acute viral hepatitis in the past or have been vaccinated (so-called anamnestic antibodies) [18, 22].

The polymerase chain reaction (PCR) method can detect the presence of hepatitis *virus* DNA or RNA in the blood, which indicates their replication, and even determine their number (the so-called «viral load»). The PCR method is extremely sensitive. Studies have shown that in 15% of patients with HBV and 20% of – patients with HCV who had no serological markers of viral hepatitis, PCR was able to detect HBV and HCV genetic material [16].

Drug-induced jaundice caused by hepatotropic medications differs from viral hepatitis in the absence of a prejaundice period, torpid course with significant cholestasis and increased activity of alkaline phosphatase. Jaundice disappears after drug discontinuation.

Viral hepatitis sometimes occurs with leukopenia and early spleen enlargement. In drug-induced toxic hepatitis, leukocytosis due to hepatocyte necrosis is usually noted during the jaundice period. The phenomena of upper respiratory tract catarrh, diarrhea, arthralgia do not occur in drug-induced hepatitis; in viral hepatitis, they occur quite often [18].

Drug-induced liver damage is often combined with toxic nephritis. In this case, oligoanuria may develop. The concentration of bilirubin in the blood and the activity of aminotransferases in both hepatitis increase. However, most mild toxic hepatitis occurs with focal liver damage. Therefore, the increase in bilirubin levels is often insignificant, while alkaline phosphatase is almost always significant. The discrepancy between these functional tests is explained by the fact that the liver's alkaline phosphatase function has a much smaller reserve than the bilirubin excretion function.

Conclusions

In drug-induced hepatitis, serum protein fractions and sediment samples remain within normal limits, while creatinine, urea, and alkaline phosphatase activity in the blood are significantly increased.

Thus, the differential diagnosis of toxic, in particular drug-induced, and viral hepatitis can be challenging. For its successful implementation, it is necessary to apply a modern complex of anamnestic, clinical, biochemical, virological, instrumental and morphological examination methods as fully as possible.

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Клінічні випадки токсичного гепатиту: аспекти диференційної діагностики з вірусними гепатитами

У сучасних умовах екологічного неблагополуччя практикуючим лікарям дедалі частіше доводиться надавати допомогу пацієнтам із гепатитами, причиною яких є не лише відомі вірусні агенти, а й хімічні отрути. Наведено загальні відомості про токсичні (насамперед медикаментозні) та вірусні гепатити, а також основні гепатотоксичні препарати. Висвітлено їхню класифікацію, механізм дії, клінічну симптоматику, біохімічні та морфологічні зміни при різноманітних токсичних ураженнях печінки. Наведено інформацію про препарати з високою печінковою екстракцією, які пов'язані з великим ризиком передозування. Хворим із груп ризику дози таких препаратів доцільно зменшити хоча б удвічі відповідно до зниження печінкового кровотоку. Лікарські засоби з низькою печінковою екстракцією асоціюються з мінімальним ризиком передозування, хоча метаболічна недостатність при тривалому призначенні таких препаратів може спричинити їхню кумуляцію. Препарати, які виділяються нирками, практично позбавлені ризику гепатотоксичності. Обговорюються інші професійні та побутові токсичні речовини, які володіють прямою гепатотоксичною дією (чотирихлористий вуглець, дихлордифенілтрихлорметилметан, жовтий фосфор, аманітотоксини і фалотоксини білої поганки, пестициди тощо).

Наведено власні клінічні спостереження токсичних гепатитів. Надано загальну характеристику вірусних гепатитів. Акцентовано увагу на їхній диференційній діагностиці з гепатотоксичними ураженнями. Для диференційної діагностики токсичних і вірусних гепатитів, окрім збору анамнезу, слід застосовувати комплекс клінічних, біохімічних, вірусологічних, інструментальних та морфологічних методів обстеження.

Ключові слова: токсичні гепатити, медикаментозні гепатити, вірусні гепатити, диференційна діагностика.

ДЛЯ ЦИТУВАННЯ

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