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Liver Diseases That Have Eponymic Names: From the Past to the Present

Khodjaeva Gulnora Abdubannonovna
Assistant, Fergana Public Health Medical Institute

Abstract: The article presents the historical and modern conception of therapeutic liver diseases, which have eponymic names. Five liver diseases with an eponymic history are considered: Addison-Gall's syndrome (primary biliary cirrhosis), Badd-Chiari syndrome, Bearn-Kunkel syndrome (autoimmune hepatitis). The discovery of these diseases and the development of hepatology as a science are closely related to those scientists whose names were subsequently given to these diseases. The review presents a historical background as well as current information on epidemiology, etiology, developmental mechanisms, diagnosis, differential diagnosis and treatment of the above mentioned syndromes, which can be recommended for physicians, gastroenterologists and hepatologists.

Keywords: Addison-Gall's syndrome, primary biliary cirrhosis, Badd-Chiari syndrome, autoimmune hepatitis, Wilson- Konovalov's disease, eponyms, etiology, pathogenesis, diagnosis, treatment.

The scientific understanding of liver diseases was formed in the 19th century. Thus, G. Budd in 1845 described thrombosis of the hepatic veins. N. Chiari in 1899 presented a description of the morphology of the liver in thrombosis of the hepatic veins. This liver pathology is called Budd - Chiari syndrome (BCS), which continues to this day. In 1888, the outstanding Russian scientist S.P. Botkin suggested the infectious nature of jaundice. He also proved the connection of jaundice with splenomegaly , kidney damage and the occurrence of complications in the form of acute yellow liver atrophy and cirrhosis. In 1898, infectious jaundice was named Botkin's disease. After the discovery of the hepatitis A virus in 1973, the name “Botkin’s disease” acquired a historical character. Studies by T. Addison , W. Gull and V. Hanot described the clinical manifestations of primary biliary cirrhosis (PBC) and for several decades it was called Addison –Gull syndrome and Hanot cirrhosis . However, in the middle of the twentieth century. Ganot's cirrhosis was proposed to be called PBC, since by that time a morphological description of the final stage of the disease had been given. A. Bearn and H. Kunkel verified aggressive hepatitis, after which the described disease was named Byrne – Kunkel syndrome . In 1956, Byrne – Kunkel syndrome became known as lupoid hepatitis, which was associated with the discovery of the association of this disease with the presence of LE cells. In 1993, lupoid hepatitis was proposed to be called autoimmune hepatitis. Thus, some of the eponymous names for liver diseases have become archaic over time. While some diseases have retained their original names (for example, Gilbert syndrome , Budd – Chiari syndrome , Wilson–Konovalov disease). It is important to preserve the memory of the contribution of domestic and foreign scientists to the formation of hepatology as a medical science and to update ideas about the pathogenesis, diagnosis and treatment of liver diseases from the perspective of the achievements of modern medical science. Purpose: to present the historical and modern concepts of therapeutic liver diseases, which have an eponymous name.

Addison –Gall syndrome

Synonyms: primary biliary cirrhosis, Ganot cirrhosis . ICD-10: K74.3. Definition. Primary biliary cirrhosis is a chronic, slowly progressive liver disease of an autoimmune nature, manifested by chronic destructive non-purulent granulomatous cholangitis of the septal and interlobular bile ducts, in the terminal stage of which liver cirrhosis is formed. Historical reference. English scientists T. Addison (1793–1860) and W. Gull (1816–1890) described 5 cases of an unknown skin disease in 1851. The observed patients were aged 24–43 years; they had prolonged jaundice and skin itching, xanthelasma and xanthoma . Despite the fact that morphological identification of the disease was impossible, the

authors put forward a hypothesis about liver damage in this syndrome. The clinical picture of PBC was described by V. Hanot (1844–1896) in 1876, and the disease became known as Hanot's cirrhosis. The term xanthomatous Biliary cirrhosis was proposed in 1949 by H. MacMahon and S. Tannhauser , who provided a morphological description of the final stage of PBC development [24]. In 1950, the name xanthomatous biliary cirrhosis was replaced by PBC. Since that time, the terms " Ganota cirrhosis " and " Addison -Gall syndrome" have a historical character. Epidemiology. The incidence of PBC is 0.07–4.9 per 100 thousand population and is mainly registered in the 5th–7th decade of life. Women develop PBC 10 times more often than men. The prevalence of PBC varies widely. So, in the USA it is 40 cases per 100,000, in northern Europe – 20–25 episodes per 100,000, in Africa, Asia and Australia – 2 observations per 100,000 population.

Etiology and pathogenesis. Significant variability in the prevalence of PBC is associated with differences in the nature of the testing methods used to detect this disease. The prevalence of PBC is thought to be influenced by environmental and/or genetic factors. Possible environmental factors for PBC include exposure to insolation, chemicals, toxins, bacteria and viruses. For unclear reasons, PBC occurs more frequently in individuals of higher socioeconomic status. The development of PBC is closely associated with recurrent sexually transmitted urinary tract infections. The infection caused by E. Coli is recognized as the most dangerous in terms of the development of PBC . A high correlation has been proven between smoking and the development of PBC. Some studies have shown that patients who use hair dyes have an increased risk of developing PBC, but these data are conflicting. Alcohol consumption is thought to reduce the risk of PBC. Genetic and family factors play an important role in the development of PBC . Concordance for PBC in monozygotic twins is 63%, and with first-degree relatives – 4%. Sisters of a woman with PBC have a 14-fold risk of developing the disease. Autoimmune diseases are more common in patients with PBC. Autoimmune thyroiditis , Raynaud's syndrome , Sjögren's syndrome usually develop before PBC by 4 years. A meta-analysis showed that HLA-DR 7 and HLA-DR 8 are risk factors for PBC, while HLA-DR 11 and HLA-DR 13 are factors with a negative association with PBC. The development of PBC is associated with polymorphism of the genes of the cytotoxic T- lymphocyte antigen, tumor necrosis factor alpha, vitamin D receptor and genes of the HLA 11 and 12 loci. Under the influence of the trigger factor, in individuals with a genetic predisposition, CD4+ T- helper lymphocytes and CD8+ cytotoxic T-cells are activated , inducing apoptosis and/or necrosis of the epithelium of the intrahepatic bile ducts. Diagnostically significant for PBC is the detection of antimitochondrial autoantibodies (AMA) to component E 2 pyruvate dehydrogenase complex of mitochondria, which indicates the autoimmune nature of the disease. For PBC, the AMA class M 2 definitions are specific .

Diagnostics. PBC is diagnosed if two of three criteria are met: 1) AMA or AMA class M2 titer greater than 1:40 ; 2) alkaline phosphatase more than 1.5 times the upper limit of normal for more than 24 weeks; 3) detection of granulomas in combination with focal obliteration of the bile ducts. Differential diagnosis. PBC should be differentiated from autoimmune hepatitis, primary sclerosing cholangitis and the overlap syndrome: PBC/autoimmune hepatitis. Treatment. Patients with asymptomatic PBC are prescribed ursodeoxycholic acid (UDCA) at a dose of 13–15 mg per kg of body weight for a long time. The presence of a suboptimal response to UDCA therapy in the first three stages of PBC requires its combination with budesonide (6–9 mg per day). The addition of S- adenosyl -L-methionine to UDCA improves biochemical parameters and clinical symptoms. If bilirubin levels are more than 103 μmol /L (6 mg/ dL) or decompensated liver cirrhosis, liver transplantation should be considered. When PBC is also treated, concomitant syndromes are treated: dyslipidemia , osteoporosis, complications, for example, ascites or bleeding from esophageal varices . The effectiveness of PBC therapy should be assessed one year after the start of treatment. The optimal biochemical response is considered to be a decrease in serum bilirubin by 40% or normalization of alkaline phosphatase (ALP) levels (Barcelona criteria), or the presence of a serum bilirubin level of no more than 1 mg/ dL (17 μmol /L), an ALP level not exceeding three times the value the upper limit of normal, and the level of aspartate

aminotransferase not exceeding two times the upper limit of normal ("Paris criteria") [1]. Forecast. The asymptomatic course of PBC often continues for more than 20 years. If clinical manifestations of PBC occur in the form of jaundice, life expectancy without liver transplantation is 5–10 years. When serum bilirubin levels reach 10 mg/ dL, the median survival of patients with PBC is 1.4 years [2].

Budd – Chiari syndrome

Synonym: obstruction of venous outflow from the liver. ICD-10: I82.0. Definition. Budd - Chiari syndrome refers to the occurrence of an obstruction, which may be located in the small hepatic veins or at the junction of the inferior vena cava into the right atrium. In this case, obstruction of the venous outflow from the liver associated with heart disease (pericarditis, sinusoid obstruction syndrome) is excluded from the definition [20]. Historical reference. The disease was first described in 1845 by the English physician G. Budd (1808–1882), who presented 3 cases of abscess-induced hepatic vein thrombosis. In 1899, the Austrian pathologist N. Chiari (1851–1916) provided a pathological description of the liver in this syndrome based on 13 cases. Epidemiology. The prevalence of BCS is 1 : 100,000 people worldwide. Etiology and pathogenesis. BCS is divided into primary and secondary, induced by external causes such as external compression or tumor invasion. Thrombosis is the main cause of hepatic vein obstruction. The occurrence of primary hepatic vein thrombosis is associated with at least one hereditary or acquired hypercoagulable state, identified in 75% of patients. More than 1 etiologic factor for thrombosis may play a role in up to 25% of patients with BCS [3]. The predisposing disorder may appear later than the onset of BCS. The first place due to the development of obstruction of venous outflow from the liver belongs to myeloproliferative diseases, diagnosed in 20% of patients with BCS. It is believed that the actual rates of association of BCS with myeloproliferative diseases reach 45–53%, but for some time they remain undiagnosed . Factor V Leiden and factor II mutations are associated with BCS in 25% and 5% of cases, respectively. In addition, primary protein C deficiency is associated with BCS in 25% of cases. Hepatic vein thrombosis occurs in 12% of patients with paroxysmal nocturnal hemoglobinuria and is the leading cause of death in this disorder. BCS is associated with Behçet's disease in 5% of cases . Taking oral contraceptives increases the likelihood of developing BCS by 2.37 times. Pregnancy, primary deficiency of protein S, antithrombin III, and increased homocysteine levels may increase the risk of BCS.

The relationship between blunt abdominal trauma, ulcerative colitis, celiac disease, cytomegalovirus infection, sarcoidosis , autoimmune diseases and the occurrence of BCS has been described. The presence of chronic diffuse liver disease is accompanied by a violation of the rheology of the blood system and can also serve as a possible cause of thrombosis. Secondary causes of BCS include compression caused by tumors of adjacent organs or polycystic kidney disease. Parasitic liver diseases, such as hydatid cyst, amoebic liver abscess, and purulent liver abscess, are rare etiological factors of secondary BCS. Blockage of 2 or more large hepatic veins increases sinusoidal pressure and decreases sinusoidal blood flow. Obstruction of one hepatic vein is usually subclinical . For the disease to appear, there must be thrombosis of at least 2 veins. The result of the resulting hemodynamic changes is sinusoidal dilatation and sweating of tissue fluid. Filtration of tissue fluid through the liver capsule occurs when lymphatic drainage is ineffective. All this is accompanied by an enlarged liver, pain in the right upper quadrant of the abdomen and ascites. Portal pressure increases and liver perfusion through the portal vein decreases. As a result of circulatory disorders, hypoxic damage to hepatocytes occurs . Non-inflammatory Centrilobular necrosis in BCS is verified in almost 70% of cases. Hepatocyte necrosis is induced by free radicals and inflammation. Massive hepatocellular injury with fulminant liver failure is rare. As a rule, the chronic form of BCS is diagnosed in the form of portal hypertension

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and ascites. Both acute and chronic forms of BCS lead to severe centrilobular overload and hepatocellular necrosis and atrophy. Several weeks after venous obstruction, fibrosis develops predominantly in the centrilobular areas. After a few months, nodular regeneration in the periportal areas is diagnosed. The course of BCS is accompanied by progressive fibrosis, nodular regeneration and cirrhosis of the liver [4]. Revascularization and development of collaterals can improve liver function and inhibit the development of cirrhosis.

Diagnostics. BCS should be suspected in patients with: 1) sudden onset of ascites and painful hepatomegaly ; 2) massive ascites with relatively preserved liver functions; 3) sinusoidal dilatation during a morphological study of a liver biopsy in a patient without cardiac pathology; 4) fulminant liver failure associated with hepatomegaly and ascites; 5) unexplained chronic liver disease; 6) a combination of liver disease and thrombogenic disorder. Doppler ultrasound is decisive in making the diagnosis of BCS. ultrasonography . Its sensitivity is 75–85%. If it is not technically possible to perform Doppler ultrasonography, magnetic resonance imaging or computed tomography is used to confirm the diagnosis. If the diagnosis is in doubt, venography should be performed. If the radiation examination turns out to be uninformative, then a liver biopsy is required. Examination of a biopsy specimen can verify thrombosis of small hepatic veins. Differential diagnosis. SBS must be differentiated from portal vein thrombosis, extrahepatic portal vein obstruction, veno-occlusive disease (sinusoid obstruction syndrome), hepatomegaly in liver pathology. Treatment. In the first stage, treatment of BCS requires the administration of low molecular weight heparin (LMWH) for at least 5–7 days in combination with anticoagulant therapy with oral vitamin K antagonists . The goal of such therapy is to achieve an international normalized ratio (INR) of 2.0–3.0. LMWH may be discontinued when the INR is within the specified range on two consecutive measurements. This treatment stops disease progression in 18% of patients. At the same time, therapy is carried out for the underlying disease that led to the development of BCS, for example, myeloproliferative . It is possible to use thrombolysis in combination with stenting or angioplasty for fresh and incomplete thrombosis. However , the degree of evidence for these methods is low, and the risk of severe complications is quite high. In the absence of effectiveness of drug treatment, thrombolysis and angioplasty, patients with BCS are recommended to undergo intrahepatic portacaval shunting or orthotopic liver transplantation . Prognosis . In 10–20% of patients with BCS, the only option for survival is orthotopic liver transplantation. The five-year survival rate of patients with BCS after liver transplantation reaches 71.0–89.4%.

Byrne – Kunkel syndrome

Synonyms: autoimmune hepatitis, lupoid hepatitis. ICD-10: K75.

Definition. Autoimmune hepatitis (AIH) is a chronic liver disease whose etiology is unknown. Characterized by the presence of a wide range of autoantibodies in the blood serum, hypergammaglobulinemia , periportal or more widespread inflammation. Historical reference. The disease was first described in 1956 by American doctors A. Bearn (1923–2009), H. Kunkel (1916–1983) as active chronic hepatitis. Scientists described aggressive hepatitis in several young women, whose age did not exceed 32 years, accompanied by hypergammaglobulinemia and lymphoplasmacytic infiltration of the liver and extrahepatic manifestations (arthralgia, rash, hemolytic anemia). However, for some time the nature of the disease was unclear. In 1956, I. Mackay discovered the association of this disease with the presence of LE cells in the blood, and after that hepatitis was called “ lupoid . ” However, the term AIH was officially adopted only in 1993 by the international group for the study of autoimmune hepatitis . After this, the terms “ lupoid hepatitis” and “ Byrne – Kunkel syndrome ” acquired only historical meaning. Epidemiology. The prevalence of AIH in European countries and the United States is 11–17 cases per 100,000 population. At the same time, the annual incidence of AIH is 0.5–1.9 cases per 100,000. It is noteworthy that type 1 AIH occurs in more than 80% of the total number of AIH cases, while 75% of such patients are women, mostly young and

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middle-aged . However, 20% of patients with AIH are people over 60 years of age. Etiology and pathogenesis. Trigger factors for AIH can be infectious agents and drugs. However, the development of AIH requires a genetic predisposition. In the development of AIH, particular importance is attached to the polymorphism of HLA class II genes - DRB1, localized on chromosome 6, cytokine genes, and mutations of the AIRE1 gene. When trigger factors interact with a person who has a genetic predisposition to the development of AIH, a T-cell immune reaction is induced against hepatocyte antigens. This leads to the emergence and then progression of inflammatory, necrotic and fibrotic changes in the liver.

Diagnostics. Making a diagnosis of AIH requires the presence of diagnostically significant clinical and laboratory signs, as well as the exclusion of various causes that can induce the development of chronic hepatitis.

Conclusion. This study presents 5 liver diseases with an eponymous history: Addison -Gall syndrome, Budd - Chiari syndrome , Byrne - Kunkel syndrome , Wilson-Konovalov disease and Gilbert syndrome . Despite the fact that the first 4 diseases are orphan , their medical and social significance is relatively high, which is due to the severity of their course. These diseases require long-term treatment, and the prognosis is often questionable. Gilbert's syndrome is a relatively common disease, but the medical and social significance of this pathology is somewhat less than that of orphan diseases characterized by a progressive course. The discovery of these diseases and the development of hepatology as a science is closely related to the scientists after whom these diseases were subsequently named. The information presented in the review with a modern view of the diseases considered can be useful for the work of therapists, gastroenterologists and hepatologists .

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