PATHOPHYSIOLOGY OF BILIARY ATRESIA

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Annotatsiya. *Ushbu tezisda yangi tug'ilgan chaqaloqlarda intra- va ekstrahepatik o't yo'llarining progressiv fibroz-yallig'lanishli obliteratsiyasi bilan kechadigan biliar atreziyaning etiopatogenetik mexanizmlari ko'rib chiqilgan. Virusli infeksiya, immun buzilishlar, genetik omillar va toksinlarning roli, xolangiotsitlar shikastlanishi, biliar fibroz va sirroz rivojlanishi hamda patogenezning klinik belgilar va erta tashxis bilan bog'liqligi yoritilgan.*

Kalit so'zlar: biliar atreziya, xolangiotsit, fibroz, xolestaz, yangi tug'ilgan chaqaloq, Kasai portoenterostomiyasi.

Аннотация. *В тезисе рассмотрены этиопатогенетические механизмы атрезии желчевыводящих путей у новорождённых — прогрессирующей фиброзно-воспалительной облитерации внутри- и внепечёночных желчных протоков. Описаны роль вирусной инфекции, иммунных нарушений, генетических факторов и токсинов, последовательность повреждения холангиоцитов, формирование билиарного фиброза и цирроза, связь патогенеза с клинической картиной и значением ранней диагностики.*

Ключевые слова: *атрезия желчевыводящих путей, холангиоцит, фиброз, холестаз, новорождённые, портоэнтеростомия по Касаи.*

Abstract. *This paper examines the etiopathogenetic mechanisms of biliary atresia (BA) in newborns, a progressive fibro-inflammatory obliteration of the intra- and extrahepatic bile ducts. It describes the roles of viral infection, immune dysregulation, genetic factors and toxins, the sequence of cholangiocyte injury, the development of biliary fibrosis and cirrhosis, and the relationship between pathogenetic mechanisms, the clinical picture and the importance of early diagnosis.*

Keywords: *biliary atresia, cholangiocyte, fibrosis, cholestasis, newborns, Kasai portoenterostomy.*

Introduction. Biliary atresia (BA) is a severe disease of the neonatal period in which inflammatory-fibrotic obliteration of the bile ducts impairs bile flow into the duodenum. Its incidence is approximately 1 case per 5,000–18,000 live births, and is higher in East Asian countries [1, 3]. BA remains the most common cause of

neonatal cholestasis requiring surgical treatment and the leading indication for liver transplantation in children [4].

Aim: to review current concepts of the pathophysiology of BA and to link the mechanisms of disease development with its clinical manifestations.

Main body. Three forms of BA are distinguished: the isolated form (about 85% of cases), the form occurring as part of the biliary atresia splenic malformation syndrome (BASM: polysplenia, situs inversus, preduodenal portal vein, absence of the inferior vena cava), and the form associated with other congenital anomalies. According to the level of obliteration, three types are recognized: I — common bile duct, II — common hepatic duct, III — porta hepatis (the most frequent, about 90% of cases) [1, 3].

The etiology of BA is multifactorial; several complementary hypotheses are under discussion. 1) Viral: perinatal infection (reovirus type 3, group C rotavirus, cytomegalovirus) triggers ductal epithelial injury and an autoimmune response. 2) Immune: patients show a predominant Th1/Th17 response with overproduction of interferon-γ, TNF-α and other cytokines, activation of CD8+ T lymphocytes and NK cells, and deficiency of regulatory T cells [2, 3]. 3) Genetic: associations have been described with variants of the ADD3, GPC1 and ARF6 genes and, in BASM, with laterality defects (CFC1) [2, 4]. 4) Toxic: the isoflavonoid biliatresone from the plant Dysphania glomulifera causes extrahepatic bile duct injury in animals similar to BA, through glutathione depletion and oxidative stress in cholangiocytes [5]. 5) Disturbed embryonic development of the ducts (ductal plate malformation).

The pathogenesis comprises several sequential stages. Primary epithelial injury (viral, toxic or due to genetic predisposition) leads to antigen expression and recruitment of T lymphocytes, macrophages and NK cells into the portal tracts. The cytotoxic action of these cells causes cholangiocyte death, epithelial desquamation, and edema and inflammation of the duct wall. Repair proceeds along the fibrotic pathway: activated hepatic stellate cells and portal fibroblasts, under the influence of TGF-β, synthesize collagen at an increased rate, the duct lumen becomes obliterated, and a ductular reaction develops [2, 3].

As a result of obstruction, bile is retained in the liver. Accumulation of toxic bile acids damages hepatocytes, sustains inflammation and enhances fibrogenesis. If bile flow is not restored within a few months, biliary cirrhosis and portal hypertension develop; therefore, the prognosis of the Kasai portoenterostomy is significantly better when it is performed within the first 60 days of life [1, 4].

The clinical manifestations directly reflect the pathophysiological disturbances. The cessation of bile flow into the intestine explains acholic stools; retention of conjugated bilirubin causes jaundice with a predominance of the direct

fraction, dark urine and elevated γ-glutamyltransferase activity. Bile acid deficiency leads to malabsorption of fats and fat-soluble vitamins (A, D, E, K), with development of coagulopathy and rickets; the onset of cirrhosis presents with hepatosplenomegaly and signs of portal hypertension [1, 6]. Persistent jaundice lasting more than 14 days in a term infant and acholic stools require immediate exclusion of BA by determination of bilirubin fractions, ultrasonography ("triangular cord" sign, gallbladder changes), hepatobiliary scintigraphy, liver biopsy and intraoperative cholangiography. A simple and effective tool for early detection is screening with the Stool Colour Card [4, 6].

Conclusions. BA results from a combination of viral, immune, genetic and toxic insults to the cholangiocyte, leading to inflammatory obliteration of the ducts, cholestasis and rapidly progressive biliary fibrosis. Understanding these mechanisms explains the clinical picture of the disease and justifies the need for early diagnosis and surgical intervention before irreversible liver cirrhosis develops.

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