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THEORIES OF THE ORIGIN OF BILIARY ATRESIA

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Abstract:
The exact causes of biliary atresia have not yet been determined. Theories such as viral, autoimmune, genetic, toxic, and congenital malformations have been put forward by experts, but they are still controversial, despite extensive scientific research. Although viruses are considered to be a major factor in the pathogenesis of the disease, the fact that viral DNA has not been identified in patients with BA denies that viruses are the complete cause of the disease. Although the role of autoimmune factors is predominant in the origin of such BAs, other authors disagree. According to the theory of congenital malformations, it is assumed that there are no primary epithelial channels in the embryonic period. However, the majority of children with BA have bile-stained meconium, which precludes the theory of congenital development, suggesting the presence of primary normal bile ducts. Although the occurrence of the disease in both twins confirms the genetic theory, the development of BA may confirm the possibility of a secondary origin as a result of viral, toxic and other factors affecting the fetus in the same way.

Keywords: Biliary Atresia, Cholestasis, Obliteration Fibrosis, Cirrhosis, Cytomegalovirus.

Biliary atresia is a cholangiopathy is caused and formed by obstructive fibrous changes of the intrahepatic and extrahepatic bile ducts and manifested by cholestatic syndrome in the early neonatal period. It requires urgent surgery [1, 2, 11, 31, 32, 33].

According to the WHO, the incidence of BA among newborns is 5/100000 in the Netherlands, 5.1 / 100000 in France, 6/100000 in the UK, 6.5 / 100000 in the US, 7/100000 in Australia and 10.4 / 100000 in Japan. According to H. Lampela's research, the incidence of BA is 1/14000 to 1/20000 in Europe and 1/9000 in Japan [26]. In Uzbekistan, BA is detected once per 10000-15000. [28]

The first information about BA disease in children was given in 1817 by J.B. Holmes, a professor at the University of Glasgow, in his book "Principles of Nursing". J.B. Holmes linked the increase in jaundice and the appearance of colorless stools in the first months of a child's life to an incurable impairment of bile duct permeability and noted a serious risk to the child's life [4,15]. In 1855, Charles West observed a 13-week-old girl with BA who was born healthy and assessed her changes during this period as follows: "On November 8, 1855, I saw a female child aged 13 weeks; the only child of healthy parents. the only child of healthy parents small, apparently healthy. At 3 days however, it began to get yellow and at the end of 3 weeks was very yellow. Her motions at no time after the second day appeared natural on examination, but were white, like cream, and her urine was very high coloured."[16]

In 1892, the Scottish physician J. Thompson gave his first comment on BA disease in the local journal "Medical". Analyzing 50 observations, he concluded that the cause of BA disease was unknown and that it could be progressive inflammation of the bile ducts. [21,22,23,24]

Although no definitive conclusions have yet been drawn about the causes of BA, the following theories have been put forward by scientists:

1. Viral theory
2. Autoimmune theory
3. Theory of congenital developmental defects
4. Genetic theory

Viral theory - In recent years, many scientists have argued that the role of viruses is high as the cause of BA. In 1974, B.H. Land's article on neonatal obstructive cholangiopathies came as a new explosive (turning point) in the study of the etiology, pathogenesis of BA. In his article, he was one of the first to acknowledge the role of viruses as a causative agent of BA disease. Land notes that neonatal

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hepatitis, BA, and biliary tract cysts are the same inflammatory process that occurs at different stages of intrauterine development[13]. They advance this theory because when children with BA and neonatal hepatitis were examined for liver biopsies by electron microscopy, the same ultrasonstructural changes were detected in both. [34,35].

Proponents of the viral theory of the origin of BA see it as a causative agent of three types of viruses - cytomegalovirus, rotavirus and reovirus. However, these theories still have a number of contradictions and remain without clear conclusions. In particular, Fishler et al identified cytomegalovirus as one of the main factors causing BA. They examined blood and liver biopsies in 21 children with BA through serological tests and found the presence of cytomegalovirus. Of the 21 children who participated in the study, 8 (38%) had antibodies to cytomegalovirus lgM in their blood. Cytomegalovirus DNA was detected in 9 (50%) of 18 children's liver biopsies by PCR. [8,34]

When Soomro et al examined 33 patients with BA for cytomegalovirus by PCR, it was found that 14 (42%) of them had persistent cytomegalovirus infection. [18,27]

Hu et al tested 85 patients with BA for liver biopsies obtained during Kasai surgery using the PCR method — Ebstein-Barr, Cytomegalovirus, and adenovirus. The tests revealed cytomegalovirus DNA in 51 (60%) patient biopsies, adenovirus in 5 (6%) and Ebstein-Barr virus in 3 (4%) [25].

In 2005, Russian scientists A.V. Degtyarev, Yu.G. Mukhin, N.N. Volodin, Yu.A. Razumovsky and others conduct research to study the role of viral infection in the development of congenital defects of the hepatobiliary system. They tested the blood, urine, and liver biopsies of 33 infants (20 with BA) from one month to three months of age with hepatobiliary system defects for cytomegalovirus, herpes, Ebstein-Barr, human papilloma virus, hepatitis B and C viruses by PCR. Histological examination of liver biopsies revealed cytomegalovirus DNA in 16 (80%) of 20 patients and Ebstein-Barr virus in 1 (5%) patients. Hepatitis B-S, herpes type 1-2, human papilloma viruses were not detected in biopsies obtained from patients 'livers. When the blood of 20 patients was examined by PCR, cytomegalovirus was detected in 5 (25%). the DNA of other viruses was not detected in the patient field. Cytomegalovirus DNA was detected in the urine of 4 (20%) of 20 patients, and no DNA of other viruses was found. Although liver biopsies were detected by cytomegalovirus DNA by PCR, cytomegalovirus was not detected on histological examination. The researchers compared the results of histological analysis of children with BA and children with congenital cytomegalovirus. The lack of confirmation of cytomegalovirus in the liver biopsies of patients with BA in studies and the similarity of histological changes in hepatocytes after cytomegalovirus infection allowed scientists to consider cytomegalovirus as a cause of biliary tract atresia in the perinatal period [29].

Similar studies are being conducted at the Children's Clinical Hospital in Moscow by ST Chulev, AV Smirnov, and others in 27 patients with post-BA liver cirrhosis. Cytomegalovirus markers (serum, saliva, urinary cytomegalovirus DNA) were detected in 25 (92.6%) of the controlled patients, anti-CMV IgM in the blood of 6 (22%) patients, and anti-CMV IgG in the remaining patients. Of the 27 patients monitored, 1 (3.7%) was found to be infected with the HCV virus. Based on observations, scientists cite cytomegalovirus infection as the cause of BA and biliary cirrhosis developing on its basis [36].

The role of rotavirus type C infection in the origin of BA is also claimed. Riepenhoff-Talty reported that Peterson observed the development of BA in 1993 by oral transmission of rotavirus type A to newborn mice [15]. Based on these experiments, lesions in the hepatobiliary system were observed after rotavirus infection. Researchers led by Peterson administered anti-rotavirus α-interferon to mice and then transmitted the rotavirus to mice. No hepatobiliary system lesions were observed in the mice after the experiment. These scientists claim to have detected type C rotavirus in patients with BA [16]. However, L. Bobo et al identified not only type C, but also types A, B, C of rotavirus in human tissues with BA through high-sensitivity reverse transcriptase enzymatic analysis. BA-like fibrotic changes were detected in the liver of mice up to 3 weeks of age when infected with 3 types of reovirus. [2, 3]

In 1984, L.S.Glaser was able to detect antibodies against 3 types of reovirus in the serum of 63% of patients under 1 year of age with BA and their mothers. When other researchers examined the liver biopsies of 45 patients with BA by PCR, 3 types of reovirus were detected in 14 (31%) patients. Modern examinations of frozen tissue samples extracted by Kasai operation revealed type 3 reovirus in liver tissue in 55% of patients with BA and 78% of patients with biliary tract cysts [8]. Drut noted that human papilloma virus was detected by PCR in 18 patients with BA as a causative agent of BA, and that the virus was detected in 16 (89%) of them [6].

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However, the evidence that human papilloma virus, Ebstein-Bar, respiratory syncytial virus was detected in liver tissue in patients with BA is not reliable. However, experimental models in animals have shown evidence of association with these viruses in the development of BA.

Immunological theory – P.Dillian et al examines the tissue obtained from liver biopsy of patients with BA and identifies an abberant intracellular type 1 molecule (ICAM-1) that infects epithelial cells of the intrahepatic bile ducts [6]. This is accompanied by the active production of growth factor that stimulates transformation by type 1 cells, which form the preductal basis of inflammation of the epithelial cells of the bile ducts. In addition, the authors note an increased role of SD-4 cells in portal tract damage. These cells cause major immunological reactions. In a study by Silveria et al., An increase in the expression of HLA class 2 antigens and CD-68 antigens on hepatocyte membranes, a major component of histococci, revealed a poor prognostic value in BA [18]. H. Kobayashi came to the same conclusion in his research [12].

Based on his experiments in mice, Schreiber develops an experimental model of immune damage to the extrahepatic bile ducts. They analyze the presence of a "two-stroke" phenomenon in the development of BA: one with immunological vulnerability to precipitation factors; the latter with the role of a virus or toxic agent [19].

An increase in HLA B12 and A9-B5 and A28-B35 haplotypes was observed in children with BA compared with the control group. HLA B12 levels have also been found to increase in children without other congenital anomalies. Some authors disagree.

The theory of congenital malformations suggests that there are no primary epithelial channels in the embryonic period. The combination of several shortcomings may advance this theory. However, biliary tract defects can occur as a result of infection, intoxication, and other pathological factors affecting morphogenesis in the early stages of intrauterine development. In addition, the majority of children with BA have bile-stained meconium, which excludes the theory of congenital development, indicating the presence of primary normal bile ducts [30].

Genetic theory- Although BA occurs in both twins, the disease is not considered congenital. In this regard, some authors suggest that the birth of twins in the family with BA disease proves the role of genetic factors in the pathogenesis of BA. However, there are proponents of the possibility of secondary origin of BA as a result of the same effect of viral, toxic and other factors on both fetuses [5, 10].

Toxic theory - Balisturi and co-authors have seen toxic-environmental factors during pregnancy as a meson inducing BA [14]. However, other authors have not identified specific toxins that cause the development of BA.

An analysis of the above theories shows that the exact causes of the origin of BA disease have not yet been determined, and the results presented by scientists have led to many different debates. This requires a more in-depth analysis of the etiology of this disease, which is still considered heterogeneous.

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