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THEORIES OF THE OCCURRENCE OF BILIARY ATRESIA

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Abstract

Today, biliary atresia is increasingly common in the structure of congenital diseases. The highest incidence is observed in Asian countries – 30 patients per 100 thousand newborns, while in Europe this figure is 15 per 100 thousand newborns. To date, there is no effective aetiological treatment of the disease, which requires the improvement of knowledge in this area. Therefore, the aim of this study was to identify and analyse theories of the development of biliary atresia in order to subsequently create a more effective treatment for the disease. To do this, an extensive literature search was carried out in the main scientometric databases, according to the criteria/exclusion. As a result, four theories of the origin of pathology were identified. Most often, scientists mention the genetic theory, which demonstrates the possible association of the disease with gene mutations, in particular the A1AT, RhoU/Wrch, Hey2, Hnf1β, GPC1, EFEMP1 and ADD3 genes. Proponents of this hypothesis believe that at the stage of prenatal ontogenesis, defective genes express altered proteins, which will further promote atresia of the biliary tract. Adjacent to this theory is the viral theory, which indicates the effect of cytomegalovirus, reovirus, rotavirus on the risk of developing biliary atresia and the immunological theory, according to which IL-2, IL-12, interferon (IFN)-γ and tumour necrosis factor (TNF) – α, due to their influence on lymphocytes and the development of the inflammatory process, lead to autoimmune damage and the subsequent development of the disease. There is also the concept of the influence of external factors of the external environment. According to it, the leading role in the development of the disease is played by the regional affiliation of a person, the presence of closely related marriages, prematurity and/or multiple pregnancy, and the

influence of toxins. Thus, this study made it possible to determine the main factors for the development of biliary atresia today, which in the future can help improve the tactics of treating the disease, taking into account the individual predisposition of the patient.
Keywords: atresia, cholangopathy, biliary tract, malformations, neonatal jaundice.

1. Introduction

Biliary atresia (BA) is a progressive fibrosing-obstructive cholangiopathy of the intrahepatic and extrahepatic biliary system, leading to impaired bile outflow and neonatal jaundice. This pathology without treatment leads to portal hypertension, fibrosis and subsequent cirrhosis, eventually developing liver failure and death at the age of 2-3 years. Without a proper approach and treatment of BA, persistent structural changes in the liver parenchyma occur, which determines the high mortality in the terminal stage of the disease during the first two years of life. Despite the fact that there are modern surgical methods for the treatment of BA, the disease remains the most common reason for liver transplantation in children. Reliable aetiological factors and pathophysiological mechanisms remain unknown to date [1]. According to official WHO data, the incidence of asthma is 5.1 per 100,000 in France, 6 per 100,000 in the UK, 7 per 100,000 in Australia, and 6.5 per 100,000 in the United States [2].

The first mention of the disease was covered in the book “Principles of Nursing” in 1817, authored by Professor J. B Holmes. Even then, the scientist associated such symptoms of newborns as increased jaundice and colorless faeces with biliary obstruction without a clear reason [3]. Today, many scientists are working to identify the most likely aetiological factors of this disease, among which are hereditary factors, autoimmune processes, persistent viral infection, exposure to toxic substances, and distribution by sex, age and ethnicity [4]. For example, the most common genetic concept states that in the presence of gene mutations, further expression of proteins will be modified, which will contribute to structural changes. In the work published in 2022, L. N. Wu et al. considered the three most associated genes of susceptibility to BA, which are involved in the embryogenesis of the hepatobiliary system [5]. The ADD3, GPC1, ARF6 genes are responsible for the morphogenesis of the intrahepatic and extrahepatic bile ducts, respectively, with their mutant polymorphisms, structural changes in the latter will be observed, in particular in the form of BA, which was highlighted in experimental models of animal diseases. The genetic theory makes it possible to improve modern approaches in the selection of treatment tactics for patients. Equally important is the immunopathological concept. For example, in the same year, J. R. Townsend considered in detail in their study, the immune mechanisms of the origin of BA, explaining them by the fact that extrahepatic ducts are extremely sensitive to an immune-mediated inflammatory process with subsequent obliteration of the latter [6]. The authors also carefully considered the viral theory, where they interpreted that infection of neonatal mice with rotavirus type C results in persistent hyperbilirubinemia, jaundice, and colourless faeces. Histological examination of liver biopsies demonstrated inflammation and obstruction of the extrahepatic bile ducts. The data of the study M. Vij and M. Rela, who in 2020 described infants with BA and a high titer of IgM to cytomegaloviruses, contradictory regarding the viral aetiology [1]. However, with sufficiently pronounced symptoms of the disease, not a single biopsy performed revealed positive immunological staining for cytomegalovirus, which sows doubts in relation to this theory. Viral and immune-mediated theories allow a better understanding of the pathogenesis of nosology. Thus, careful monitoring and understanding of all possible

aetiological factors guarantee the timeliest diagnosis of the disease, the development of advanced and modern methods of prevention, as well as the renewal of treatment tactics, which will be based not only on symptomatic therapy, but also on aetiological and pathogenetic ones. Therefore, the purpose of this study was to analyse and summarize all currently known theories of the occurrence of biliary atresia on the element of their influence on the development and course of the disease in order to subsequently create a more effective treatment for the disease.

2. Materials and methods

An initial comparative review of the literature was carried out according to the updated PRISMA guidelines [7]. This approach avoided inaccuracies and contributed to a more detailed description of the research methodology. To determine the acceptance criteria, various aspects were taken into account: the accuracy and reliability of the results, the ethics, and acceptability of the information mentioned. In order to ensure the high quality of the study, a generalized algorithm was developed, which included detailed instructions for conducting the study and analysing the results.

To carry out a literary search in order to obtain relevant articles, by keywords, an analysis of sources from Web databases was carried out. of Science, Scopus, Pubmed. At the initial stage of the study, the literature search was limited to English, Spanish, French, Russian and Ukrainian, which could be the reason for excluding relevant studies by other authors in foreign languages.

For inclusion of the publication in the list of developed, broad selection criteria were deliberately chosen in order to better cover the research area. Publications that considered possible theories and mechanisms for the occurrence of biliary atresia over the past 5-10 years were automatically considered. Extreme attention was paid to original clinical studies, systematic reviews and meta-analyses, which considered and analysed all possible factors of biliary obliteration, as well as pathophysiological mechanisms at the gene and molecular levels. Publications that had flaws in study design, or contained more promotional material than scientific material, were not considered for further study. This was done to avoid unreliable information or false conclusions. This approach allowed increasing the reliability of the results and increase their significance.

The main primary terms for the search for scientific publications and studies in this work were: “biliary atresia”, “obliteration”, “viral factors”, “gene polymorphisms”, and “aetiological factors”to identify possible theories of occurrence and pathophysiological mechanisms for the implementation of biliary atresia in newborns. Further search for each of the factors identified at the initial stage was carried out using the terms-names of these factors and their possible links in pathogenesis, for example: “rotavirus”, “cytomegalovirus”, “hepatotropic viruses”, “A9-B5”, “A28-B25”, “B8” and “DR3”.

The main study models that were subject to further review and study were:

1. Studies where participants were divided into control and experimental groups, with a minimum of >10 people.
2. Systematic reviews and meta-analyses.
3. Studies that were conducted to confirm or refute possible theories for the development of biliary atresia.
4. Scientific publications on the study of pathophysiological links and mechanisms of obliteration of the intrahepatic and extrahepatic bile ducts.

To be excluded from scientific analysis were publications with dubious results, advertising publications, as well as personal opinions of the authors regarding the theories of the occurrence of biliary atresia, without any scientific justification. After searching the literature databases for keywords and inclusion/exclusion criteria, 116 articles were found for the primary study. During iterative meetings, the authors collectively analysed the feasibility of a particular scientific publication to achieve their goals. As a result, 74 publications were included in the study as sources of literature.

3. Results and discussion

3.1. Virus theory

According to the viral theory, in the development of this pathology, infection with hepatotropic viruses during the prenatal period or after it is important. This may be the result of virus reactivation in the mother's body or infection during and after pregnancy. The viruses that are involved in BA are cytomegalovirus, reovirus, rotavirus, and hepatitis viruses [8]. Cytomegalovirus (CMV) Scientists in 2023 after a survey of a group of infants with BA came to the conclusion that 10% of them have IgM to CMV [9].

It is worth noting that at the time of diagnosis, infants were older than study participants with other aetiologies of asthma and, accordingly, received medical and surgical care later, and therefore had worse prognostic chances of recovery. In addition, these patients had higher levels of bilirubin and cytolysis enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (ALT), lactate dehydrogenase (LDH), and others), signs of splenomegaly [10, 11]. In addition, in the studied infants, cholestasis resistant to conservative treatment was observed, and, accordingly, higher risks of mortality. It should be noted that antibodies to CMV were not found in the biopsy of hepatobiliary samples. Therefore, asymptomatic carriage of CMV by women of childbearing age is worth the attention of medical personnel involved in pregnancy planning [12].

In the work, G. B. Soomro et al. examined 33 patients with asthma for cytomegalovirus using the polymerase chain reaction (PCR) method, they concluded that 14 (42%) of them had persistent cytomegalovirus infection and although the sample was not significant, the results can be considered reliable and representative [13, 14].

Rotavirus is another representative of the virus kingdom involved in BA. Its RNA was found in 50% of patients diagnosed with BA [15]. L. Huang et al. modelled the pathophysiological mechanisms of AD in a mouse model [16]. They proved that mice at the age of two days, which were orally vaccinated with rotavirus tropic to the hepatobiliary system, had active virus replication both in the intrahepatic and extrahepatic bile ducts and in the liver itself two days after infection. Approximately 7 days after infection, from 25% to 50% of mouse pups, depending on the virus strain, showed signs of inflammation and subsequent swelling of the bile ducts, followed by persistent inflammation and damage to the epithelium of the bile ducts. The obstruction was complete in about half of the animals that had obvious symptoms of the disease. Although there was no obvious atresia as described in infants, the obstruction was irreversible in about half of the affected mice, and the subsequent fibrosis and proliferation of the bile duct epithelium in the liver were strikingly similar to those seen in the liver of newborns with biliary atresia. Other researchers also obtained similar data, in particular, this is covered in the works of G. Czech-Schmidt et al. [17], J. A. Bezerra [18]. In particular, in the work, G. Czech-Schmidt et al. argue that the earlier the infection of mice with rotavirus occurs, the higher the risk of mortality in them [17]. Thus, mice infected in the first 12 hours from birth had a 100% chance of death, 86% of them had clear signs of cholestasis. In addition,

the clinic depended on the viral load. A significant result of the researchers was that prenatal infection of pregnant mice does not induce BA in offspring. Female mice that are immunized against rotavirus protect their neonates from developing rotavirus-induced cholestasis and subsequent BA. This protection is transmitted transplacentally and not through breast milk. This result is of great importance for endemic regions with regard to rotavirus, since pre-immunization of women of childbearing age can lead to a decrease in the incidence of asthma in infants. Since the mouse model is maximally similar in its characteristics to humans, therefore, this study is valid and reliable [19].

G. Mathiyazhagan and B. Jagadisan analysed 64 biopsies of patients with asthma (mean age of hospitalization was 52 days) obtained during the Kasai operation [20]. Given the possibility of its implementation and the patency of the extrahepatic bile duct, 2 different anatomical subtypes of BA have been described: corrective and non-corrective. The subtype to be corrected is characterized by an open hepatic duct to porta hepatis without connection to the duodenum, which, in turn, may allow a direct extrahepatic anastomosis of the bile duct and intestinal tract by performing the Kasai operation. Unfortunately, this subtype, which can be corrected, accounts for only 10-15% of patients with biliary atresia. In the absence of a possible anastomosis between the duct and the intestine, this type is called uncorrectable and, accordingly, it occurs in most cases of asthma and has a poor prognosis for the survival of infants with asthma. The samples that the scientists received during the operation were examined using the PCR method to determine the Ebstein-Barr virus, cytomegalovirus, and adenovirus. Cytomegalovirus DNA was found in 51 (60%) patient biopsies, adenovirus DNA in 5 (6%), and Ebstein-Barr virus in 3 (4%) [21]. C. Yang et al. noted that in 18 patients with BA, the human papillomavirus was detected as the causative agent of the disease using the PCR method [22]. However, evidence for the detection of human papillomavirus, Ebstein-Barr virus, respiratory syncytial virus in liver tissue in patients with BA is not reliable, although experimental animal models have shown evidence of a link between these viruses in the development of BA.

As for the reovirus, the data are contradictory; at the beginning of the study of aetiology, a number of works claimed the influence of this virus on the development of BA in newborns [23]. Having analysed a number of works by S. K. Mohanty et al., it was possible to detect antibodies to reovirus in the blood serum of 63% of asthma patients under 1 year of age and, no less interesting, in the blood serum of their mothers [24]. In the study of this issue by other researchers in liver biopsy specimens of 45 patients with BA, PCR revealed 3 types of reovirus in 14 (31%) patients. Examination of frozen tissue samples isolated using the Kasai operation revealed reovirus type 3 in liver tissue in 55% of patients with BA and in 78% of patients with cystic changes in the biliary tract. But later, results began to appear that disproved the involvement of reovirus in the pathology. Among the developed sources M. Vij and M. Rela there was a study in which samples of 50 infants with asthma were analysed, and it was concluded that reovirus does not cause atresia of the bile ducts or its role is insignificant, since only one of the examined was found to have reovirus RNA [1]. In addition, a meta-analysis by T. Saito et al. indicates that the role of viruses is insignificant, but still possible [25]. This theory is confirmed by the fact that in the mouse model, the elimination of the virus occurs within a few weeks, as noted by E. Carvalho et al. [26].

Most of the problems in diagnosing viral invasion are associated with a short infectious period, possible rapid elimination of the virus, and instability of the virus in the obtained samples, which causes difficulties in finding the aetiology of BA [27, 28].

3.2. Immunological theory

If consider the immunological theory, then it is based on lymphocytic infiltration of the portal tracts, such data indicate a primary inflammatory process, which can later lead to gradual atresia and BA. In addition, cytokines such as interleukin IL-2, IL-12, interferon (IFN)-γ and tumour necrosis factor (TNF)-α play a significant role in this case. The mechanism of their action is that they are able to increase the permeability of the cell wall, which, in turn, can provoke inflammation, in addition, they are part of the monocyte-macrophage system, so they can affect immune responses both directly and at the expense of other cells [29].

M. Davenport et al. analysed tissues obtained from liver biopsies of patients with acute cholangitis and found an abnormal intracellular molecule type 1 (ICAM-1) that resides in the epithelium of the intrahepatic bile ducts [30]. An important role is played by the cell growth activating factor, which stimulates the transformation of cells of the first type, which are the basis for inflammation of the epithelium of the bile ducts of the hepatobiliary system. In addition, the authors note an increased role of CD-4 cells in damage to the biliary tract. These cells cause significant immunological responses [31]. In the study by C. L. Mack et al., an increase in the expression of HLA-A, -B, -C antigens on hepatocyte membranes were confirmed, and also noted that this is a poor prognostic marker in BA [32]. Other researchers came to the same conclusion in their scientific work, they note that in the case of an immunological cause of BA, drug treatment is less effective, in addition, the range of permitted biological drugs is quite limited in infants, so in this case, surgical treatment should be considered immediately [8].

Other scientists, notably G. B. Soomro et al., developed an experimental mouse model, and conducted an experiment on immune damage to the extrahepatic bile ducts [13]. They presented the theory of the “two-hit” phenomenon as the cause of the development of BA. The first step is the immunological damage to the elements of the biliary tract, which have immunological vulnerability, the second is the role of a virus or a toxic agent that causes inflammation and atresia. C. Ye et al. paid attention to the population of CD4 and CD8 T-cells that cause autodamage of biliary tract cells. It should be noted that these patients were seronegative for hepatotropic viruses in this study, as they were subject to PCR testing for the above viruses [33].

Equally important, there was impaired activity and migration of macrophages, defects in Kupffer cells, manifested in a violation of the absorption of foreign antigens, an increased number of cytotoxic T cells and, conversely, a deficiency of CX3CR1+ effectors and natural killer (NK) cells in infants with BA, this is what should ensure the recognition of self and foreign antigens. More importantly, it was found that hepatic B-cell lymphopoiesis was not interrupted or impaired, compared to T-cells after birth, such tolerance defects contributed to the accumulation of autoantibodies to immunoglobulin G (IgG) in BA [34].

3.3. Genetic theory

Proponents of the genetic theory tend to associate BA with certain genomic mutations, according to which genes important for the normal development of the hepatobiliary system at a certain point in embryonic development express pathological proteins that ultimately cause atresia of the biliary tract. Therefore, several forms of BA can be distinguished. Namely: the first form of BA (5%) obstruction is at the level of the common bile duct. In the case of the second form of BA (2%) – at the level of the common hepatic duct. In the third form (90%) – atresia at the level of porta hepatis. The development of ductal atresia and other congenital liver diseases is associated

with deficiency of α-1-antitrypsin encoded by the A1AT gene; the presence of at least one mutant allele is a predictor of rapid progression of fibrosis and atresia and, accordingly, an earlier need for surgical treatment or even transplantation in these children liver [35]. In addition, a mutation in the Jagged 1 gene, which normally plays an important role in cell development and differentiation, is also a cause of BA. Expression of the pathological protein in embryonic cells was accompanied by the production of inflammatory cytokines TNF and IL-8 [36]. Another possible gene involved in BA is HLA, the gene for antigenic compatibility. HLA responsible for the type of human leukocyte antigen is also considered as a genetic predisposition factor for the formation of non-functioning bile ducts. An increased frequency of HLA B12 alleles has been repeatedly associated with BA, namely haplotypes: A9-B5, A28-B25, B8 and DR3 [31, 37].

One form of BA is cystic biliary atresia, which is primarily associated with the CFC-1 gene (encoding the Cryptic protein). For example, in the French population, approximately 50% of newborns with this form of BA were found to have this mutation [38]. As noted by the authors, the above-named gene is the cause of "polysplenia syndrome" or "spleen malformation syndrome with biliary atresia (BASM)". In this syndrome, affected children often have an abnormality of the spleen (e.g., polysplenia, double spleen, asplenia) associated with situs inversus, gastrointestinal anomalies and/or heart defects. Many of these malformations are related to sagittal rotation anomalies.

Biopsies from patients with biliary atresia have demonstrated increased expression of the RhoU/Wrch1 and Hey2 genes in cholangiocytes. Thus, another novel pathway for injury to the bile duct epithelium in a mouse model with biliary atresia has been presented that is relevant to human BA and may offer potentially effective future therapeutic agents [39].

U. F. Shaalan et al. conducted a retrospective study that included 60 pediatric patients, 30 with BA and 30 with neonatal cholestasis (NC) [40]. The objectives of this study were to investigate the expression of two important genes that regulate remodelling of ductal plate during embryonic development, namely: hepatocyte nuclear factor 1-beta (Hnf1β) and fork head protein A2 (FoxA2). As a result, reduced expression of Hnf1β and FoxA2 was found in the liver tissue of BA patients. In addition, Hnf1β significantly correlated with fibrosis stage, bile duct proliferation, and bile stenosis in the ducts of the hepatobiliary system. In addition, pathological expression of Hnf1β showed high sensitivity and specificity in cases of BA. The same data were obtained for the FoxA2 gene, although it has a slightly worse prognostic value compared to the first gene.

In 2020, the work of Chinese scientists on the influence of the ADD3, GPC1 and EFEMP1 genes on the development of BA was completed. M. R. Bai et al. referred to data obtained by scientists even earlier and pursued the goal of disproving or proving and evaluating the association of these genes with BA in the Chinese population. Therefore, they examined 340 patients with BA and 1665 people from the control group for the presence of 20 single nucleotide polymorphisms (SNPs) of these four genes. The obtained results demonstrate that three SNPs in the EFEMP1 and GPC1 genes were significantly associated with BA, but among the SNPs of the ADD3 gene, no patterns of BA development were found in the Chinese population (Figure 1) [41].

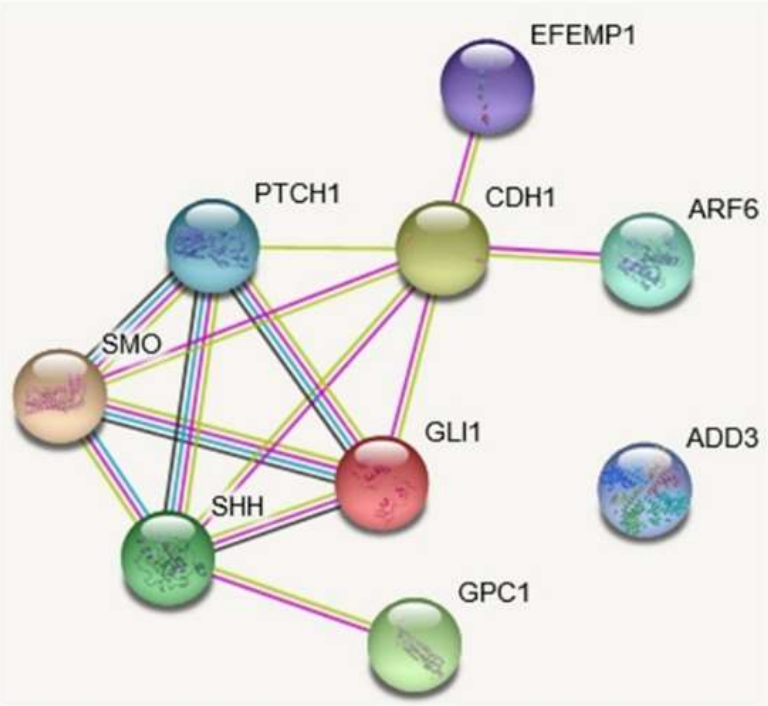

Figure 1. A network of gene interactions based on the STRING database of studied genes

Source: [41].

In the figure, the network is built for the three genes under study, where the nodes of the network are proteins. The edges represent putative functional associations. The edge is drawn with up to four different coloured lines, and these lines represent existing associations that have been predicted. The green line: signs of the neighbourhood; the blue line: proofs of the general case; the purple line: experimental evidence; the yellow line: evidence of text mining; the black line: proofs of co-expression [41].

It should be noted that in some genetic syndromes, namely: cat's eye, Mitchell-Riley, Zimmermann-Laband and Fanconi anemia, BA occurs quite often as part of the syndromes. Also, BA is quite common in both twins born in a family of patients with this pathology, this disease is not considered congenital. However, among scientists there are supporters of the possibility of a secondary origin of BA due to the simultaneous intrauterine action of viral, toxic and other factors on both fetuses [42]

3.4. Theory of influence of external factors

There is a regional theory of the distribution of BA, according to which living in a certain area of the earth's surface is more favourable for the development of BA, in particular, this applies to Taiwan, then there is 1 case per 5000 healthy babies, other sources indicate that BA occurs in Taiwan and French Polynesia with a frequency of 1 per 3000 live births. In Japan, about 1 case per 10,000, and a higher incidence has been reported in Asia and Hawaii, which is an island surrounded by the Pacific Ocean, this may be due to territorial separation and,

accordingly, a greater chance of consanguineous marriages. A higher incidence is also seen among Inuit and Native Americans [43].

There are some suggestions that female infants are more prone to asthma than males, which is associated with the presence of two X chromosomes, which in turn cause greater production of female sex hormones (mostly estrogen) in contrast to men. Among other reasons, one can single out an increase in the incidence of children of elderly mothers, multiple pregnancies and premature babies [44].

Regarding the seasonal variability of this disease, at first, scientists did not come to a specific result on this factor. However, Chinese scientists have come to the final point of view so far, they studied infants with BA and came to the conclusion that seasonal factors are not related to this hepatobiliary problem [45].

Among the toxins that can cause BA, bilioatreson is of key importance, which through a number of pathophysiological reactions causes an increase in the permeability of the duct epithelium due to a change in their polarity, further fibrosis and atresia of the biliary tract. But timely qualified medical care could halt development and cause complete or partial regression [45].

According to the work of J. J. Zhu et al., published in 2022, bilioatreson is indeed one of the aetiological factors of BA in newborns, it is not able to get from mothers through the placenta or breast milk, but it can get with vegetables or fruits or be a metabolic product of the child's microflora. It is important to note that not only bilioatreson itself, but also its derivatives, can cause BA [46].

So, factors contributing to the development of BA in newborns include: various variants of the gene sequence and anatomical features, damage to the bile ducts by viruses, toxins, or other external factors, as a result of which the extrahepatic bile ducts of the newborn become prone to damage to the epithelium of the hepatobiliary tract. Thanks to new findings that in infants with biliary atresia in the first days of life, the level of conjugated bilirubin in the blood serum, as well as other signs of cholestasis, can be traced at an earlier stage of the relationship between the aetiological factor and the symptoms of a particular patient with asthma.

4. Conclusions

As a result of the study, several theories of the development of BA were identified. One of the most common among them is viral. Causative viruses include: CMV, reovirus, rotavirus, as they affect the intrahepatic and extrahepatic bile ducts. In addition, it is worth considering the immune theory, according to which some immune components can have a significant contribution to the development of BA. In particular, it was found that the determination of IL-2, IL-12, interferon (IFN)-γ and tumour necrosis factor (TNF)-α, due to their effect on lymphocytes CD-4, CD-8, CD-68, as well as the development of an inflammatory process and subsequent fibrosis and atresia can lead to autoimmune damage and the subsequent development of the disease. It is important to keep in mind that the influence of the genome is no less important, therefore, among the above works, a number of genes were identified that are the cause of BA, among them A1AT, RhoU/Wrch, Hey2, Hnf1β, GPC1, EFEMP1, ADD3 – this is not the whole list of genes associated with the development of BA in infants. As for the latter, its involvement in BA has not been confirmed in the Chinese population, but this does not mean that it cannot cause BA in Europeans or African Americans, which may be the goal of further research. The last established one was the theory of the action of external factors. It has been determined that a person's regional affiliation (in particular, residents of the Pacific Islands and hard-to-reach highlands), the presence of closely

related marriages, prematurity and/or multiple pregnancy, the influence of toxins (bilioatreson) statistically significantly increases the risk of developing biliary atresia in children. Thus, the currently known and collected in this study theories of the emergence of biliary atresia allow a deeper consideration of the aetiological and pathophysiological factors of the onset of the disease, as well as to draw up an algorithm for optimal treatment for each patient, taking into account his individual predisposition. However, the relationship of various theories with each other and their influence on the development and course of pathology still requires more practical research.

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