BILE DUCT ATRESIA. LITERATURE REVIEW

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Abstract

Biliary atresia is a rare but severe congenital disease characterized by progressive obstruction of the extrahepatic and intrahepatic bile ducts and leading to cholestasis, fibrosis and cirrhosis of the liver in newborns. Epidemiological data demonstrate the variability of prevalence in different regions, which indicates the possible influence of genetic and environmental factors. The pathogenesis of the disease remains the subject of active study and includes the interaction of immune, viral and molecular mechanisms leading to damage to the bile ducts. Clinical diagnosis is difficult due to non-specific symptoms such as jaundice, light feces, and dark urine, which makes early detection critical to improve outcomes. Surgical intervention, known as Kasai surgery, remains the main treatment method and is aimed at restoring bile outflow, however, a significant proportion of patients eventually require liver transplantation. Current research focuses on the search for biomarkers for early diagnosis, the study of molecular targets, and the development of innovative therapeutic approaches, including immunomodulation and cellular technologies. The literature data emphasize the need for an integrated approach to disease management and further scientific research to improve clinical outcomes.

Introduction

In the structure of childhood diseases, an important place is occupied by congenital liver diseases, characterized by a variety of clinical forms, varying degrees of severity of liver damage, progressive course with a frequent outcome in cirrhosis of the liver (LC) and disability of patients. As a rule, the early stage of such diseases is asymptomatic. Liver diseases are one of the most difficult problems in modern hepatology. Liver damage in children is characterized by a high frequency of genetic disorders (both structural and metabolic) and a pronounced effect of the disease on the growth, mental and physical development of the child.[1]

The current stage of studying liver diseases in children is characterized not only by significant achievements, but also by the presence of many unresolved issues. One of them is the problem of early diagnosis of biliary atresia. In the Republic of Kazakhstan, there is no banal screening for the detection of biliary atresia (acholia / hypocholia of the stool). In this regard, early diagnosis was missed, and at the time of contacting our center, 82% of children with biliary atresia already have cirrhosis of the liver, which requires liver transplantation. More than 80% of patients with extrahepatic biliary atresia who undergo Kasai surgery before 60 days of life have jaundice, compared with 20-35% of patients who undergo portoenterostomy later. Age at the time of surgery remains an important predictor of the outcome of Kasai portoenterostomy. In cases with successful bile drainage, the 15-year survival rate is 87%. Kasai portoenterostomy is effective if the operation is performed within 45 days of the child's life. In world practice, the indication for Kasai portoenterostomyis clearly regulated. In the presence of cirrhosis of the liver, this operation is contraindicated. Timely diagnosis and treatment helps to avoid liver transplantation in children in 80% of cases. After 120 days, when cirrhosis of the liver has formed, the only way to save a child's life is liver transplantation.[2]

To date, the criteria for the differential diagnosis of congenital liver diseases have not been clearly defined. The issue of the frequency of formation and rate of progression of liver cirrhosis, as well as factors contributing to its development in other congenital liver diseases, chronic viral hepatitis, autoimmune hepatitis, and metabolic liver diseases in children, remains relevant.[3]

Issues related to the patient's route and the system and algorithm for monitoring patients with biliary atresia remain insufficiently studied, which indicates the need for an in-depth study of this important childhood problem.

The frequency of the disease occurs on average in 1 case per 20,000-30,000 births, accounting for about 8% of all internal organ defects in children, in Japan and China - 1 in 9600, in the USA 1 in 10,000 - 15,000, in Europe 1 in 16,000. About 15-25% of children have other congenital malformations.[4]

Materials and Methods

To prepare this literature review, a systematic search was conducted for publications on biliary atresia in international and national medical databases. Original articles, reviews, clinical recommendations, and case reports published in English and Russian were included.

The literature analysis was carried out in order to identify modern ideas about the pathophysiology of the disease, methods of early diagnosis, surgical and conservative treatment, as well as outcomes in patients of different ages. The articles were evaluated based on data quality, research methodology, and reliability of the information provided. The systematized information was grouped into thematic blocks: epidemiology, etiology, clinical picture, diagnostic approaches, surgical interventions and long-term treatment outcomes.

This approach allowed us to obtain a comprehensive understanding of the current state of knowledge about biliary atresia and identify promising areas for further research.

Ethical approval. This study is a review of published scientific evidence and did not include interventions involving humans or animals. In this regard, the approval of the ethics committee was not required. All the sources used were publicly available, and the work was carried out in accordance with the principles of scientific honesty and correct citation.

Results

Among diseases of the hepatobiliary system in infants of the first months of life, biliary atresia occupies a dominant position, occupying 45% of all cases.[4] Studies conducted by both domestic and foreign specialists confirm that asthma is the most common reason for the need for liver transplantation in children.[5,6] Kasai surgery, or portoenterostomy, is universally recognized as the optimal treatment for biliary atresia. During this operation, obliterated bile ducts are eliminated, restoring the normal outflow of bile through the bile ducts. The effectiveness of surgical intervention in biliary atresia (BA) is assessed according to the following criteria: the appearance of yellow stools, the disappearance of jaundice and a decrease in the concentration of total bilirubin to less than 34 mmol / l within 3-6 months after surgery.[7,8,9]

Diagnostics

1. Screening programs using fecal coloration assessment (acholia/hypocholia) are widely used in the early diagnosis of biliary atresia.

2. Biochemical blood analysis.

3. Ultrasound of the abdominal organs, MRCP.

However, in the conditions of the Republic of Kazakhstan, late diagnosis is noted due to non–compliance with diagnostic standards. In the world [5] and in our country, biliary atresia is the main indication for liver transplantation (Figure 1, 2, 3, 4).

Picture 1(a,b). The stool chart. Characteristic signs of biliary tract atresia, present from the first days of a child's life, are acidic (discolored) stools (1, 2, 3) and intense dark ("beer") colored urine. A stool chart is used to evaluate the feces of a newborn. The card includes directions to contact Perinatal Services British Columbia for follow up if their newborn's stool colour looks abnormal. (*http://bit.ly/biliary_atresia*).

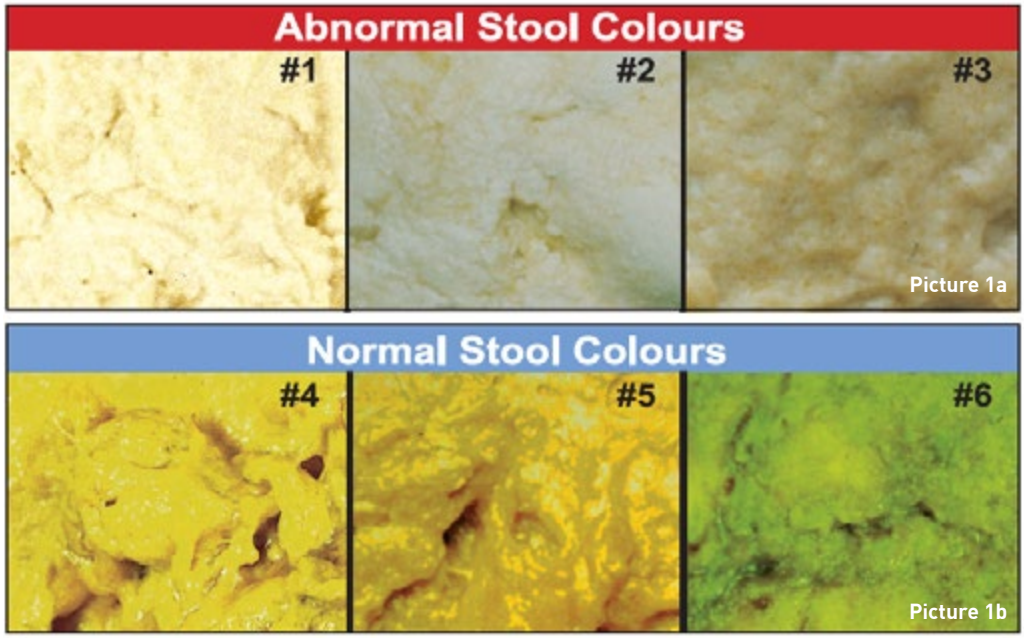


Figure 1. Evaluation of the Pediatric Patient for Liver Transplantation: 2014 Practice Guideline by the American Association for the Study of Liver Diseases, American Society of Transplantation and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Robert. (*Squireset al. Hepatology, Vol. 60, No. 1, 2014)*

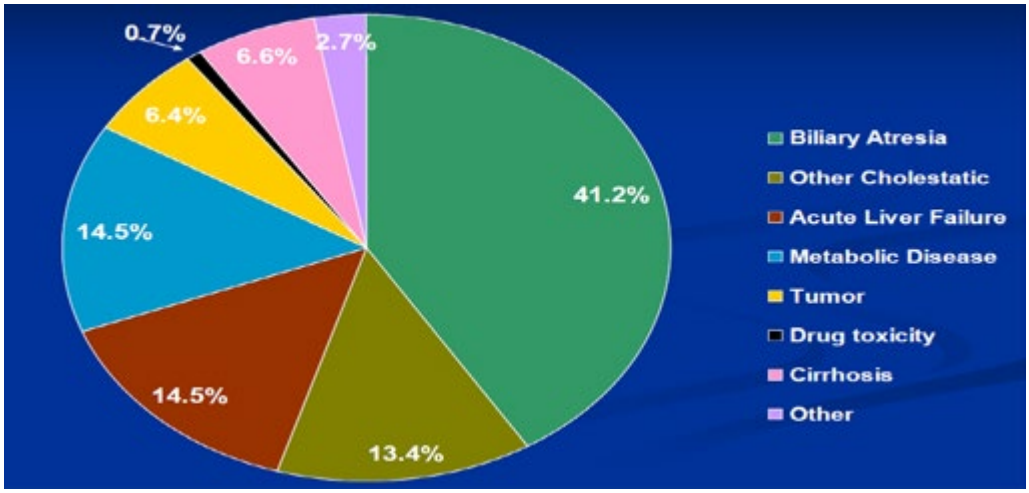
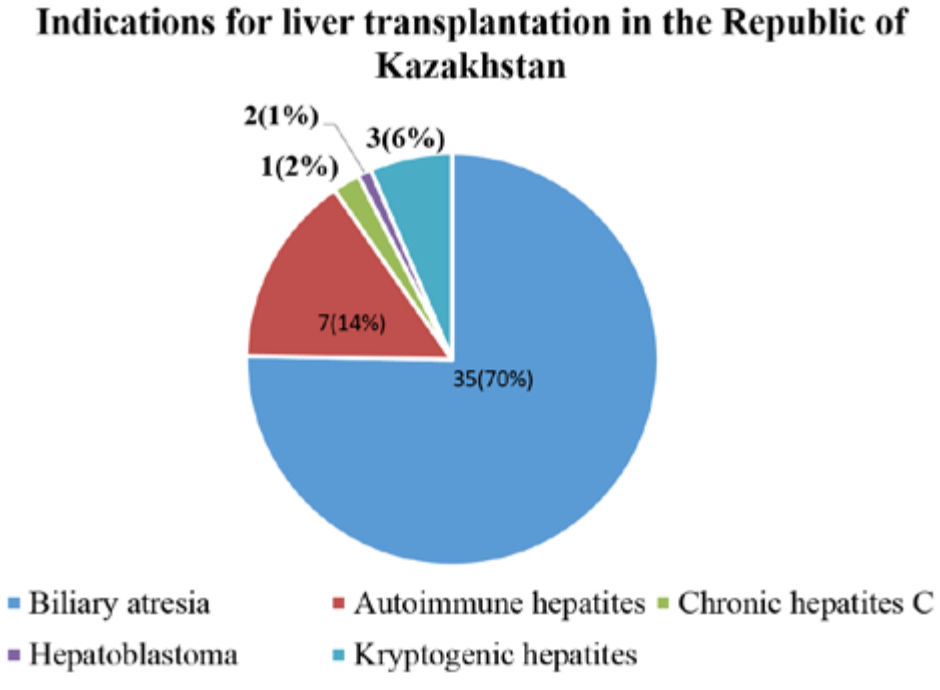


Figure 2. Indications for liver transplantation in children in the Republic of Kazakhstan (data from Syzganov National Scientific Center of Surgery).



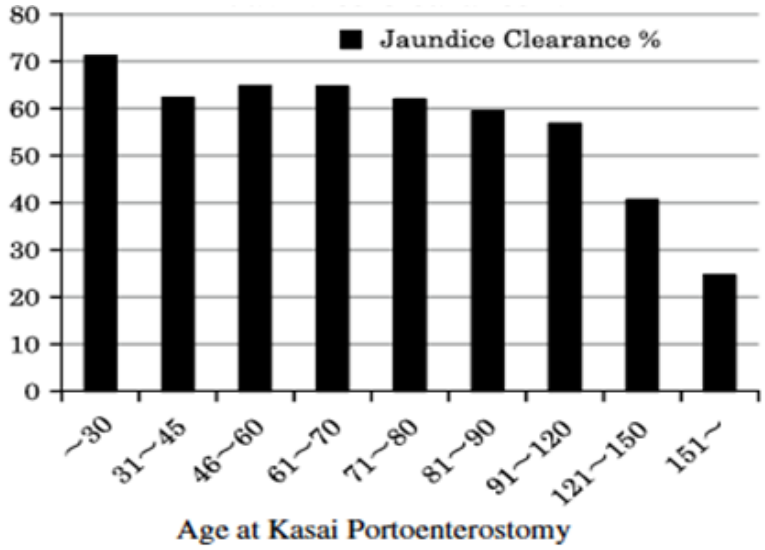


Figure 3.
The effectiveness of the Kasai procedure depending on the age of the child *(Japanese BA Registry) Nioetall. SurgeryToday 2015*

As can be seen in the figure, Kasai portoenterostomy is effective if the procedure is performed on time.[6] Thus, timely diagnosis and treatment helps to avoid liver transplantation in children in 50% of cases.

The success rate of surgical intervention ranges from 36% to 87.2%. In case of ineffectiveness of KPE (Kasai portoenterostomy), it is necessary to perform LT within 6-12 months after surgery, otherwise death is possible due to the development of liver failure.[10] To date, not all the determining factors affecting the effectiveness of surgical treatment have been fully identified.

Late diagnosis of diseases remains an urgent problem at the global level. Untimely detection of liver disease can not only negatively affect the prognosis, but also lead to an increased risk of complications. Hemorrhagic syndrome, which occurs in various locations, and intracranial hemorrhages are considered particularly dangerous, which, even with the restoration of liver function after transplantation, are irreversible.[5,11] Early diagnosis and administration of vitamin K preparation can prevent the development of hemorrhagic syndrome in children with congenital vitamin K deficiency.[12] Therefore, the study of clinical, laboratory and ultrasound signs of the disease in the early postpartum period is a primary task for the timely detection of BA.

The patient's age during Kasai surgery plays a significant role, but is not the only factor influencing the outcome of surgical treatment.[10,13] Several studies have been devoted to the study of both pre- and postoperative laboratory parameters, ultrasound data, and the results of morphological analysis of liver biopsy in order to identify factors predicting the effectiveness of surgical intervention. However, the results obtained are ambiguous and vary significantly.[14]

The development of molecular genetic research methods has significantly expanded our knowledge of the genetic mechanisms of biliary atresia. The scientific literature presents a wide range of studies, including the analysis of candidate genes, genome-wide association search (GWAS), the study of variations in the number of copies of genes (CNV), and exome sequencing (WES), aimed at identifying the causes of this disease.[1,15] Due to the phenotypic heterogeneity of Alzheimer's disease (AD), the genetic characteristics of each patient can significantly affect the severity of the disease and the success of surgical intervention. Despite this, the influence of genetic factors on the results of surgical treatment of BA has not yet been sufficiently studied.

Despite significant progress, the search for noninvasive markers capable of reliably diagnosing severe liver fibrosis and cirrhosis in children with Bauer's disease remains an urgent task. After

all, the progression of liver fibrosis after Kasai surgery and related complications have a significant impact on survival with native liver, and timely diagnosis of such changes makes it possible to determine the optimal time for transplantation.

Analyzing the presented information, it can be concluded that the research topic is highly relevant and consists in identifying factors predicting the effectiveness of Kasai surgery, based on a comprehensive analysis of clinical, ultrasound, and molecular genetic parameters.

Biliary atresia is a progressive disease of the bile ducts, both intrahepatic and extrahepatic. Without timely therapy, death occurs in the first two years of life. The causes of BA are still not fully understood. Kasai surgery is the main therapeutic approach, which, however, is palliative in nature and only prolongs life while preserving the native liver. If the Kasai operation is ineffective, the LT is performed.

The essence of the operation is to eliminate the obliterated bile ducts in order to ensure the outflow of bile into the intestine and thereby stop the development of the disease. However, the result of the operation is not always positive, and its effectiveness varies over a wide range – in about 32-59% of cases, it is possible to prolong life with a preserved liver up to 5-10 years. Recently, several studies have been conducted to identify the factors that influence the results of surgery. Among them, the age of the patient at the time of the operation, the qualification of the surgical surgeon,[16] the presence of other congenital anomalies in the child, the anatomical features of biliary atresia,[17] and the use of steroid drugs in the postoperative period[18] are particularly highlighted.

Although gene variants have been identified in patients with BA and their correlation with the course of KPE has been established, the exact effect of genetic factors on the etiology and prognosis of treatment of patients remains unclear, given the polygenic nature of the disease. The data obtained in the studies are contradictory, and at the moment there is no single concept defining the predictors of the outcome of KPE.

The ineffectiveness of KPE in BA is often accompanied by rapid progression of the disease, resulting in cirrhosis of the liver (LC), which requires urgent liver transplantation (LT). The identification of factors predicting the effectiveness of KPE will make it possible to timely hospitalize a child in a transplant center, organize the selection and training of a donor, as well as optimize therapy, preventive measures, and conduct full-fledged counseling and education for parents. This statement formulates the purpose of this study and demonstrates the importance of the chosen topic for identifying factors affecting the effectiveness of KPE in children with BA.

Biliary atresia is characterized by an inflammatory process and subsequent fibrous obliteration of the extrahepatic bile ducts, which eventually spreads to the intrahepatic bile system, leading to the formation of biliary cirrhosis of the liver.[19] In the vast majority of cases (about 85%), BA occurs in an isolated form, not accompanied by other syndromes, that is, in the perinatal period. The embryonic (syndromic) form is diagnosed less frequently, accounting for 10-15% of all cases of the disease, while the cystic form of BA is detected in 5-8% of cases.[1]

The prevalence of biliary atresia in the population varies depending on the region, ranging from 1 in 8000 people in Asian and African countries to 1 in 18,000 in Europe. The prevalence of the disease is observed in girls.[20,21] Neonatal cholestasis is a characteristic clinical manifestation of asthma. In the first months of life, children need to be differentially diagnosed with a wide range of congenital and hereditary diseases that may disguise themselves as BA symptoms.[4,22] To confirm the diagnosis, a morphological examination of a liver and bile duct biopsy is required during surgery. Treatment of this pathology includes surgery and liver transplantation, which together increases the overall survival rate of children with this disease to 90%.[4,8,10,22] The exact causes of biliary

atresia and the factors influencing the effectiveness of its treatment remain the subject of active scientific research. Among the suggested etiopathogenetic mechanisms are genetic predisposition, immune disorders, and the influence of external influences, such as viral infections and toxins. Numerous studies have highlighted the significant role of immune dysregulation in the occurrence of this disease. Alzheimer's disease (AD) is characterized by a fibroinflammatory process, manifested by the infiltration of inflammatory cells, increased expression of cytokines and chemokines during microscopic analysis of liver biopsies of patients. The pathogenesis of asthma is based on an innate immune response that triggers the activation of NK cells and Th1-type cells, which are a subpopulation of adaptive immunity helper T cells. This mechanism attracts effector T cells, which eventually leads to inflammation and impaired patency. There is also a decrease in the number of Treg cells, which play a key role in suppressing inflammatory processes. After biliary tract obstruction occurs, the immune system continues to cause damage, even when bile outflow is restored. This situation is caused by the activation of T2 and T17 immune responses.[23] Unlike other immune diseases of the bile ducts, after liver transplantation, remissions of the disease are established and are not accompanied by relapses.[1,24]

Viral or toxic damage to the bile duct epithelium can provoke the appearance of new antigenic epitopes, which can cause or increase autoimmune inflammation.[25,26] Various viruses are considered as potential culprits for the development of the disease, including cytomegalovirus (CMV), human papillomavirus (HPV), herpes virus type 6, Epstein–Barr virus (EBV), reovirus and rotavirus.[27] Some studies using PCR to detect viral DNA/RNA or immunostaining for viral IgM+ or Mx protein have shown the presence of traces of a previous viral infection in liver tissues, but this fact has not been confirmed in all cases.[28] Currently, there is no convincing evidence to confirm a link between viral infection and the development of asthma. The results of research in this area are contradictory, due to the lack of control groups, methodological limitations, and ambiguous interpretation of the data obtained.[1,27,29] Despite the fact that a viral infection can worsen the course of BA and increase the risk of adverse consequences, it is interesting that adults infected with these viruses do not develop BA.[1,28,30]

In Australia, scientists have discovered the plant isoflavonoid, biliatreson, which can act as an exogenous toxin and provoke biliary tract atresia in various species. This substance is found in plants. The plant isoflavonoid, biliatreson has a devastating effect on the extrahepatic bile ducts of the larvae of the Danio rerio (Zebrafish) fish, which is a standard model system in biological research. Even without direct exposure to biliatreson, understanding the key mechanisms of bile duct damage can help identify toxins that may be associated with the development of biliary atresia in infants.[1]

Data on the genetic predisposition of patients to biliary atresia and its features are increasingly accumulating. However, the inheritance of this disease does not follow the usual Mendelian laws. Despite the fact that there are known examples of hereditary transmission of BA, the main cause of the disease does not have a direct genetic origin. The widespread occurrence of BA in some Asian regions may indicate a more frequent occurrence of genetic variants associated with asthma in these populations. However, it is impossible to exclude the influence of environmental factors such as nutrition, viral load, etc., as well as differences in diagnostic criteria used by Asian specialists.[1,31] When analyzing the genetic aspects of BA, it is necessary to take into account the results of studies performed with the participation of twins. In 2020, an international meta-analysis of clinical observations on the birth of twins, where one of them suffered from BA, analyzed 35 pairs of twins, including 19 monozygotic and 15 dizygotic pairs, as well as one pair with an unknown ge-

netic nature. The results showed that in only one dizygotic pair, BAwas diagnosed in both twins, whereas in the remaining 34 pairs, the disease was detected in only one of the twins (97.1% of discordant pairs). In a retrospective study conducted by Chinese scientists, 19 pairs of twins were identified, all of which had different BA status, including 8 monozygotic and 11 dizygotic pairs.[32] In the case when monozygotic twins have an identical genotype, but there is a discordance in the presence of a hereditary predisposition, this indicates that genetic factors are not the determining factors. The progression of the disease may vary between twins. On the other hand, if the disease is caused by an infectious or toxic factor, it is expected that it will affect both twins in the intrauterine period, which should lead to the same dynamics of the disease development, which does not correspond to what is observed in the case of discordance in twins.[1] In cases of toxic or infectious embryopathies, especially in monozygotic twins, there is a high frequency of concordance, reaching 80%. This indicates that in most cases both twins suffer from the same disease at the same time, which indicates a significant influence of genetic factors on the development of these pathologies.[1,30] In addition to genetic mutations, the phenotype can be influenced by epigenetic modifications that are transmitted according to non-classical laws of inheritance. Thus, even monozygotic twins with Alzheimer's disease (AD) may show differences in the manifestation of the disease, despite the same genotype, which indicates a possible role of epigenetic factors in the development of BA.

According to studies by various authors, the incidence of BA ranges from 5 to 32 cases per 100,000 newborns.[29,33] The disease is more often diagnosed in girls than in boys.[5] The first mention of this disease dates back to 1817 and belongs to *J. Burns*. He suggested that the appearance of jaundice and whitish stools in infants in the first months of life may be the result of an irreversible violation of the patency of the biliary tract, which poses a serious threat to the child's life. In 1852, *Ch. West* documented a case of the disease in a 13-week-old girl born on time from healthy parents. Despite the successful outcome of the birth, on the third day the child developed jaundice, which worsened every day, and his general condition worsened. *Zhou W.* emphasizes the importance of a comprehensive approach to the diagnosis of AF, combining traditional and modern ultrasound technologies with artificial intelligence to improve the accuracy and effectiveness of diagnosis.[23]

The etiology of BA is still not fully understood, and various hypotheses are being considered: viral, immune,[23] theory of congenital anomalies, genetic.[7,23] The question of the causes of BA is still debatable, and there are many works on its etiology in the world literature. Currently, international experts [33] distinguish two main anatomical types of biliary atresia: syndromic (approximately 10% of cases), which is accompanied by other congenital anomalies, such as polysplenia, asplenia, malformations of the abdominal cavity and heart (Situs inversus, pre-duodenal portal vein, gastrointestinal malformations), and non-syndromic (about 90% of cases), also known as isolated biliary atresia. There are two main classifications of this phenomenon: French, which includes 4 types, and Japanese / British, consisting of 3 types.[33-36] Within the framework of the French classification, type I is characterized by an isolated common bile duct and coincides with type 1 of the Japanese / British classification.[33] The French classification of type II is characterized by the presence of a cyst in the area of the liver gate and obstruction of the common bile duct, which coincides with type 2 in the Japanese / British classification.[33] In turn, type III according to the French classification is determined by obliteration of the left and right bile ducts, while maintaining the patency of the external bile ducts (gallbladder, cystic duct, hepatic duct and choledochus), which corresponds to type 3 in the Japanese / British classification system. Type IV BA is characterized by obstruc-

tion of all external bile ducts while maintaining the patency of the intrahepatic ducts. In the Japanese-British classification, this form is classified as type 3. The effectiveness of treatment in this case is determined by the type of BA.[33,35,36] To date, it is not possible to diagnose AD in the prenatal period with sufficient accuracy and information.[37,38] Diagnosis of biliary atresia is a difficult task, since a single conclusion about the presence of pathology cannot be made based on only one research method. In children with asthma, physical examination may reveal jaundice, acolic stools, and enlarged liver and spleen. However, the manifestation of specific symptoms varies depending on the age of the child. For the early diagnosis of BA, "stool color chart" were created in Japan, which are focused on the color of the stool and are widely used. To diagnose BA, a complex of studies is carried out: general and biochemical blood analysis, coagulogram, determine the spectrum of amino acids and acylcarnitines, the level of oxysterols, the spectrum of bile acids in urine, the concentration of lactate in the blood on an empty stomach and 20 minutes after eating, as well as the hormonal profile of the blood. A distinctive feature of cholestasis in the differential diagnosis of asthma from neonatal hepatitis is an increased level of gamma-glutamyltranspeptidase (GGTP). In children with asthma, the concentration of GGT is significantly higher (902.7 mmol/l) compared with children suffering from other cholestatic liver diseases (263/2 mmol/l). A study by *Tang et al* [39] showed that an increase in GGT levels above 300 mmol/L has a high specificity (98%) in the differential diagnosis of asthma from neonatal hepatitis, but its sensitivity is only 38%. Tan concludes that the ratio of GGT to AST above 2 indicates a high probability of biliary tract atresia and requires additional examination to confirm the diagnosis. An important diagnostic indicator is the relationship between GGT levels and age. The study by *Chen et al* notes that for the assessment of cholestasis by the level of GGT, the most optimal age is the period up to 120 days. In newborns aged 31 to 60 days, the diagnosis of asthma using GGT levels (more than 268 mmol/L) demonstrates high sensitivity (80.5%) and specificity (75.6%), which leads to a diagnostic accuracy of 79.1%. For older age groups (61-90 days), the recommended limit for GGT is 303 mmol/l, for 91-121 days – 298 mmol/l, and for children older than 121 days – 252 mmol/l. It is important to note that data from foreign studies may show a different picture of GGT levels for different age categories. In their study, *Lyu et al*[40] revealed a difference in optimal GGT levels in BA depending on age. For children younger than 4 weeks, the optimal GGT index is 150 mmol/l, at the age of 4 to 8 weeks this indicator rises to more than 250 mmol/l, and in children older than 8 weeks it reaches 300 mmol/l. Laboratory analysis data turn out to be an essential factor in the diagnosis of BA. Ultrasound diagnostics using expert-level devices has high information content and physiological safety in the study of the hepatobiliary system, without the need for preliminary patient training. A distinctive feature of this method is its non-invasiveness, painlessness, atraumatism and absence of contraindications to use.[41] During the newborn period, the diagnosis of biliary atresia is based on certain ultrasound features.[42] These include: the absence of a gallbladder or its unexpressed lumen, the size of the gallbladder not exceeding 19 mm, the absence of its contractile activity after eating, as well as the presence of a fibrous formation (fibrous triangle) in the area of the liver gate. In the case of BA, there is an increase in the ratio of the diameter of the portal vein to the diameter of the hepatic artery, and poly-splice, pre-duodenal portal vein, and situs inversusmay also occur. However, these ultrasound signs are rarely combined in one case. For example, in the third type, the gallbladder may be clearly visible, while in the second type, a cyst with anechoic filler may be found in the area of the hepatic gate. Studies have shown that the sensitivity of the ultrasound method varies from 83% to 100%, and the specificity ranges from

71% to 100%. The diagnostic arsenal also includes radioisotope testing and nuclear magnetic resonance imaging. However, none of these methods is absolutely accurate and cannot guarantee 100% effectiveness. Even with the use of all the listed diagnostic methods, it is not possible to exclude the need for laparoscopic revision of the liver gate and intraoperative cholangiography.[33] However, *Anouti et al*. believe that laparoscopy, unlike biopsy, does not provide information about the patency of the bile ducts and diagnosis of biliary atresia by laparoscopy is impossible. During hepatobiliary scintigraphy, in which technetium-labeled iminodiacetic acid derivatives are used,[23] the movement of bile with radiopharmaceutical (RFP) into the duodenum is analyzed. However, this method is difficult to interpret, as noted by *Wang et al.* and can only be effective in combination with other diagnostic procedures. The sensitivity of the method varies from 84% to 100%, and its specificity ranges from 34% to 93%. If noninvasive methods do not allow the diagnosis of BA, especially in the presence of a gallbladder and an acholic stool, intraoperative cholangiography is required. Pathomorphological analysis of liver biopsy is the most accurate and sensitive method for early diagnosis of biliary atresia, which is critically important for successful surgical intervention. Many researchers agree with this position.[35] Researchers *Liuet al.* 19 patients with biliary atresia (mean age 64 ± 18 years) were examinedusing various diagnostic techniques. The diagnostic accuracy of these methods was: liver biopsy – 96.9%; clinical examination – 70.8%, ultrasound scan – 69.2%, hepatobiliary scintigraphy – 58.5% and liver enzyme analysis – 50.8%. The authors of the study claim that percutaneous liver biopsy has a high diagnostic value not only in the diagnosis of biliary atresia, but also in the detection of other cholestatic liver diseases. Diagnosis with high accuracy is possible with sufficient quality of the liver biopsy. *Anouti et al*. It has been proven that percutaneous liver biopsy has diagnostic accuracy only if there are at least 5-7 portal tracts in the sample. In the case of asthma, the degree of morphological changes in the liver in children correlates with their age. At the age of one month, children showed mild manifestations of cholestasis, bile duct proliferation, and fibrosis in liver biopsies, but by the age of three months, these signs became more pronounced in all children. According to *Davenport M et al*., histological examination plays a key role in the diagnosis of BA, as in 87% (27 out of 31) patients, histological criteria reliably confirmed the diagnosis. The differential diagnosis of biliary atresia includes a distinction from other neonatal cholestases, such as Alagille syndrome, Byler's disease, Karoli syndrome, alpha-1-antitrypsin deficiency, tyrosinemia, Niemann-Pick type C disease, and others.[33,36] To accurately identify the etiology and exclude a wide range of metabolic and endocrine disorders manifested by cholestasis, panels of molecular genetic studies are conducted. Surgical treatment of biliary atresia was first undertaken by *J. B. Holmes* in 1916. It was he who proposed the classification of this disease into "correctable" and "uncorrectable" types. The first successful operations in the "correctable" type of asthma, which showed the effectiveness of surgical intervention, were presented by *W. E. Ladd* in 1928 in the prestigious edition of the American Medical Journal. The results of 11 successful operations led to the conclusion that the clinical and laboratory symptoms of the disease regressed during surgical treatment.[7,23] Despite numerous subsequent attempts at surgical intervention, according to *Zhou W*., out of 147 operations, only 25 allowed to create a functionally complete portoduodenoanastomosis, which in 13 cases had a positive therapeutic effect. The patients had stool staining, decreased jaundice, and decreased bilirubin levels. However, the positive effect proved to be short-lived, and as a result, all children experienced a recurrence of cholestasis, which progressed to biliary cirrhosis, which ended in death.[23]

The variation in estimates of life expectancy in the presence of a native liver

varies among European and Asian authors. European researchers cite data on a 5-year survival rate ranging from 32 to 55%, while Asian authors show higher rates ranging from 60 to 78%. After the 5-year milestone, the survival rate of children with native liver is significantly reduced. In particular, the 10-year survival rate is estimated at 25-33%, and the 20-year survival rate is 10-20%. There is a known case in the medical literature of the longest catamnestic follow-up of a patient with biliary BA, conducted by *Professor Chardot* from France, which was 30 years.[33] There are many publications in the world and Russian scientific literature on the diagnosis and treatment of BA. BA is a multicomponent disease that requires highly specialized treatment, and centers with more experience in treating this pathology show better results. The study of foreign and Russian studies indicates that the life expectancy of children with congenital biliary atresia and preserved liver is determined by a number of factors: timely detection of pathology, the age of the patient at the time of surgery, the severity of liver fibrosis and obliteration of the intrahepatic bile ducts, the number of working ducts, the clinical form and type of asthma (syndromic or non-syndromic), the presence of episodes of ascending cholangitis and bleeding from the gastrointestinal tract after surgery, as well as the qualifications of the surgeon and the clinic's experience in treating children with this disease. Despite significant progress, a number of issues remain open. Scientists have not yet come to a unified theory about the occurrence of BA, and the optimal duration of surgery is still being debated. In addition, clear prognostic criteria based on biochemical blood parameters have not been developed.

The main symptoms of the BA are manifested in the form of jaundice, white stools and dark urine in newborns born on time and corresponding to their gestational age according to anthropometric indicators.[14,33,43] In the initial stage of the disease, hepatosplenomegaly is usually not observed, however, with the progression of BA and the development of portal hypertension (PH), it can occur. In infants with bilirubinemia, jaundice appears on the 2nd - 3rd day of life, after which its intensity decreases, and by the end of the first or second week of life, it increases. At the same time, about 60% of full-term and 80% of premature babies show symptoms of jaundice during the first week of life. In this regard, this manifestation of the disease is often interpreted as physiological jaundice or jaundice caused by breastfeeding. Acholia of the stool is usually a characteristic sign of congenital acholia, but its appearance does not always coincide with the birth of a child. Most often, it is noted after the discharge of meconium, when the baby is already at home. This circumstance creates difficulties for an accurate assessment of the stool condition by a neonatologist, since parents do not always manage to correctly determine the normal color of the newborn's stool. Screening programs using a newborn stool chart have already been implemented in a number of countries.[5] The main goal of these programs is to help parents correctly interpret the color of their child's stool and consult a doctor in a timely manner if necessary.[5,44] Stool chart contain information about normal shades and those that may indicate pathology.[5] The introduction of screening programs based on the analysis of the newborn's stool chart contributed to an increase in the percentage of early diagnosis.[43] Nevertheless, despite the successes achieved the problem of delayed diagnosis remains relevant at the global level. Vitamin K-deficient coagulopathy is a serious threat in asthma, and hemorrhagic syndrome, including intracranial hemorrhages, may be the first sign of the disease and a reason for examining a child. This complication is not only life-threatening when it occurs, but can also have long-term negative consequences for the child's health, even after transplantation. The development of hemorrhagic syndrome is caused by a violation of the outflow of bile into the intestine, which is characteristic of cholestatic liver diseases. It is important

to note that the absorption of fat-soluble vitamins, including vitamin K, occurs only in the presence of bile in the intestine. Vitamin K, in turn, plays a key role in the synthesis of blood clotting factors II, VII, IX and X produced by the liver.

Early and characteristic signs of cholestaticliver diseases, including BA, include an increase in the level of direct bilirubin fraction. At the same time, other biochemical parameters of cholestasis, for example, γ-glutamyltranspeptidase (GGT), alkaline phosphatase (ALP), cholesterol, bile acids and transaminases (ALT and AST), in newborns in the first months of life may not exceed the age norm. Markers of protein-synthetic liver function, such as albumin and fibrinogen, remain stable in the first months of life until liver failure develops. Currently, screening programs aimed at early diagnosis of liver diseases are based on the determination of both bilirubin fractions: total and direct, as well as on the analysis of their relationship to each other. Previously, the diagnosis of cholestasis was based on an analysis of the ratio of direct bilirubin to total, and if it exceeded 20%, cholestatic liver disease was diagnosed. However, modern studies show that cholestatic liver diseases, including neonatal jaundice, can be diagnosed with a high degree of confidence already in the first two weeks of life at a concentration of direct bilirubin above 17.1 mmol/l.[45] The study of ultrasound manifestations of Alzheimer's disease (AD) is of particular importance, since ultrasound is not only informative, but also a widely available imaging method. The key ultrasound signs of asthma include changes in the structure of the gallbladder (gall bladder), manifested in the form of its non-manifestation or visualization in the form of cords on ultrasound.

The absence of a reaction of the digestive tract to food intake and choleretics, as well as the presence of a "hyperechoic strain" are characteristic features of BA. One of the most striking ultrasound signs of the disease is the symptom of a "triangular scar", which is visualized as a hyperechoic seal located above the trunk of the portal vein. Some researchers also consider enlargement of the diameter of the hepatic artery as an ultrasound sign of asthma. In the early postnatal period, before the signs of portal hypertension appear, pathological changes in the liver and spleen, such as an increase in size and modification of the echostructure, are usually not observed. Magnetic resonance imaging and hepatobiliary scintigraphy, like other methods of imaging organs of the hepatobiliary system, are not widely used because they are invasive procedures, and their sensitivity and specificity remain extremely low.[46]

The diagnostic significance of liver biopsy is due to the fact that it allows to detect cholestasis, proliferation of bile ducts and giant cell transformation of hepatocytes. In addition, a liver biopsy makes it possible to determine the degree of fibrosis in this case. The diagnosis of BA is established on the basis of a morphological examination of a biopsy of the liver and external bile ducts, as well as upon detection of obliteration of the common bile duct.[7] Kasai surgery, or portoenterostomy, is considered the gold standard of BA treatment, it was developed by *Professor Morio Kasai* in the 1950s. The essence of surgery is to eliminate the blocked bile ducts and create a new connection between the duodenum and the bile ducts, which allows bile to flow freely through them again. Despite this, the effectiveness of the operation can vary significantly, and the factors influencing its success are still not fully understood. In the postoperative period, a number of complications may occur after Kasai surgery, such as bacterial cholangitis, dilation of the intrahepatic bile ducts, renal failure and hepatopulmonary syndrome, as well as progression of liver fibrosis. After surgery, 70% of children with biliary agenesis have increased liver fibrosis, which can later develop into cirrhosis of the liver. Cirrhosis of the liver, in turn, provokes portal hypertension and liver failure. The main motive for liver transplantation in children with BA is complications caused by cirrhosis. Liver biopsy is considered

the most reliable way to determine the degree of fibrosis. This procedure is invasive and carries the risk of complications, including pain, blood loss, and decreased blood pressure.[47]

Diagnosis of liver fibrosis by liver biopsy is difficult due to the need for general anesthesia, which precludes the possibility of repeated studies and dynamic monitoring of disease progression or regression.[7,48] Some studies have revealed certain disadvantages of liver biopsy, among which one can note the inaccuracy of the choice of biopsy material, as well as the subjectivity of interpretation and evaluation of histological data.[6,7] In the diagnosis of chronic liver diseases in adults, such as alcoholic liver disease, viral hepatitis B and C, and non-alcoholic fatty liver disease, doctors use non-invasive methods to determine the degree of fibrosis, as recommended by clinical guidelines.[7,49] To date, there are no such recommendations for determining the degree of liver fibrosis in children with chronic liver diseases.[7]

Liver fibrosis in adult patients with chronic liver diseases is often assessed using the APRI index (the ratio of aspartate aminotransferase activity to platelet count). This diagnostic method is considered simple and does not require invasive interventions.[7] Nevertheless, the use of the APRI index for the diagnosis of fibrosis in children with chronic viral hepatitis B, cystic fibrosis, and bronchial obstructive BA does not yet have clear recommendations.[19] Currently, visual diagnostic methods, including Doppler ultrasound, are being actively developed to determine the degree of liver damage by fibrosis and cirrhosis in chronic diseases.[7] Studies show that ultrasound signs, such as splenomegaly, a slight increase or decrease in the size of the liver lobes, an uneven contour, increased echogenicity of the parenchyma with an uneven structure, narrowing of the hepatic veins, dilation of the portal and splenic veins, as well as an increase in the index of resistance of the liver arteries, have high diagnostic value in predicting cirrhosis and portal hypertension in patients with chronic liver diseases.[7,10] However, the research was focused on adults and older children, which highlights the need to find non-invasive biomarkers of liver fibrosis and cirrhosis in toddlers, especially in patients with biliary atresia, for earlier diagnosis and intervention.

The success of Kasai's surgery is determined by such indicators as the appearance of stained stools, a decrease in jaundice, and a decrease in total bilirubin (T) to 34 micromol/L within 3-6 months after the intervention. In the long term, the criterion of success is survival with the preservation of a functional liver. However, data from different authors indicate a different effectiveness of the operation, which varies from 36% to 61% in European clinics, while according to *Masaki Nio*, the effectiveness of PE in Japan reaches 87.2%. Despite a significant amount of research conducted in recent decades, the mechanisms influencing the effectiveness of surgery and the prognosis of survival while preserving the native liver are still not fully elucidated.[25] Currently, the authors identify a number of factors affecting the outcome of treatment, which can be divided into modifiable and unmodifiable. The first group includes the patient's age at the time of KPE, the surgeon's professional experience,[17] and the use of steroid drugs in the postoperative period.[50] Unmodifiable factors include the type of biliary atresia, the presence of concomitant developmental abnormalities, indicators of biochemical markers, as well as histological examination data from a liver biopsy: the degree of fibrosis, inflammatory changes, and the diameter of the bile ducts.[14,50]

The genetic characteristics of each patient can significantly correlate with the severity of the disease, however, despite the variety of manifestations of the disease, research on the study of genetic factors affecting the results of surgical treatment, for example, Kasai portoenterostomy, is still limited.[1] Some scientists have suggested that genes such as A1AT, JAG1, and CFTR may influence the outcome of surgery.[21,48-50]

An inherited disease caused by alpha-1-antitrypsin deficiency manifests

itself as an autosomal recessive genetic disorder (genotype ZZ according to the A1AT gene) and is accompanied by pathological changes. In studies conducted with the participation of children,[1] it was revealed that the pathological alleles Z, S and others (in the heterozygous variant) are found more often in patients with chronic liver diseases, among which diseases such as Budd-Chiari disease (n = 67) are distinguished, compared with the data the general population. Children with asthma and the presence of these genotypes were more likely to require liver transplantation compared with children with asthma and having a normal MM genotype.[1] In Thailand, researchers conducted a WES analysis of DNA obtained from liver biopsy samples from 20 patients with intrahepatic jaundice after portoenterostomy.[1] As a result, seven patients had complete disappearance of jaundice after surgery, three had partial improvement, while ten patients had no improvement in portoenterostomy. 13 rare mutations in 9 genes associated with known hereditary diseases have been identified in patients with BA. Among them are cholestatic, although no clinical manifestations have been reported. The list includes: JAG1 (Alajille syndrome), MYO5B (congenital microvilli atrophy/progressive familial cholestasis type 6), ABCB11 (familial intrahepatic cholestasis type 2), ABCC2 (Dubin–Jones syndrome), ERCC4 (Fanconi anemia), KCNH1 (Zimmerman–Laband syndrome), MLL2 (Kabuki syndrome), RFX6 (Mitchell–Ray syndrome) and UG1A1 (Crigler–Najjar syndrome type I). Scientists believe that BA and other liver diseases may have the same causes and course. The detection of such links indicates the severity of the condition and an unfavorable prognosis for patients with asthma whose liver is healthy.[51]

9% of patients with BA, out of 102 examined, had a missense mutation in the JAG1 gene, but the classic signs of Alagille syndrome were not diagnosed. The researchers emphasize that children with this genetic variant have a less favorable prognosis and course of the disease. At the same time, recent studies indicate that Alagille syndrome (AGS) can manifest itself as clinical symptoms of BA: five children who were diagnosed with BA at an early age and pathogenic variants in the JAG1 gene were found to have developed a symptom complex characteristic of AGS by the age of three.[1,26]

Over the past decade, a lot of data has been accumulated on the compensatory mechanisms of the liver in cholestasis, which are associated with the regulation of hepatocyte transporters (BSEP, MDR1, MDR3, OSTb) and nuclear bile acid receptors (FXR, PXR, CAR).[1,52] The liver's high adaptivity to the accumulation of bile acids allows it to effectively cope with this condition. In children with normal development, a genetically determined deficiency of these receptors does not lead to clinical manifestations due to the presence of compensatory mechanisms.[1] However, in cholestatic diseases, including biliary atony, such changes can act as an additional factor contributing to the progression of pathology.[1] Normally, hepatocytes are protected from bile acid toxicity due to the work of hepatocyte transporters, which remove them through the BSEP transporter, and the biliary epithelium due to FIC1 and MDR3. Based on this, studies have been conducted to determine the expression level of genes encoding liver nuclear factors and hepatocellular transporters as potential predictors of liver failure in children with BA.

Studies have shown that in patients with an unfavorable course of liver failure, the expression of the PXR and CAR receptor genes in the liver is significantly lower than in patients with a favorable outcome.[1] In 5 out of 6 patients with decreased expression of both genes, liver transplantation was required before they reached one year of age (at the age of 7 to 11 months). Earlier studies on rats with the PXR gene turned off showed that they had significantly higher liver damage due to the accumulation of bile acids compared with the control group.[1] It is assumed that the decrease in CAR and PXR levels in humans may be due to both a genetic predisposition and in-

flammatory diseases.[1] It has been studied that the nuclear receptors of LC regulate the homeostasis of bile acids by interacting with them and penetrating into the cell nucleus. Inside the nucleus, they decrease the activity of genes responsible for the synthesis and reabsorption of LC, but at the same time enhance the expression of genes encoding transporters BSEP, MRP4 and OSTa-OSTb, which push LC out of the hepatocyte.[1,31,52]

The WES-analysis study was conducted to identify genetic mutations that are more common in children with biliary atony who require early liver transplantation due to the inefficiency of KPE, compared with children whose liver is functioning normally. As a result of the analysis of 98 children who needed early liver transplantation, it was found that the p.A934T variant in the ABCB4 gene was more common than in the group of 97 children with a normally functioning liver after portoenterostomy. A decrease in the activity of the ABCB4 gene responsible for the synthesis of MDR3 leads to a decrease in the content of phospholipids in bile, which can provoke damage to cholangiocytes due to the action of bile acids.

A study conducted in 2020 using full-transcriptome mRNA sequencing of 25 liver samples from patients with Alzheimer's disease (AD) identified two potential markers for predicting the progression of PE: MMP7 and PCK1. MMP7 is an enzyme that participates in the restructuring of the extracellular matrix during the development of liver fibrosis, and PCK1, despite its well-known role in gluconeogenesis, it has not yet been fully studied in the context of the development of BA. A significant increase in the expression of the MMP7 gene was observed in patients with incurable jaundice who underwent KPE and in patients with end-stage liver failure.[1] In contrast, patients with a favorable KPE outcome showed increased expression of the PCK1 gene, while patients with an unfavorable KPE prognosis showed a marked decrease.[1] Therefore, the study of gene expression models in liver and biliary tract tissues can become the basis for the creation of biomarkers predicting the outcome of KPE, which will pave the way for the development of new therapeutic approaches to BA.[1]

The pathogenesis of BA maybe caused by epigenetic changes, including DNA methylation, histone modifications, non-coding RNA expression, and other similar processes.[1] Studies have shown that in the cells of the bile ducts of patients with asthma, there is a significant decrease in the level of DNA methylation compared with patients suffering from other types of cholestatic liver diseases.[1,53] Such a decrease can lead to activation of the IFNy signaling pathway and, as a result, to the development of inflammatory processes.[1] Various epigenetic changes in peripheral leukocytes, such as CD4+ T cells, have already been noted in individual patients with bronchial asthma.[1,18,54] It was revealed that the platelet growth factor A gene underwent hypomethylation, and increased (over expressed) PDGFA production in liver biopsies of patients probably indicates its significant role in this process. The mechanism of BA development [1] is associated with the action of PDGF family proteins, which stimulate the processes of proliferation and fibrosis in various organs. In this context, the rs9690350 (G > C) variant in the PDGFA gene correlates with an increased probability of developing BA in 506 patients, which was revealed when compared with a group of 1,473 healthy people. In patients with Alzheimer's disease (AD), there are differences in the expression of certain microRNAs in the liver compared with healthy people. For example, mir-29b and mir-142-5p microRNAs show increased activity in the liver of patients with asthma, and their targets are the DNMT1 and DNMT3 genes encoding key enzymes involved in DNA methylation.[1] At the same time, the expression of mir-145-5p microRNA, which regulates the ADD3 gene, is reduced in the liver tissues of some patients with BA.[1,55]

The Kasai surgical procedure hepatoportoenterostomy, proposed in 1955, is a method of treating asthma aimed at preserving liver functionality and delay-

ing the need for transplantation in children. However, until now, little is known about the parameters that determine the effectiveness of this operation and the life expectancy of patients with preserved liver. The genetic characteristics of each patient, as well as the activity levels of various genes in liver and bile duct tissues, can serve as prognostic biomarkers, but further scientific research is required to confirm them.

Discussion

BA is a complex disease with a high risk of progression to fibrosis and cirrhosis of the liver, despite modern approaches to diagnosis and treatment. Current data confirm that an early Kasai procedure significantly increases the likelihood of restoring biliary outflow. However, a number of studies have shown significant variability in outcomes even during surgery in the first 30-45 days of life, which indicates the presence of additional prognostic factors, including the morphological features of the ducts and the degree of hepatic fibrosis at the time of the intervention.[1]

There are contradictions in the literature regarding the role of preoperative diagnosis. Some authors emphasize the high informative value of ultrasound and serial biochemical tests for early detection of BA, while others point to the low specificity of these methods and the need for invasive confirmation of the diagnosis (liver biopsy, cholangiography). This highlights the importance of developing standardized screening protocols and a multidisciplinary approach to patient assessment.[3,6]

Long-term outcomes remain problematic. Even after successful Kasai, a significant proportion of patients demonstrate the progression of fibrosis, cholestatic complications, and the need for liver transplantation. Literature data on the use of immunomodulatory therapy or anti-inflammatory strategies after surgery are still limited to small cohorts and different surveillance protocols, which makes it difficult to conclude the actual effectiveness of these approaches.

Thus, current data indicate the need for an integrated approach, including early diagnosis, individual choice of surgical tactics, and standardized postoperative follow-up schemes. To improve the prognosis, it is necessary to conduct multicenter studies with sufficient statistical power aimed at identifying predictors of a successful outcome and developing optimized algorithms for managing patients with BA.[15]

Limitations. The review is limited to retrospective and small cohort studies with different methodologies, which makes it difficult to compare data. Not all studies included long-term outcomes, and publications were reviewed only in English and Russian, which could exclude relevant studies.

What's Known? Biliary atresia is a rare neonatal disease causing progressive liver fibrosis and cirrhosis. Early diagnosis and Kasai portoenterostomy improve bile flow, but outcomes vary with age and liver damage. Standardized early detection and management protocols are lacking; many patients eventually require liver transplantation.

What's New? This review highlights current gaps in early diagnosis, heterogeneity of treatment outcomes, and long-term prognosis in biliary atresia. It emphasizes the need for standardized screening, unified management protocols, and further multicenter studies to improve patient outcomes.

Conclusion

Biliary atresia remains a serious neonatal liver disease with variable outcomes despite surgical intervention. Early diagnosis and timely Kasai portoenterostomy improve prognosis, but long-term complications and need for liver transplantation persist. Standardized diagnostic and management protocols, along with multicenter research, are essential to optimize care.

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К 90–ЛЕТИЮ ДОЦЕНТА УРАШЕВА С. Т.

Урашев Сапар Темирбаевич родился 2 июля 1933 года в поселке Чапаево Западно-Казахстанской области. После окончания Уральской фельдшерско-акушерской школы поступил в Алма-Атинский государственный медицинский институт. В 1958 году с отличием закончил АГМИ и был оставлен аспирантом кафедры госпитальной хирургии, возглавляемой профессором М.И. Брякиным. В 1961 году – по конкурсу на ученом Совете был избран на должность ассистента кафедры госпитальной хирургии.

Урашев С.Т. защитил кандидатскую диссертацию на тему: «Особенности изменения гемодинамики и оксигенации крови при право- и левосторонних чресплевральных операциях».

Будучи ассистентом кафедры госпитальной хирургии лечебного факультета АГМИ, с 1961 года по 1967 год заведовал общим хирургическим отделением больницы скорой медицинской помощи г.Алма-Аты, совмещая учебно-педагогическую деятельность с работой в системе практического здравоохранения.

Урашев С.Т в 1967 году по конкурсу избирается на должность доцента родной кафедры. Сапар Темирбаевич – автор 57 печатных трудов, 35 из них посвящены экспериментальным клиническим исследованиям по сравнительной оценке лечения терминальных состояний методом аутореинфузии с внутриартериальным нагнетанием и вспомогательным искусственным кровообращением аппаратами ИСЛ-2 и ИСЛ-3, остальные научные работы посвящены актуальным вопросам торакальной и абдоминальной неотложной и плановой хирургии.

Доцент Урашев С.Т. был хирургом широкого диапазона, владеющим оперативными вмешательствами на органах грудной и брюшной полости. Выполнял операции при сочетанной черепно-мозговой и спинальной травме, травмах магистральных сосудов, при переломах конечностей.

Несмотря на большую занятость клинической и учебно-педагогической работой, он выполнял изначимую общественно-политическую работу в институте.Благодаря природному орагнизаторскому таланту и высоким моральным качествам, гуманизму 11 лет избирался председателем профсоюзного комитета АГМИ. Урашев С.Т. в течение многих лет работал секретарем первичной партийной организации лечебного факультета.

При создании подготовительного отделения при АГМИ, для поступления в медицинский вуз, первым деканом был доцент – Урашев С.Т. Вместе со своим учителем профессором Брякиным М.И., участвовал в организации и проведении съездов хирургов Казахстана и Средней Азии, Пленумов правления Республиканского общества, где выступал с основными докладами, в прениях по программным докладам

Сапар Темирбаевич был высококвалифицированным педагогом, лекции и практические занятия проводил на высоком учебно-методическом уровне с демонстрацией больных по теме занятий.

С 1982 года доцент Урашев С.Т. работал на кафедре хирургических болезней лечебного, стоматологического

факультетов, возглавляемой профессором Ш.Н. Абдуллаевым. Параллельно с педагогической работой, клиническая работа занимала значительную часть его времени: консультировал службу экстренной хирургии ЦГКБ, являлся наставником молодых хирургов.

Доцент Урашев С.Т. заслуженно пользовался авторитетом и уважением среди студентов, сотрудников кафедры и больницы, любовью пациентов.

За заслуги в профессиональной и научно-педагогической деятельности С.Т.Урашев награжден медалью «За доблестный труд», государственным знаком «Отличник здравоохранения», почетными грамотами, имеет ряд благодарностей от правительства Республики, руководства медицинского университета.

Ушёл из жизни Сапар Темирбаевич 18 февраля 2004 года.

Дело его жизни продолжают дети и внуки. Память о благородном человеке, рыцаре медицины навсегда сохранится в сердцах его сподвижников, коллег и учеников.

Проф. Ибадильдин А.С.
Врач Аталыков Б.