Pathogenesis and Treatment Opportunities for Biliary Atresia

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Biliary atresia is a devastating liver disease of the newborn with an unpredictable outcome occurring in about 1 in 14,000 live births. The first clinical symptoms of this rare disease are difficult to distinguish from the frequent and mostly benign neonatal (physiologic) jaundice. Therefore, diagnosis and surgical therapy often occur late, reducing the chance for a good outcome. Despite successful surgery, fibrosis of the liver often becomes an ongoing process and results in cirrhosis in the majority of patients. As a consequence, biliary atresia is the most frequent indication for liver transplantation in childhood.

The long and eventful history of this disease is a story of innovative ideas and promising therapeutic options as well as frustrating curative attempts against an etiologically incomprehensible entity. Nowadays, interdisciplinary and international initiatives enable experts to coordinate their individual competence, taking up the challenge to uncover the cause and to improve the outcome of patients who have biliary atresia.

Pathogenesis

History and classification

More than 100 years ago, the observation of destruction and obliteration of extrahepatic bile ducts with progression to biliary cirrhosis was first described.
in children undergoing autopsies [1,2]. This observation had no impact or any therapeutic consequences, however. In the early twentieth century, the obstruction of the common bile duct was considered to be one reason for prolonged neonatal jaundice and cholestasis in newborns. The disease was named “congenital extrahepatic biliary atresia,” and for the first time a classification strategy was proposed: patients presenting with an isolated distal and short atresia of the common bile duct were considered surgically curable if the proximal ducts were still patent and wide enough to be drained by a biliodigestive anastomosis. Unfortunately, most of the patients remained surgically not curable, and their outcome was death within the first 2 years of life. Another surgical approach was developed at the end of the 1950s, when Kasai introduced portoenterostomy to “correct the uncorrectable” [3]. Through this innovative technique, more knowledge of the diversity of changes along the extrahepatic biliary tree was gained. During the following years, more classifications and sophisticated subgroups were defined to improve the understanding of biliary atresia [4,5]. In 1972, Landing [6] theorized that biliary atresia might be an ongoing inflammatory process induced by an external agent such as viral infection. From then on, etiologic possibilities were that biliary atresia is a congenital morphogenic disorder or that biliary atresia is an acquired disease. As a consequence, the attribute “congenital” was dropped, and the term extrahepatic biliary atresia became widely used.

Despite Kasai’s successful procedure with initially good bile flow, several patients presented with continuous deterioration of the liver function. This phenomenon was the turning point in realizing that biliary atresia is an ongoing inflammatory process of the extra- and the intrahepatic bile ducts with an unpredictable clinical course. Therefore the limiting factor for the outcome in patients who have biliary atresia is related not only to the timely removal of atretic extrahepatic bile ducts and the surgical restoration of bile flow but rather is an autonomous and probably self-limiting process of intrahepatic inflammation. To encompass this spectrum, the disease is usually referred to as “biliary atresia,” which includes all types of destructive obliteration along the whole bile duct system. Hence, the challenge for the future and a potential key for a new and useful classification is to uncover the still unknown pathogenic mechanisms of biliary atresia.

Defective morphogenesis

With regard to the unknown origin, the onset of morphologic or functional changes in patients who have biliary atresia is of crucial interest. Antenatal detection of prestenotic cystic dilatation of the common bile duct has been reported in rare cases [7,8]. In these patients, biliary atresia is not necessarily combined with other anomalies, such as polysplenia, a preduodenal portal vein, and an interrupted inferior portal vein, which are summarized by the term “biliary
ataresia–splenic malformation” [9] or various congenital laterality defects. It is still unclear whether these patients form a subgroup in which a defective embryogenesis of the biliary tree might play a causative role. Therefore, whether the so-called “ductal plate malformation,” which is defined as the persistence or lack of remodeling of the embryonic ductal plate [10], relates to the pathogenesis of biliary atresia and several other diseases of the intrahepatic bile ducts remains a matter of discussion. Studies of biliary remnants in patients who had biliary atresia revealed morphologic similarities with the remodeling process of the ductal plate in fetuses with a gestational age between 11 and 13 weeks [11,12].

A recent study exploring the molecular basis for biliary atresia found a liver gene expression profile that differentiates patients who have biliary atresia from patients who have other cholestatic liver diseases [13]. A similar specific approach was applied to a different group of patients and found a coordinate expression of regulatory genes that distinguished the so-called “embryonic and perinatal forms of biliary atresia” [14]. These studies provide preliminary results of a new and promising research direction. Before continuing these important basic studies, which also focus on the morphogenetic aspect, it is necessary to generate a better definition for etiologically relevant terms, such as “embryonic,” “syndromic,” “congenital,” “acquired,” “perinatal,” and other forms of biliary atresia [15].

Viral infection

In the early 1970s, Landing [16] and Hays [17] proposed that a single, probably infective, cause induces inflammation of the intra- and extrahepatic bile ducts or the liver parenchyma, clinically manifesting as neonatal hepatitis, choledochal cyst, or biliary atresia. This hypothesis was the starting point for several studies searching for hepatotropic viruses in patients who had biliary atresia. Starting in the 1980s, different viruses were sporadically found in patients who had biliary atresia, but the studies were inconclusive. A few years later, when the polymerase chain reaction (PCR) technique became routine, larger series of patients were tested. Within the last 10 years, many studies have been published focusing mainly on four specific viruses. Compiling the results from several studies, 34% (range, 0%–50%) of 50 liver biopsies were positive for cytomegalovirus [18–21], and 14% (range, 0%–55%) of 79 patients were positive for reovirus [22–25]. Rotavirus C was detected in 50% of 18 liver biopsies [23], and human papilloma virus was found in 16 of 18 patients [26]. It still remains unclear whether viruses are an important etiologic factor for biliary atresia. The main problems with these studies are threefold: first, patients who have biliary atresia are such a heterogeneous group that the number of biopsies performed in each series is too small. Second, all studies are restricted to one or two viruses; it would be much more effective to test all candidate hepatotropic viruses in a large series of liver biopsies. Third, the most important and overriding problem is the time at which samples are obtained for the PCR studies. Biopsies are taken when the disease
has already reached an advanced stage and the patients present with severe clinical symptoms. Therefore, it is impossible to distinguish, whether findings are a trace of an etiologically relevant process or simply represent an unrelated or secondary effect. The crucial point, and the dilemma in most clinical research programs addressing the viral etiology of biliary atresia, is that investigations begin too late in the disease course for viral causation to be determined.

**Immunologic factors**

The same problems exist in immunologic investigations in patients who have biliary atresia, who present with well-established disease and an ongoing inflammatory process. First, immunologic parameters were tested to evaluate whether they determine the outcome after Kasai’s procedure. Some factors, such as CD68 and intracellular adhesion molecule (ICAM)-1, seem to be related to the postoperative course [27]. Nevertheless, it is obvious that at the time of diagnosis livers of patients who have biliary atresia display a T-cell–mediated inflammation [28]. Several factors of this immunologic cascade have been described in these patients. Antigen-presenting cells, such as Kupffer’s cells, have been reported [29], as have CD4+ cells and natural killer cells [27], which differentiate into T-helper 1 or T-helper 2 cells (cellular or humoral-mediated immunity, respectively) [30]. Major histocompatibility complex class I and class II molecules, which are necessary to allow T cells recognize foreign antigens, have also been described [31,32], although their function in biliary atresia remains questionable [33]. Additionally, the expression of cell adhesion molecules (ICAM-1, vascular adhesion cell molecules, leukocyte factor antigen-1, nerve cell adhesion molecule), which are involved in leukocyte recruitment, is increased in biliary atresia [27,34]. Cytokines, such as interferon-α, tumor necrosis factor-β, and osteopontin, also play an important role in the signaling pathways of T-cell– and macrophage-mediated immune reaction and can be found in liver biopsies of patients who have biliary atresia [35,36].

Collectively, these data support the hypothesis that the ongoing inflammatory process in the liver of patients who have biliary atresia is closely related to T-cell activity and cytotoxicity. It remains unclear whether these observations are the result of any secondary effects or if the immune response is induced by a triggering agent that is etiologically relevant. Therefore, it is necessary to search for genomic signatures of biliary atresia. A study by Bezerra and colleagues [37] focusing on the inflammatory aspect revealed a predominant cluster of genes that regulate immunity and inflammatory processes in the liver of patients who have biliary atresia. The overexpression of osteopontin and interferon-γ matches the abovementioned findings and supports the theory of an inflammatory pathogenesis of biliary atresia. At this point, further studies are mandatory to extend the knowledge about the genetic background of the ongoing process in biliary atresia and to trace this back process to its origin.
Other mechanisms

Apart from these hypothetic approaches, several other factors may be involved in the genesis of biliary atresia. A population-based study from Sweden identified several risk factors that facilitate exogenous factors to induce the development of biliary atresia [38], but in contrast to other studies [39], seasonal clustering could not be found [40]. The observation of risk factors matches the two-hit theory from Schreiber and Kleinman [41], who speculated that a still unknown exogenous factor meets a genetically predisposed condition of the innate immune system, which is restricted to the perinatal period. Nevertheless, hereditary transmission of biliary atresia or any predisposing additional factor is not likely, because recurrence in siblings is rare, as is concordance in dizygotic and monozygotic twins [42].

Other potential pathogenetic mechanisms in biliary atresia have also been discussed. Ischemia-related biliary obstruction can be induced by a vasculopathy of the hepatic vessels, potentially associated with an autoimmune process. It is also possible that other nonviral agents, such as bacteria, toxins, or environmental factors are responsible for triggering inflammatory processes that finally lead to biliary atresia. No consistently evidence has been shown for this triggering as a mechanism of disease [43].

Animal models

If the pathogenesis of a disease cannot be elucidated in humans, it might be useful to simulate it in animals. In biliary atresia, numerous attempts have been made to occlude the extrahepatic bile ducts in different species or by infecting mice with reovirus. Those studies were helpful in investigating the consequences of artificially induced cholestasis but failed to simulate the dynamic pattern of developing biliary atresia [44]. In the early 1990s, Riepenhoff-Talty and colleagues [45] reported that newborn Balb/c-mice that were orally infected with rhesus rotavirus developed irreversible bile duct obstruction. This observation was the starting point for establishing a reproducible animal model for biliary atresia [46]. Further studies revealed that this model is based on the hepatotropic effect of rhesus rotavirus, which targets the biliary system during the immunologic gap when the immune system of newborn Balb/c-mice is immature. The virus seems to trigger a T-cell–mediated immune response independently from the virus load of the liver [47]. These observations were confirmed by an interesting study from Shivakumar and colleagues [48], who observed that interferon IFN-γ plays a key role in developing biliary atresia in Balb/c-mice. Despite remarkable similarities between the model and patients who have biliary atresia, it is not possible to relate the findings in mice directly to the human disease. Nevertheless, the pathogenesis of developing biliary atresia in Balb/c-mice is relatively clear. Descendants of nonimmunized mothers present postpartum with a short immunologic gap and are susceptible to a virus-triggered T-cell–mediated immune
response, finally leading to fibrotic obstruction of the bile ducts. The missing link in the pathogenetic cascade is the biologic basis for the localized atresia within the extrahepatic, but not the intrahepatic, bile ducts. Inflammatory reaction of the arterioles, which are potentially mediated by interferon and autoimmunity factors, may induce an ischemia-related fibrotic transformation of the extrahepatic bile ducts. This hypothesis matches a study in patients who had biliary atresia, which described arteriopathy from the trunk of the common hepatic artery to its peripheral branches supplying the entire biliary tree [49,50].

All these observations support the hypothesis that biliary atresia is an acquired disease and throw a new light on Perlmutter’s provocative speculation as to whether biliary atresia is a single disease or a phenomenon of superior pathogenic mechanism [51]. Therefore discovering more details of the pathogenesis of biliary atresia in the mouse model is a priority.

Treatment opportunities

The first therapeutic opportunities were restricted to patients who had the so-called “correctable” form of biliary atresia [52]. Therefore, the most patients were still incurable until Kasai’s portoenterostomy was introduced. This procedure was the first breakthrough in the treatment of patients who had biliary atresia. The second milestone was liver transplantation, which continues to be perfected. Today, surgical treatment is still the only approach, although the outcome of patients who have biliary atresia depends on multiple diagnostic and therapeutic factors and close interdisciplinary cooperation.

Diagnosis and Kasai’s procedure

The first hurdle with biliary atresia is to identify babies who have pathologic hyperbilirubinemia among the large number of newborns who present with common and uncomplicated jaundice. It is important to refer these patients to a pediatric hepatologist when the clinical signs of cholestasis persist longer than 2 weeks. The second hurdle is to exclude the most frequent diseases that also present with direct hyperbilirubinemia by using a reasonable diagnostic algorithm. Imaging and functional methods, such as ultrasound (the triangular cord sign [53]), MRI cholangiography [54], and hepatobiliary scintigraphy, are indispensable tools, but they are not accurate enough to exclude the presence of biliary atresia. The same is true for liver biopsies, which are helpful either to rule out several other liver diseases or to be consistent with an extrahepatic bile duct obstruction. If the bile duct obstruction cannot definitely be ruled out, the entire biliary tree must be visualized, because biliary atresia is still defined as fibrotic obstruction of the extrahepatic bile ducts. In pediatric centers where endoscopic retrograde cholangiopancreatography in babies is routine, the patency of the common bile duct can be shown by this less-invasive method, probably sparing
an unnecessary laparotomy. In all other cases, an open cholangiogram, which can also be performed by a minimally invasive approach, is necessary to confirm the diagnosis.

If the intraoperative cholangiogram reveals that the extrahepatic bile duct is partially or completely atretic, a portoenterostomy can be performed during the same operative procedure. The technical recommendations originating from Kasai’s first papers are still state of the art. Meticulous preparation of the duodenal ligament is necessary to identify the branches of the hepatic artery and the portal vein as well as the remnants of the hepatic ducts. The gallbladder must be dissected, and the remnants of the extrahepatic bile ducts are the guide to the fibrous cone in the porta hepatis. The original description of the Kasai procedure restricts the preparation of the porta hepatis to a central area, which is surrounded by the bifurcation of the portal vein [55]. Today, a much more extensive portal dissection is recommended to open as many small intrahepatic bile ducts as possible and to make better bile flow possible [56]. This change is the only variation of the original technique that is accepted worldwide as a new standard.

Numerous modifications of the original Kasai hepatic portojejunostomy version have been proposed, which can be summarized as total or partial diversion of a biliary conduit with or without intestinal valve formation. None of these variations proved to be beneficial, however, and most surgeons returned to the original procedure, using a 4- to 60-cm Roux-en-Y loop [57,58]. The portoenteral anastomosis must be performed so that the funnel-shaped end of the jejunal loop overrides the completely transected porta hepatis, so as to catch every drop of bile. From the surgical point of view, the preparation and the transection of the porta hepatis is as important as the perfect placement of the intestinal funnel.

The postoperative management after the Kasai procedure is a matter of ongoing discussion. The benefit of peri-, postoperative, and long-term antibiotic prophylaxis is indisputable, although the drug used, its administration, and the duration of therapy, vary widely [57]. Long-term treatment with choleretic agents and administration of fat-soluble vitamins are widely used; a high-caloric formula with medium-chain triglyceride oil is recommended [42]. Positive effects on the outcome of postoperative treatment with corticosteroids are frequently reported. The design and many details of single-institution studies are incongruent, however, and no recommendation can yet be made [59–61]. Hence, a prospective multicenter study is mandatory to determine whether corticosteroids are really helpful in improving the outcome of patients who have biliary atresia after the Kasai procedure.

The criterion for successful portoenterostomy in patients who have biliary atresia is survival with their own liver. Over the years the results have improved remarkably, but the data from single-institution and national multicenter studies vary greatly. The rate of survival with native liver ranges between 32% and 60% after 5 years and between 22% and 53% after 10 years [57,61,62]. The results for jaundice-free survival are significantly worse, and after 20 years nearly all patients are expected to suffer from liver cirrhosis (Table 1) [63,64].
Determination of variables that might influence the outcome of portoenterostomy reveals that age at operation is a crucial factor. The highest rate of bile flow restoration can be achieved in patients who are operated on before they are 60 days old, and the success rate decreases dramatically beyond the 90-day limit [57]. Denomination of these limits should not exclude patients from a surgical approach, however, because a successful clinical course can also be seen in patients who were older than 3 months when the Kasai procedure was performed [65,66]. There is agreement that, apart from exceptional cases, portoenterostomy should be performed in all patients who have biliary atresia, at least to bridge the time between diagnosis and liver transplantation. Achieving long-term, jaundice-free survival is an important goal for every patient who has biliary atresia, but prolonged survival with the native liver is always desirable. Another important factor influencing the outcome is the experience of the center [67,68]. Although it could be shown that the surgical outcome is related to the frequency of operations, successful treatment of patients who have biliary atresia depends both on the professional skills of the surgeon and on the interlocking cooperation of pediatric surgeons, pediatric gastrologists and hepatologists, and transplant surgeons.

Early complications that may influence the postoperative prognosis are ascending bacterial cholangitis and mechanical obstruction of the Roux-en-Y loop. Early diagnosis and adequate treatment of the cholangitis are essential to prevent deterioration of the intrahepatic bile flow [69]. Primary or secondary construction of antirefluxive intestinal valves has not been beneficial and is not recommended. On the other hand, recurrent episodes of ascending cholangitis can be induced by mechanically impaired bile flow along the biliodigestive conduit and should be verified by hepatobiliary scintigraphy. In these cases, and after acute cessation of initial good bile flow, a surgical revision of the situs would be useful (eg, correction of a secondary kinking of the Roux-en-Y-loop). Débridement or revision of the porta hepatis has been advocated mainly by Japanese centers and should be left for specific cases [70].

Because of the unpredictable outcome of patients who have biliary atresia, several attempts were made to identify prognostic parameters facilitating the postoperative management and a potential marker for an indication for liver transplantation. Most of the studies focused on fibrosis markers or on clinical,

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<th>Study</th>
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<td></td>
<td>Overall</td>
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<td>Davenport et al 1997 [89]</td>
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<td>Chardot et al 1999 [67]</td>
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morphologic, and immunologic parameters, but none of the criteria proved to be valuable for predicting the individual prognosis [29,71–75]. The only outcome-related classification can be made by assessing the parameters of liver function within the first 6 months after the Kasai procedure. Patients who have normal bilirubin levels and no signs of portal hypertension seem to have a relatively favorable outcome [76–78]. As long as the ongoing postoperative destructive process of the liver in biliary atresia is not understood, these investigations overlap with programs studying the etiology of biliary atresia.

In conclusion, surgery in biliary atresia is a symptomatic approach to an enigmatic and self-limiting process of the liver, which manifests along the intra- and extrahepatic biliary tree. Despite the limited therapeutic options, every effort must be made to reinforce early detection, timely diagnosis, perfectly performed Kasai procedure, and optimal postoperative care of patients who have biliary atresia. These measures will help increase the jaundice-free survival with the native liver and decrease the number of liver transplantations in children who have biliary atresia.

**Liver transplantation**

The replacement of the affected organ signifies the beginning of a new chapter that carries no specific holdovers from the first disease. The introduction and rapid development of liver transplantation have been highly beneficial for patients who have biliary atresia, because the overall survival exceeds 80%, and the outcome of liver transplantation in these patients is not different from that in patients who have other end-stage liver diseases [79–82]. Technical innovations, such as split-graft or living related-donor liver transplantation, continuously improve the long-term results [83], and liver transplantation in children younger than 1 year has already become routine in highly specialized centers [84–86]. Pediatric liver transplantation is reviewed elsewhere in this issue by Tiao and Ryckman.

In most patients, biliary atresia is an ongoing process, with progressive portal hypertension and deterioration of the liver function sooner or later requiring liver transplantation. The question has been raised as to whether primary liver transplantation should be recommended. In the light of continuously improving results of liver transplantation, especially in infants, advocates argued that primary liver transplantation would spare the risks of the Kasai procedure and its postoperative complications; also, an untouched situs offers better conditions for the transplantation and decreases peritransplantation complications [87]. On the other hand, more than 50% of the patients who have biliary atresia are jaundice free after the Kasai procedure, and most of them have a realistic chance of surviving with their native liver for more than 10 years. Therefore, portoenterostomy still remains a curative option for a minority of patients who have biliary atresia and for all others is an important bridge to the expected liver transplantation. Given these arguments, sequential surgical therapy must be recommended.
in all cases of biliary atresia. It is obvious that a correctly performed Kasai procedure does not interfere with the transplantation, although multiple operations should be avoided [88–91]. In some specific cases, however, determining the right procedure is difficult. Late referrals of patients who have biliary atresia, presenting with complete liver cirrhosis and clinical signs of portal hypertension, do not necessarily profit from the Kasai procedure. In these rare cases, the optimal treatment for each individual must be found by mutual consent between all participating disciplines.

A crucial problem of the sequential surgical therapy of patients who have biliary atresia is the optimal timing for liver transplantation. There are no available parameters that reliably monitor the ongoing intrahepatic process of the disease. Therefore, the clinical sequelae of portal hypertension and impaired physical development are the only criteria for timing of liver transplantation. Close cooperation within the interdisciplinary team is also mandatory because any therapeutic decision depends on the physical condition of the recipient [92,93].

No fundamental breakthrough in surgery for biliary atresia seems to be in sight. In series from experienced centers, outcomes after the Kasai procedure are comparable, and over the years the rate of bile flow restoration remains unchanged. It cannot be expected that further development of the Kasai procedure will improve the survival with native liver of patients who have biliary atresia. Nevertheless, technical innovations, such as minimally invasive surgery or robotically assisted procedures, are feasible and might be beneficial in relieving the perioperative stress of the patients [94,95]. Because the surgical approach to biliary atresia addresses only the symptoms of the disease, it will never address its cause. Until there is an origin-related therapeutic approach, every effort must be made to optimize the results of the Kasai portoenterostomy.

Future prospects

In the face of so many unsolved problems in biliary atresia, the challenges for the near future are clear. The first is that health care providers should refer every baby with neonatal jaundice lasting more than 14 days. Screening programs are feasible [96] and essential, but in most countries, they are not available for economic reasons. Therefore, the second condition becomes more evident: every neonate thought to be suffering from biliary atresia must immediately be referred to a center with expertise in pediatric hepatobiliary disorders. There a modern management strategy will be available to rule out other diseases, and the Kasai portoenterostomy is a familiar procedure for the team. In addition to early diagnosis and adequate surgical therapy, long-term postoperative care is indispensable to improving the overall outcome. Unfortunately, despite optimal treatment modalities, the deterioration of the liver is an ongoing process in most patients who have biliary atresia; the tools to slow the process are limited, and there is no way to stop it. Hence, the third challenge has the highest prior-
ity: to develop curative treatment strategies, every effort must be made to uncover the cause of biliary atresia. This discovery is the only way to understand the pathogenesis, to guide the treatment opportunities effectively toward the key pathogenetic mechanisms of disease, or, optimally, to prevent newborns from developing biliary atresia [62,97,98].

During the several last years, more and more working groups have accepted this challenge, and several activities have been initiated or intensified. Existing biliary atresia registries in Japan and France and treatment-optimization programs in the United Kingdom stimulated the community of researchers in biliary atresia to coordinate their activities and increase their effectiveness [67,68,99]. In the United States, the new Biliary Atresia Research Consortium (www.med.umich.edu/borc/barc/sites.htm) is a network of 10 clinical centers that serves as a clinical database and a coordinating center for clinical and basic research studies [100]. In Europe, the Biliary Atresia Registry (www.biliary-atresia.com) was founded to coordinate the data from the participating countries [101], and the new European Foundation for Biliary Atresia Research (www.orpha.net) uses the existing infrastructure to sponsor multicenter research studies. Intensive and close cooperation among these initiatives helps improve the interim results and achieve the definite objective: uncovering the etiology and pathogenesis of biliary atresia and finding a cure.

**Summary**

Biliary atresia is a cholestatic disease affecting the intra- and the extrahepatic bile ducts of the newborn; with unpredictable outcome, it is the main indication for pediatric liver transplantation. The cause of this rare entity still remains unclear, hypothetically ranging from defective morphogenesis to viral infection or an immunologic defect. Although most patients finally need liver transplantation, the interim objective is to optimize patients’ survival with their native liver. Early diagnosis, timely and perfectly performed portoenterostomy, and optimal postoperative care are indispensable to reduce the frequency of liver transplantation for biliary atresia. The sequential surgical approach to biliary atresia (obligatory Kasai procedure and optional liver transplantation) improves the symptoms of the disease but does not address its cause. Therefore, clinical and basic research is mandatory to elucidate the origin of biliary atresia. To compensate for the infrequency of biliary atresia, international multicenter studies should focus on clinical and on etiologic aspects. Unfortunately, basic research in biliary atresia is retrospective, because it always starts when the disease has already reached an advanced stage. Using animal models, the dynamic pattern of biliary atresia can be simulated, and with a coordinated research program the pathogenesis of the disease can be better understood. Intensive and close interdisciplinary cooperation will be beneficial for the patients and will help solve the riddle of biliary atresia.
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