How well do we understand biliary atresia?

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ABSTRACT

Biliary atresia forms the prime surgical cause for neonatal jaundice, although the differential diagnoses of jaundice in the neonatal and infantile age group includes an exhaustive list of several medical causes. Despite various studies looking at the aspects of the pathology of the condition, it is not clear as to how exactly Biliary atresia is caused. The review attempts to look at the current literature concerning the etiopathogenesis of Biliary atresia.

INTRODUCTION

In a child presenting with cholestasis, Biliary Atresia (BA) is one of the important surgical causes. About one third of the neonatal cholestatic children turn out to be BA. BA is a diagnosis of exclusion in children presenting with cholestasis.

TYPES BASED ON ETIOLOGY

Based on the clinical features and etiopathogenesis, BA is divided into the perinatal type and the embryonic type. The perinatal type or the acquired type is known to be the commonly seen among the two types, accounting for about 80% of BA. The congenital or the embryonic type, as the name implies, is believed to be causatively associated with certain genetic aberrations such as BASM (Biliary Atresia Splenic Malformation). Polysplenia, intestinal malrotation, preduodenal portal vein, absent inferior vena cava, aberrant hepatic artery, abdominal heterotaxia) are other associations with the BASM. When genetic mutations occur in the genes controlling the bile duct development, the end result is proposed to be the embryonic type of BA. In contradistinction to the embryonic type, the perinatal type is the final product of viral offending agents as triggers initiating complex interactions between innate and adaptive immune responses.

Studies on animal models showed that when complete deletion of inversin gene in mice took place, it lead onto cause laterality defects in the abdominal organs in addition to malformations of the hepatobiliary system, drawing a parallel to that of the embryonic type. Subsequently, in humans, the role of inversin gene in the causation of embryonic type was refuted by studies undertaken by Schon et al.

Viruses have been implicated in the causation of Biliary atresia for a long time. The list of viral agents includes human papilloma virus, cytomegalo virus, respiratory syncytial virus, Reovirus, Rotavirus, Epstein Barr virus, Herpes virus, Hepatitis B virus . Although there are isolated reports of their causative association, there have not been large scale studies to strengthen the consistent and convincing notion that they are indeed associated with the pathogenesis of Biliary atresia in humans.

ETIO-PATHOGENESIS AT THE MICRO LEVEL

The perinatal type is understood as an exaggerated autoimmune directed inflammation of biliary ducts proceeding to secondary biliary cirrhosis, in view of progressive ductal injury and bile ductal obstruction. It is interesting to note that an initial viral infection acts as the triggering event setting off the collateral damage of the biliary duct.

It has been shown in mouse models that Rota virus specifically attacks cholangiocytes which cause tissue specific inflammation and pathogenetic effects. On the basis of this murine model, it has been put forth that viral mediated damage and progressive oblitative inflammation of bile ductules can occur, similar to the perinatal type BA. The ability of the virus to be tropic to cholangiocytes, appears to the underlying crucial factor. Once the cholangiocyte is infected, the cellular inflammatory events involve the gamma interferon producing CD4 & CD8
lymphocytes which target the hepatobiliary system, culminating in fibrosis of the injured ductal elements, bearing the striking resemblance to Biliary atresia.15

Thus, gamma interferon is assumed to be the root cause of the inflammatory changes responsible for progressive bile duct obstruction & obliteration. It is proposed that the hypomethylation changes of DNA in CD4 lymphocytes leads onto the uncontrolled gamma interferon expression.16 The response to the inciting viral agent, which is of the neutrophilic inflammation initially, does not seem to be altered by the gamma interferon. Nevertheless, once its release from T lymphocytes, gamma interferon as the pivotal player, orchestrates the sequence of events, specifically the later occurrence of intraductal inflammation, ductal fibrosis, loss of epithelial integrity and subsequent damage and loss of extrahepatic bile ducts.17 It is noteworthy that, in their attempt to achieve viral clearance, the CD8 lymphocytes secondarily effect ductular damage resulting in the experimental type of Biliary atresia. Alpha 2beta1 integrin has been identified to be the via media of interaction responsible for predisposition of the cholangiocytes to Rhesus Rota virus infection.18

Regulatory T lymphocyte defects in the presence of viral infection, has also found to be contributory to the unchecked bile ductal inflammation and destruction.19

LABORATORY MODELS

Animal models have been used to study the pathogenesis in more detail at the micro cellular level and also the possible interventions which can be used to manipulate the evolution of BA. Use of intrahepatic injection of chemicals such as carbon tetrachloride, ethanol, formalin have been found to simulate inflammation similar to Biliary atresia in adult rat.20,21 Lamb fetus has also been utilised as an animal model.22 In all these animal models, some kind of manipulation like bile duct excision or ligation is needed to replicate the pathology of BA. However, as an exception to the above manipulation, Sea Lamprey presents as a model which has the seamless progress into Biliary atresia without the need for intervention with injection of chemicals or surgical bile duct ligation.23

Although the literature presents the various intricacies in the etio-pathogenesis of BA, much more work has to go into, before clearly delineating and declaring the cellular events of BA.

REFERENCES


