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Review article

Biliary atresia: A comprehensive review

Bhanumathi Lakshminarayanan, Mark Davenport*

Department of Paediatric Surgery, King's College Hospital, London, UK

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ABSTRACT

Biliary atresia presents as an obliterative cholangiopathy with neonatal jaundice and pale stools. The disease exhibits aetiological heterogeneity with a multiplicity of potential causative factors, both developmental and environmental. A number of clinical variants making up a minority of all cases can be defined relatively precisely which match suggested aetiology better although in most it still remains speculative. These include the syndromic form (BASM), the cystic form and those associated with CMV IgM antibodies.

We review not only the clinical evidence for a developmental or an immune-mediated aetiology perhaps triggered by perinatal viral exposure but also several other recently suggested concepts such as microchimerism, gene susceptibility and environmental toxins.

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1. Introduction

Biliary atresia (BA) comes to us as a peculiar, possibly unique,

Abbreviations: CMV, cytomegalovirus; T cells, T-regs regulatory; RT-PCR, reverse-transcriptase polymerase chain reaction; IL, interleukin; FISH, fluorescent in situ hybridization; ERCP, endoscopic retrograde cholangiopancreatography; MCT, medium chain triglycerides.

* Corresponding author. Dept. of Paediatric Surgery, King's College Hospital, Denmark Hill, London, SE5 9RS, UK.
E-mail address: Markdav2@ntlworld.com (M. Davenport).

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disease presenting in infancy with established obliteration of their biliary tree. The condition is rare and one of its peculiarities is that it may have many parents, i.e. it may only be an end-stage phenotype with a multiplicity of different aetiological mechanisms. There is in some of these affected infants a pronounced inflammatory milieu in which there are hallmarks of immune activation and as a result organ damage. Much work has been done on trying to define the nature of the offending trigger and its immunological consequence. Observed evidence of what is happening inside their liver and biliary tract and speculation as to its cause will form the backbone of this article.

2. Historical context

The earliest reference to this condition appeared in a textbook published in 1817 by Dr John Burns from the University of Glasgow, who mentions this condition in passing as an "incurable state of the biliary apparatus" [1,2]. A case report and review was published as a thesis by John Thomson an Edinburgh physician in 1891 [3]. At the time these were simply considered as a congenital obliteration of the bile ducts with his example showing two small bile-containing cysts in the porta hepatis unconnected to an otherwise normal gallbladder and common bile duct.

Some notable surgical successes were reported by William Ladd working in Boston, USA during the 1920's but only because he found proximal bile-containing ducts to anastomose with adjacent intestinal loops [4]. Increasing surgical experience however became more pessimistic as it was realised that the majority did not have anything resembling proximal bile ducts, rather a solid extrahepatic biliary tree. The phrase "uncorrectable biliary atresia" conveyed this rather brutal truth and there were few if any survivors.

Morio Kasai described a more radical approach to surgery in the 1950s involving simple transection of an apparently solid proximal biliary tract with Roux loop reconstruction anyway [5]. This did lead, somewhat amazingly, to bile flow and resolution of jaundice in some, due to the transection of microscopic bile ductules and has remained the surgical procedure of choice in most to the present day. The alternative is liver transplantation which although pioneered in the 1960s [6] by Thomas Starzl and a group in Denver, CO. only truly became realistic in the 1980s. Currently we regard the two options as complementary with an initial attempt at salvage of the native liver, followed by liver transplant if this demonstrably fails [7].

3. Clinical context

It is clear that BA is not a single disease with a defined aetiology and predictable response to treatment. Rather it seems to a phenotype characterised by extrahepatic biliary obliteration or absence connected to an array of abnormal, intrahepatic ductules often lacking the usual branching pattern of mature ducts. We have tried to define three specific entities which seem to share enough similarities to be considered homogenous.

3.1. Biliary Atresia Splenic Malformation (BASM) syndrome

These infants (usually female) are characterised by a constellation of unusual anomalies including polysplenia (sometimes asplenia), vascular anomalies (preduodenal portal vein, absence of the cava), situs inversus and cardiac anomalies. There appears to be a primary failure of extrahepatic bile duct development – the gallbladder is invariably atrophic and the CBD absent. This developmental failure probably occurs early from 20 to 40 days gestation to account for the other anomalies and maternal diabetes appears to predispose [8,9].

There are other congenital anomalies such as oesophageal atresia, jejunal atresia and the cat eye syndrome [10] which do appear as rare associations but these appear to be different to those within the BASM grouping.

3.2. Cystic biliary atresia

This can be defined as cystic change in an otherwise obliterated biliary tract and is seen in about 5–10% of most large series [11]. The cyst itself may contain bile (~20%) implying onset after establishment of continuity between intra- and extra-hepatic bile ducts (10–12 weeks gestation), or mucus [11]. Around half of these are picked up antenatally on the maternal ultrasound scan and they have a good prognosis post Kasai surgery.

3.3. CMV-IgM + ve associated biliary atresia

Recently we have defined on a group of infants with BA who have IgM antibodies to CMV [12]. These made up 10% of our clinical series and were more commonly seen infants from non-caucasian parents. Clinically they were older at diagnosis and came to Kasai surgery later. Biochemically they had higher bilirubin and AST levels, with larger spleens as measured on ultrasound than comparable IgM-ve BA infants, even when corrected for their older age. Their histological appearance of the extrahepatic duct was more inflammatory with prominent nodes. This inflammatory appearance carried over to the histological appearance within the liver with an obvious mononuclear cell infiltrate consisting of largely $CD4^+$ Th1+ T cells [13]. Interestingly none of the liver biopsies in our clinical series stained positive for actual presence of CMV. Of all the clinical groups we have defined these appeared to have the worse response to Kasai surgery and also appeared susceptible to death during infancy.

Of all the clinical groups described this is the group that appears to fulfil most of the requirements to support an immune-destructive pathogenesis following viral triggering.

3.4. Isolated BA

In the absence of any distinguishing features this forms the largest (70–80%) clinical grouping. Real evidence of what has caused BA in this group is minimal and remains open to speculation. Such infants could equally well have a developmental pathogenesis or alternatively a secondary obliterative cholangiopathy. Some recent evidence towards the former was presented by a review of early liver biochemistry (day 1 and day 2 of life) in about half of a series of infants from Texas later shown to have BA [14]. This showed that all had elevated conjugated bilirubin by 24 h implying biliary obstruction at the time of birth.

4. Epidemiological context

There is marked variation in incidence of BA ranging from about 1 in 5–10,000 live births in Taiwan [15,16] and Japan [17] to about 1 in 15–20,000 in mainland Europe [18], England & Wales [19] and North America [20]. Furthermore there is marked geographical variation among the specific variants mentioned above. The incidence of BASM varies widely, and is rarely reported in Asian series but accounts for about 10% of European and North American series. The incidence of CMV IgM + ve BA also varies from 10 to 20% in European series [12,21,22] but up to half in series from China [23]. Some small studies have suggested a seasonal variability [24] although not larger national studies [19].