



Review Article

REVIVAL OF LANDING'S CONCEPT OF INFANTILE OBSTRUCTIVE CHOLANGIOPATHY – A PLEA TO HAND OVER THE 2 WEEK OLD JAUNDICED FULL TERM NEONATE TO THE SURGEON!

S SHARMA¹, DK GUPTA²

Abstract :

The concept of infantile obstructive cholangiopathy started in 1974 by Landing and remained till early 1980s. However, the concept has not been used much since then as nothing new has developed over the last 40 years sufficient enough to change the course of the disease or identify its etiology. This review article is an attempt to consolidate evidence on review of literature pointing towards a common etiopathological process leading to the spectrum of anomalies constituting neonatal cholestasis. The importance of early referral of any case with neonatal jaundice in a full term neonate, preferably at 2 weeks age is highlighted. This will help to identify and treat more cases within the correctable range and prevent the disease from progressing to a life threatening situation especially in developing countries where the resources for liver transplantation are meagre.

Introduction:

Newborn babies are at increased propensity for developing hyperbilirubinemia due to increased bilirubin production or its decreased excretion. The increased production is attributed to a greater red cell mass per kg as compared to adults and a shorter life span of red blood cells. The decreased excretion is attributed to defective uptake of bilirubin due to hepatic immaturity and decreased ligandin, defective conjugation due to decreased uridine diphospho glucuronyl transferase (UDPG-T) activity, decreased hepatic excretion of bilirubin and increased entero-hepatic circulation due to higher levels of glucuronidase

enzymes in neonatal gut and decreased intestinal bacteria.

Physiological Jaundice:

The physiologic jaundice seen in newborn babies appears on the third day of life and usually lasts till the tenth day in full term babies. It appears slightly earlier in preterm babies and may last upto two weeks. However, the serum bilirubin levels do not exceed 12 mg % in full term babies and 15 mg % in preterm babies. The normal range of total and conjugated bilirubin are <1 mg/dl and <0.25 mg/dl respectively, although jaundice can only be appreciated in newborn babies only when the total bilirubin is greater than 5 mg/dL

Physiological jaundice may be accentuated by immaturity, birth asphyxia, acidosis, hypothermia, hypoglycemia, septicemia, blood group incompatibilities, drugs like salicylates, gentamycin, sulpha drugs, cephalhematoma, polycythemia, hypothyroidism intrauterine infections and breast milk jaundice. At high levels, unconjugated bilirubin can cross the blood-brain barrier and cause brain injury (kernicterus). The usual therapy for unconjugated jaundice is phototherapy and occasionally exchange transfusion.

Neonatal Cholestasis :

Infants with the persistence of jaundice beyond the physiologic limits, in the absence of an apparent medical cause, need to be investigated without much delay. The causes for Conjugated Hyperbilirubinemia (neonatal cholestasis) include obstructive and nonobstructive disorders. These are broadly called extrahepatic biliary obstruction and neonatal hepatitis. Cholestasis thus results from either to slow bile flow or an actual obstruction to bile flow.

1. Dr. Shilpa Sharma, Assistant Professor, Department of Pediatric Surgery, Postgraduate Institute of Medical Education and Research and Dr RML Hospital, New Delhi.
2. Prof. Devendra K Gupta, Professor and Head, Department of Pediatric Surgery, All India Institute of Medical Sciences, New Delhi-110029,
Email.: profdkgupta@gmail.com

Correspondence to: Dr. Shilpa Sharma, Assistant Professor, Department of Pediatric Surgery, Postgraduate Institute of Medical Education and Research and Dr RML Hospital, New Delhi.

Neonatal cholestasis, both due to medical and surgical causes leads to cholangiopathy. The causes for neonatal hepatitis include infections (TORCH), metabolic (galactosemia), Endocrine causes (hypothyroidism), genetic (alpha 1 antitrypsin deficiency), miscellaneous and idiopathic. When the bile is inspissated and thick in these conditions, it requires a surgical flushing of the bile before irreversible liver damage sets in. Thus, all these need to be excluded before a diagnosis of extrahepatic biliary obstruction is made.

The common causes of Neonatal cholestasis requiring surgical intervention include : Extrahepatic biliary atresia (EHBA) 80%, Choledochal cyst associated with biliary atresia 5%, Infantile Choledochal cyst, Neonatal hepatitis (NH) 10%, Inspissated bile syndrome (Hereditary spherocytosis, Hemolytic anemia) - Rare and Biliary hypoplasia (Syndromic-Alagille's syndrome and non syndromic) - Rare. Apart from these, other extremely rare causes include spontaneous perforation and tumors.

In these conditions, the clinical presentation, laboratory data and radio-logic investigations show lot of similarities and on this basis it was named as neonatal obstructive cholangiopathy. Some authors prefer to use the term infantile obstructive cholangiopathy promoted by Landing that includes the entities extrahepatic biliary atresia, choledochal cyst and neonatal hepatitis¹. The actual hypothesis on the etiology and pathogenesis of neonatal hepatitis, intrahepatic and extrahepatic biliary atresia and choledochal cyst is that these disorders can be different results or permissible outcomes of a single basic process: infantile obstructive cholangiopathy². They have been considered different stages of one disease process³⁻⁵. It is proposed that some cases of biliary atresia and neonatal hepatitis may be initiated by an adverse effect of unsaturated monohydroxy bile acids on the fetal and infantile hepatobiliary system⁶. The hypothesis is founded on morphological observations in patients with biliary atresia and on the toxic effects of monohydroxy bile acids on the hepatobiliary system.

In 1979, Miyano T et al propagated abnormal choledocho-pancreatico ductal junction in relation to the etiology of infantile obstructive jaundice diseases⁷. The congenital stenosis associated with anomalous choledocho-pancreatico ductal junction was considered to be the most important etiologic factor

in congenital biliary dilatation. Furthermore, the possibility of pancreatic juice reflux into the biliary tract due to the abnormal choledocho-pancreatico ductal junction, which could lead to obstructive cholangiopathy, was suggested in relation to the pathogenesis of congenital biliary atresia⁷.

Glaser et al reported that 62% of babies with extrahepatic biliary atresia and 52% of infants with idiopathic neonatal hepatitis had reovirus 3 antibodies compared to less than 12% of either normal infants or babies with other cholestatic disorders. They suggested that perinatal infection with reovirus type 3 may serve as an initiating event in the genesis of two closely related forms of infantile obstructive cholangiopathy: extrahepatic biliary atresia and idiopathic neonatal hepatitis⁸

Ogawa T et al reported an experimental study of the pathogenesis of infantile obstructive cholangiopathy and its clinical evaluation⁹. 1,4-phenylenediisothiocyanate was given to five groups of 97 rats of different developmental stages, and the changes in the hepatobiliary system were compared histopathologically. Three groups of rats given the drug after birth showed dilatation of the extrahepatic bile ducts with inflammation. Two groups given the drug during the fetal period or added after birth showed stenotic or atretic extrahepatic bile ducts due to thickening and fibrosis of the wall. This experimental model suggests that differences in the pathologic features of infantile obstructive cholangiopathy (biliary atresia, neonatal hepatitis, and bile duct dilatation) may be the result of various developmental stages in the pathogenic process. After the experiment, 11 cases of correctable type biliary atresia were compared to 24 cases of noncorrectable type in various aspects. It is suggested that the correctable type may have suffered pathogenic process later in the developmental stages than noncorrectable type .

In a series of one hundred twenty one infants with neonatal cholestasis, jaundice (94.2%) and hepatomegaly (66.1%) were the most frequent symptom and signs on admission. Idiopathic neonatal hepatitis (36.4%), extrahepatic biliary atresia (24.8%), metabolic disease (20.7%), intrahepatic ductal paucity (10.7%), intrauterine infection (3.3%) were the most frequent causes of neonatal cholestasis¹⁰.

The Cholestasis Guideline Committee recommends that any infant noted to be jaundiced at 2 weeks of age be evaluated for cholestasis with measurement

of total and direct serum bilirubin¹¹. However, breast-fed infants who can be reliably monitored and who have an otherwise normal history (no dark urine or light stools) and physical examination may be asked to return at 3 weeks of age and, if jaundice persists, have measurement of total and direct serum bilirubin at that time¹¹.

Biliary Hypoplasia:

It is quite a rare disorder in which bile ducts are small or hypoplastic but patent throughout¹². The clinical presentation is similar to EHBA. The disorder is not a specific disease but a manifestation of hepatobiliary disorders like neonatal hepatitis, alpha-1-atitrypsin deficiency, intrahepatic biliary atresia (early stage) and Alagille syndrome. The quantity of bile flowing through the ducts is significantly less and hence the condition has been compared to the unused microcolon (in neonatal intestinal obstruction). The condition is invariably diagnosed only by operative cholangiogram. Liver is found enlarged, smooth and soft. The diagnosis of biliary hypoplasia has been established by several criteria, the most important of which have been gross inspection of the duct at operation and the demonstration of marked reduction in the lumen of intra or extrahepatic ducts, or both, by operative cholangiography¹³. Liver biopsy has at times given confirmatory evidence. It seems likely that cases of biliary hypoplasia may have been classified as atresia or neonatal hepatitis in other series. It also seems quite likely that the patency of these small fibrotic hypoplastic ducts most likely explains the recovery of certain reported cases in which surgical exploration has revealed no evidence of an extrahepatic biliary system, and a fatal outcome has been predicted.

Hypoplasia, with partial but inadequate biliary drainage, may also explain the prolonged survival of certain patients with all of the stigmata of biliary atresia. Hypoplasia may exist in all degrees, and involve various anatomical segments of the biliary system. It may also be associated with areas or segments of biliary atresia. Recognition of biliary hypoplasia may help to explain the unusual clinical course of certain patients with neo- natal jaundice. For example, it may explain the course of patients who recover spontaneously when a patent ductal system has not been identified at operation or those with signs of neonatal biliary obstruction who survive in reasonably good general condition for years .

No attempt should be made to do the dissection at the portahepatis¹⁴. The abdomen should be closed after taking a wedge liver biopsy. Peter Altman has used cholecystostomy catheter for long to decompress the biliary systems¹⁵. However, the results are quite variable and it is difficult to comment on its utility at this stage. Previously, all these patients were subjected to HPE but the long-term results were not favorable¹⁶.

Choledochal Cyst Associated With EHBA:

Occasionally, an isolated thick-walled cyst, about a cm in diameter is seen in the extrahepatic biliary pathway. It contains mucus only. Sometimes the cysts are located at the portahepatis. The diagnosis is based on operative cholangiogram. The management is exactly like that for EHBA. The prognosis is also comparable to EHBA only.

Infantile Choledochal Cyst:

Choledochal cyst is a dilatation of the common bile duct. The incidence is 1:13,000. It is commoner in Asian countries, especially Japan, Korea, Vietnam, (perhaps up to 1 in 1000)¹⁷.

Females are affected 4 times more than males. In 1959, Alonso-Lej et al originally classified choledochal cysts into 3 types¹⁸. In 1977, Todani et al further classified this anomaly into 5 types . The exact cause for choledochal malformation is unknown. Certainly, most appear to be truly congenital given their usual presentation in children and the fact that cystic dilatations can be detected on antenatal ultrasonography. Some may well present later and have more of an acquired aetiology with a number of hypotheses being proposed. The following theories have been suggested as the possible etiologic explanation¹⁹:

1. Reflux of trypsin and other pancreatic enzymes into the common bile duct secondary to anomalous pancreaticobiliary junction^{20,21}
2. Distal obstruction due to abnormal pancreaticobiliary junction with a long common excretory duct and a wide angle^{22,23}
3. Weakness of the duct wall due to a congenital cause, pancreatic enzymes or chemical substances (bile + pancreatic Juice)^{16,20}
4. Increased intraluminal pressure due to abnormal choledochus sphincter inferio, fibrosis of sphincter of Oddi or post inflammatory ductal stenosis.

The wall of the typical choledochal cyst is usually thick, vascular and has an incomplete mucosal lining (this will vary with the age of child and length of symptoms).

Miyano et al (1981) established an experimental model of an anomalous choledochopancreatic ductal junction by creating a choledochopancreatic end-to-side ductal anastomosis in puppies²⁴. They successfully reproduced the dilatation of the CBD in all experimental animals without exception.

In 1984, Todani et al conducted an analysis of endoscopic retrograde cholangiopancreatograms and other cholangiograms and confirmed a long common-channel anomaly found in most patients²⁵. Other authors have reported the same findings in their series^{26,27}. Reflux of pancreatic enzymes into the CBD can happen early in life, even in fetal life, resulting in damage to the ductal wall. The distal portion of the CBD is most at risk, and with repeated irritation, it can become stenotic.

The two most accepted theories are still reflux of pancreatic enzymes into the CBD secondary to an anomalous pancreaticobiliary junction and obstruction of the distal CBD.

In the *infantile choledochal cyst*, the picture is indistinguishable from that of EHBA. Infants presenting with persistence of neonatal jaundice, acholic stools and dark-colored urine with smooth hepatomegaly should be suspected for choledochal cyst also. There is no pain and no palpable mass in the abdomen. Children below one year of age tend to present with obstructive jaundice, acholic stool with or without obvious hepatomegaly. In early life, this group may be difficult to differentiate from cystic biliary atresia.

Total excision of the cyst with adequate bile drainage is the standard treatment for choledochal cyst. Cyst excision, cholecystectomy and biliary reconstruction using Roux-en-Y hepaticojejunostomy, are the treatments of choice. Hepaticoduodenostomy has also been preferred by some in cases where the cyst is not involving a major part of the common hepatic duct. However, in the setting of extensive inflammation, a cyst mucosectomy and cystoenterostomy can be performed. **Forme Fruste Choledochal Cyst**

In 1985, a new variant of choledochal cyst known as forme fruste was described in the pediatric literature²⁸.

Forme fruste choledochal cyst (FFCC) is characterized by minimal dilatation of the extrahepatic bile duct which does not grow with time. The normal diameter of the common bile duct in children ranges between 2 and 6 mm. FFCC is associated with a diameter between 6 and 10 mm. Most patients with FFCC have a long common channel, in which the common bile duct-pancreatic duct junction is away from the duodenal papilla, with partial obstruction of the terminal common bile duct. FFCC is associated with fever, jaundice, abdominal pain, recurrent pancreatitis and altered liver function tests. Additionally, the patient presents with recurrent cholangitis and some have evidence of gross or microscopic cholecystitis, and abnormalities of intrahepatic biliary channels. The histopathological changes are identical with choledochal cyst demonstrated by thickened fibrous connective tissue, absent muscular layer with flattened, ulcerated and dysplastic mucosa. The diagnosis is established with ultrasound. ERCP or MRCP can help delineate the anatomy and presence of a long common pancreaticobiliary channel in FFCC. The management consists of cyst excision and Roux-en-y hepaticojejunostomy. Due to the smaller size, the anastomosis is technically difficult and should be performed carefully to avoid stricture and postoperative cholangitis. To maintain ductal anastomosis patency it is imperative that the diseased ductal tissue is not incorporated in the anastomosis, to avoid the most likely reason for the high incidence of anastomotic stricture in choledochal cyst post drainage operations.

Inspissated Bile Syndrome:

The incidence of inspissated bile syndrome is 1 per 175,000 live births in England and accounts for about 8% of all surgical jaundice during infancy²⁹. Biliary sludge appears sonographically as low-level echoes. On microscopy a mixture of particulate matter appears when various biliary solutes precipitate cholesterol, calcium bilirubinate or other calcium salts, mucus, undefined residues, and protein-lipid complexes. The diagnosis of sludge is almost always based on imaging. The pathogenesis of sludge is similar to that of gallstones, which are formed from precipitating sludge³⁰. There are many predisposing factors to the development of inspissated bile, sludge, or cholelithiasis in neonates^{31,32}

Ceftriaxone pseudolithiasis, composed of precipitated ceftriaxone, is reported to occur in 29.5% to 45.7% of

children treated with ceftriaxone³³. The pseudolithiasis occurs after 4 to 22 days (mean, 9 days) of ceftriaxone therapy and resolves after 2 to 63 days (mean, 15 days) from the end of treatment³⁴. Cefotaxime, was previously reported to be associated with pseudolithiasis in 2 of 34 infants (6%) who had cholelithiasis³¹.

Extrahepatic Biliary Atresia (EHBA)

A whole or a part of the extrahepatic bile duct is absolutely atretic in biliary atresia causing complete obstruction of bile flow established at perinatal period. The disease occurs worldwide, affecting an estimated 1 in 8,000 to 12,000 live births.

Etiology

The etiology of biliary atresia remains obscure. Several hypotheses have been proposed including developmental anomaly, inflammation caused by toxin or viral infection, ischemic insults, anomalous bile acid metabolism, pancreaticobiliary malfunction and immune sclerosing injury of the extrahepatic bile duct^{1,7, 35,36}.

In 1977, Danks DM et al hypothesized that most cases of EHBA were the result of inflammatory destruction of previously formed bile ducts during cholangitic hepatitis and the hepatitis was probably caused by an agent or agents different from those involved in neonatal hepatitis³⁷. This hypothesis differed from that of Landing (1974) who suggested a common aetiology for neonatal hepatitis and EHBA..

Since then all plausible factors have been explored without any identification of the definitive inciting agent that may be targeted for treatment purposes.

In 1994, Tan et al proposed "ductal plate malformation theory"³⁸. Using immunohistopathological studies in normal human embryos, they demonstrated that mesenchymal proliferation separates the ductal plate structure from the margin of hepatic parenchyme and actively molds the biliary muralium into a network of tubes. A so-called "solid stage" was not observed in the development of the extrahepatic bile duct. They proposed that biliary atresia may be caused by a failure of the remodelling process at the hepatic hilum, with persistence of fetal bile ducts poorly supported by mesenchyme. As bile flow increases perinatally, bile leakage from these abnormal ducts may trigger an intense inflammatory reaction with subsequent obliteration of the biliary tree. Concerning the

mechanism of ductal plate malformation, they attributed this to epithelial-mesenchymal interactive disorder due to abnormal expression of transforming growth factor, TGF-beta 1.

On the other hand, Terada and Nakanuma in 1995, proposed the impaired regulation of apoptosis (programmed cell death) in the fetal development of intrahepatic bile ducts³⁹. They found that C-myc protein and fas antigen which stimulate apoptosis were constantly positive in the ductal plate, remodelling ductal plate and remodeled ducts. Bcl-2 protein, an inhibitor in the process of apoptosis was negative or faintly positive in the ductal plate and remodelling ducts, but was positive in remodeled ducts. From these results they speculated that apoptosis were involved in the normal development of intrahepatic bile ducts.

As far as a viral etiology is concerned, Reovirus type 3 infection has been proposed as the offending agent during the intrauterine period, but this has not been circumstantially documented by using the PCR assay to detect Reovirus 3 RNA in the liver of patients with biliary atresia^{40,41}.

Other viruses implicated include cytomegalovirus, respiratory syncytial virus, Epstein-Barr virus, and human papillomavirus, and rotavirus type A⁴²⁻⁴⁵

There are also various animal models which can mimic the pathological features of BA and rely upon exposure of the newborn animal to viruses such as rotavirus [46,47]. EBV trace was observed in hepatocytes in two cases and in biliary epithelium in one case of EHBA in a series of 16 proven EHBA cases by Chromogenic in situ hybridization technique⁴⁸.

The etiology is unknown, and one theory is that it may involve a primary perinatal hepatobiliary viral infection and a secondary generation of an autoimmune-mediated bile duct injury.⁴⁹

In some infants there is evidence to suggest that the process begins early in gestation. Thus antenatal ultrasonography allows detection of that sub-group of BA that show cystic changes within the extrahepatic ducts⁵⁰. Furthermore, about 10% cases of all cases have other congenital anomalies. These anomalies are unusual but characteristic as polysplenia, asplenia, situs inversus, absence of inferior vena cava and pre-duodenal portal vein, for which the term Biliary Atresia Splenic Malformation (BASM) syndrome)has been coined⁵¹. In these infants there is a high incidence of first trimester maternal problems such as diabetes

and it is a reasonable supposition that all of the constituent anomalies occur during the critical period of organogenesis within that period. The incidence is 10% in North American and European series while it is reported as about 3% in Japanese series. There were no differences in liver histology (eg, degree of liver fibrosis) or in the HLA genotype between BASM and nonsyndromic infants. BASM is a distinct subgroup, with an implied onset during the embryological phase of organ development.⁵²

There are similarities between the appearance of developing bile ducts at the porta hepatis at 12-14 weeks gestation and the appearance of the residual biliary ductules at the porta hepatis in BA patients, suggesting that even some cases of isolated BA may be due to alteration in bile duct development and remodelling.⁵³

The disease is most probably due to the inflammatory degeneration of the preformed biliary channels, starting in the extrahepatic tree and involving slowly and steadily the intrahepatic components. Reovirus or a hepatotropic virus specific to the infancy produces hepatitis and cholangitis. Depending on the severity of infections, there is a constant damage to the bile duct and the liver parenchyma. There is generalized bile duct obliteration and periductular inflammation. This results in intra and extra hepatocellular cholestasis. Abnormal presence of bile pigment incites inflammatory reaction within the hepatocytes. Gradually, these are replaced by fibrous tissue. Till date this is most widely accepted etiology for the development of biliary atresia. It is still obscure if the biliary atresia could result from the functional obstruction in the biliary channels and reduced flow of bile or hepatic excretion. The fact that some infants clearly have bile in their stool at birth shows that the bile ducts were open in at least one point in time and suggests that biliary atresia is not a single fetal event, but rather a progressive inflammatory process that begins either just before or shortly after birth.

A vascular accident with ischemia of the bile ducts during the intrauterine period, resulting in the avascular degeneration of the bile ducts and replacement by fibrous tissue has also been proposed and documented in animals

A congenital theory with a developmental insult to the biliary system around the 4th week of intrauterine period has also been suggested. It is also seen that biliary atresia is sometimes associated with the

developmental anomalies like malrotation, preduodenal vein, polysplenia and congenital heart disease.

That biliary atresia is the result of an autoimmune reaction remains to be substantiated.

Genetics may play a role in the pathogenesis of BA, although this is probably a fairly minor role in most. Familial cases of BA have been rarely reported⁵⁴⁻⁵⁷, but there are also reports of discordant monozygotic twins [58-60]. Genetic mechanisms likely play important roles, even regarding susceptibility to other specific causes, but no gene whose altered function would result in obstruction or atresia of the biliary tree has been identified⁶¹.

The clinical observation that biliary atresia is rarely encountered in premature infants would support an agent acting late in gestation [Bates MD]. However, no infectious or toxic agent has been conclusively implicated in biliary atresia.

While infectious agents have varied in different patient populations, studies of liver specimens at different phases of disease point to a pro-inflammatory commitment of lymphocytes at the time of diagnosis, and to their potential role in regulating bile duct obstruction.⁶² The variety of clinical presentations support the notion that the proposed mechanisms are not mutually exclusive but may play roles individually or in combination in certain patients.

Pathogenesis

The pathogenesis is complex. EHBA is a heterogenous disease, resulting from a combination of genetic factors, insults, and activation of different genetic and immunologic pathways. Though the exact etiology remains unknown, and hypotheses abound, the process leads to complete obliteration of the lumen of extrahepatic bile ducts and progressive cellular inflammation of the intra-hepatic ducts.

Schweizer P et al (2005) studied the pathomorphological findings in patients with EHBA and compared them with human and rat embryos⁶³. They found stages of normal embryogenesis of the bile duct system in human and rat embryos in patients with EHBA. Each histological finding in Biliary Atresia corresponded to a finding in an interrupted stage of the normal development in human and rat embryos. They concluded that the similar findings in patients and embryos could be explained completely by a disturbed intrinsic epithelium/mesoderm interaction.

Also, some findings in Biliary Atresia could not be explained easily by the assumption of an extrinsic factor. Thus all findings in biliary atresia could be completely explained as the result of an intrinsic developmental error, probably due to disturbances or interruption of epithelium/mesoderm interaction during embryogenesis.

The mechanisms responsible for increased collagen production and hepatic fibrosis in biliary atresia are unknown. A population of nonparenchymal cells known as hepatic stellate cells (HSCs) is responsible for excess collagen deposition, fibrosis and cirrhosis in liver injury. They have been shown to be "activated" and therefore responsible for the increased production of type I collagen leading to hepatic fibrosis⁶⁴. The Hepatic stellate cells are transformed into myofibroblasts when exposed to liver toxins such as excess iron, bile salts due to cholestasis, viral infection or tumour invasion. These myofibroblasts (activated HSCs) produce increased levels of fibrillar collagen and express an intracellular microfilament protein, α -smooth muscle actin, which is traditionally used as a marker protein of the activated HSC phenotype⁶⁵. Activated HSCs also express a number of different cytokine receptors, including the transforming growth factor (TGF- β_1) receptor.

Pathology

The gross appearance of the extrahepatic biliary tract varies from an inflamed, hypertrophic occluded biliary tract to an atrophic remnant. The whole or part of the extrahepatic biliary is replaced by fibrous tissue. Gall-bladder becomes atretic and without bile. Liver is firm and greenish and with the passage of time it becomes quite cirrhotic. Unlike in neonatal hepatitis, which could be considered the early phase of EHBA, there is a cholestasis, but liver remains apparently smooth and brown in color. Presence of occasional cysts in the line of the extrahepatic biliary pathways suggests that the process of obliteration is gradual and proceeds from below upwards. This has been confirmed by serial sections of the excised extrahepatic biliary tree and tissues from the portahepatis. Prof. Morio Kesai devised hepaticoportenterostomy (HPE) in 1968 and suggested that, if operation is performed around 60 days of age, it may be possible to find some patent bile channels at the portahepatis. With advance in age, the chances of finding a patent bile duct at the portahepatis decrease. It can be called correctible

(5%) forms depending on the presence and incorrectible with the absence of the patency of the hepatic ducts (95%), available for the bilioenteric drainage procedure⁶⁶. Prognosis has also been correlated with the size of the bile ducts found at the porta hepatis. If the size is less than 50 micron in diameter, the prognosis is very poor. The prognosis is moderate if the duct size is between 50-150 micron and excellent if the duct size is more than 150 micron. Biliary atresia has also been classified pathologically into 3 types : Type I ; Atresia of the common bile duct, Type II; Atresia of the common hepatic duct and Type III (90%);Atresia of the whole extrahepatic biliary tree up to the portahepatis (non-correctable type).

EHBA is divided in a fetal, prenatal or embryonic, and a more common, perinatal, acquired

form.[Kahn E] .In the fetal group, abnormalities in different genes seem to play a role; ductal plate malformation is another possibility. Different etiologies have been postulated in the perinatal form of EHBA: genetic susceptibility, vascular factors, toxins, and infections mainly by rotavirus and reovirus⁶⁷.

An important variation is that of cystic change, seen in about 5% of cases, within some part of the extrahepatic biliary tract. Some cysts contain mucus, while others contain bile. If it is bile, there may be diagnostic confusion with that of a true choledochal cyst. In cystic biliary atresia, the wall is invariably thickened, lacks an epithelial lining and communicates poorly with abnormal non-dilated intrahepatic ducts. This should be evident at operative or percutaneous cholangiography.

Histopathology

Histologically, the liver has features of portal tract inflammation, with a small cell infiltrate, bile ductule plugging and proliferation. Later on, bridging fibrosis and ultimately biliary cirrhosis occurs. Histologically the excised extrahepatic biliary tree reveals degree of fibrosis, inflammatory cell reaction and remnants of bile duct epithelium at places. Liver biopsy in an established case reveals that there is intracellular cholestasis, inflammatory cell infiltration, interstitial fibrosis, degeneration and proliferation of bile ducts and intracellular giant cell reaction. The findings resemble giant cell hepatitis but the severity is less. However, more often than not, it is difficult to differentiate advanced neonatal hepatitis from biliary atresia on histology alone.

Presentation:

In biliary atresia, the symptoms start from 2-3 weeks of life or occasionally right from the birth. The presenting symptoms of obstructive jaundice include clay-color (acholic) stool dark urine and hepatomegaly. Splenomegaly also follows hepatomegaly. Ascites with prominent abdominal wall veins is evidence of advanced liver disease. In developing countries, it is not uncommon for patients to present with recurrent attacks of fever, chest infection and diarrhea. Clay colored stools is a worrisome symptom. Moreover, some patients with advanced disease present for the first time with ascites, umbilical hernia, prominent abdominal veins and respiratory discomfort. Approximately 40% patients passed normal meconium at birth and yellowish or light yellowish faeces were seen for a week or so. The symptoms of the fetal form start shortly after birth and there is frequently an association with a variety of congenital anomalies in 9% cases. Children with the perinatal form become jaundiced several weeks after birth; no associated congenital anomalies are present in the short period of time after birth in about 60% of the patients.

Diagnosis

The diagnosis of biliary atresia should be made as early as possible, because the timing of operation is a key to the success of the surgical therapy. Though most cases present late in developing countries, leaving little to diagnostic modalities to confirm a clinical diagnosis of biliary atresia, yet a relay of investigations are done to differentiate between neonatal hepatitis and biliary atresia.

There are number of investigations like blood chemistry, nuclear scanning (99m Tc-2-6 diethyl acetanilide iminoacetic acid), ultrasonography, lipoprotein-x, duodenal drainage test and liver biopsy that may be done to establish a diagnosis. None of these tests alone or in combination can help in distinguishing the neonatal hepatitis from biliary atresia. However, the two most appropriate tests that need to be done are nuclear scanning (HIDA) after priming with chlorectics (phenobarbitone combined with steroids for a week) and per operative cholangiogram to confirm the diagnosis. Laparoscopic cholangiogram can also be performed with reasonable safety to avoid an open surgery in sick cases to confirm the diagnosis. Recently, with the development of smaller endoscopes, ERCP is gaining popularity in

developed centres replacing the need for HIDA scanning and operative cholangiogram.

Liver function tests

These are found abnormal in all patients of EHBA and neonatal hepatitis. There is rise in serum bilirubin levels but mainly as conjugated. There is a fall in serum proteins (especially albumin) and a reversal of the albumin/globulin ratio in advanced cases. Alkaline phosphatase and SGOT and SGPT levels rise. The derangement of the liver enzymes is proportional to the degree of parenchymal damage and not to the duration of disease. The ratio of serum gamma-glutamyl transpeptidase to SGOT is elevated in infants with infantile obstructive cholangiopathy.⁶⁸ This appears to be a sensitive method for distinguishing infants with extrahepatic biliary atresia from those with neonatal hepatitis. This distinction was evident as early as 5 to 14 days of age and was clearly manifest in ten of 12 infants with biliary atresia. The ratio was also elevated in patients with alpha 1-antitrypsin deficiency that had bile duct proliferation. Though the ratio cannot clearly distinguish extrahepatic biliary atresia from neonatal hepatitis, but an elevation raises a strong presumption of biliary obstruction and invites early consideration of laparotomy and examination of the biliary tree [68]. A cut off level of > 150 IU/l has been found to be suggestive of biliary atresia with 100% sensitivity in a study from the authors' institution⁶⁹.

Nuclear scanning

Technetium 99m-labeled diisopropyl iminodiacetic acid (99m Tc-DISIDA) hepatobiliary scintigraphy is a reliable test. The excretion of the isotope into the gut within 24 hours establishes the patency of the biliary tract. However, a negative scan even after 24 hours may be consistent with both EHBA and advanced stage of neonatal hepatitis (with cholestasis). After priming with phenobarbitone and betamethasone therapy to stimulate the hepatic enzymes, increase the flow of bile and decrease the inflammation, more patients with neonatal hepatitis excrete the isotope into the gut within 24 hours while that of EHBA fail to do so. Priming thus increases the specificity of the test. It has been reported that 40% patients with neonatal hepatitis excreted the isotope into the gut within 24 hours in post-luminal HIDA scan while that of BA again failed to do so⁷⁰.

Verreault J et al retrospectively studied the 99m Tc-DISIDA hepatobiliary scintigraphy of 26 patients with

pathologically proven infantile obstructive cholangiopathy according to two types of criteria. In the first criteria, the parameters considered were 1) hepatocyte clearance 2) hepatobiliary transit time and 3) visualisation of intestinal activity. For biliary atresia, sensitivity of 88.2%, specificity of 88.9%, positive predictive value of 93.8% and negative predictive value of 80.0% were obtained. For neonatal hepatitis, those parameters were 57.1%, 94.7%, 80.0% and 85.7% respectively. The second criteria identified only biliary atresia. The parameters considered were 1) presence or absence of intestinal radioactivity through 24 hours and 2) birth weight. Sensitivity, specificity, positive and negative predictive values were 88.2%, 88.9%, 93.8% and 80.0% respectively. Even though there are a few false negatives, biliary scintigraphy does remain one of the most important diagnostic tests in the context of biliary atresia. Thus, a positive excretion of the isotope in the gut, rules out severe obstruction eg. Biliary atresia, while a severe cholestasis (NH) may not show positive excretion of the isotope into the gut even in the presence of patent biliary channels.

Ultrasonography

The visualisation of the gall bladder suggests the possibility of neonatal hepatitis. Non-visualisation of gall bladder is seen in severe cholestasis with EHBA or neonatal hepatitis. Abdominal ultrasound may reveal a very small or completely absent gallbladder in EHBA. To have a better visualization of gall bladder, infant should be fasting for at least 4 hours otherwise a false negative result is likely. This is not a reliable modality as it is operator dependent. However, it may impart valuable information regarding the presence of a small choledochal cyst at the portahepatis in association with the EHBA. It can show intra and extrahepatic dilatation as well as changes in liver architecture indicative of cirrhosis. The evidence of dilated intrahepatic biliary channels rules out EHBA. Experienced operators can identify the triangular cord sign. The triangular cord sign alone had sensitivity of 49%, specificity of 100% and accuracy of 72.5%. Histopathology compatible with extrahepatic biliary obstruction alone had 90.2% sensitivity, 84.6% specificity and 87.8% accuracy⁷¹. The triangular cord sign and histopathology in isolation or combination resulted in sensitivity of 93.2%, specificity of 85.7% and accuracy of 90.3% .

Percutaneous needle biopsy

Interpretation of the biopsied material has been of great concern to the pathologist and the surgeon both. There

is a lot of overlapping in the histologic finding of EHBA and neonatal hepatitis. Diagnostic errors have been more towards diagnosing the cases of EHBA as that of neonatal hepatitis and hence there could be a dangerous delay with the expectant treatment in such cases. There are also inherent risks of performing needle biopsy, and the sample may also be too tiny to interpret. Pediatricians would still depend on liver histology, possibly as they happen to see these cases more early. Most of the cases seen by the surgical teams are usually in the advanced stage, a delay can be avoided by planning an early surgery rather than performing an open wedge-biopsy. In experienced hands, liver biopsy has been reported as 100% accurate and the best method to differentiate BA from NH⁷². The outcome of BA cases with ductal plate malformation (DPM) was worse. One-third of all NCS in India is due to BA and among the intrahepatic causes acquired infection and galactosaemia are common. In a typical case of neonatal hepatitis, the liver histology would show inflammatory reaction with hepatocellular necrosis, and mild portal proliferation and fibrosis around the porta hepatis. In biliary atresia, the histology shows, bile duct proliferation, bile plugs, portal fibrosis yet the architecture of the liver is maintained. The overlapping histological features in both the NH and the EHBA include, multinucleated giant cells, pseudoglandular transformation and hematopoiesis.

The liver biopsy may point towards a different entity at different times. Hence, patients with neonatal conjugated hyperbilirubinemia need to be carefully followed to be certain that their courses continue to conform to the original diagnoses⁷³. Percutaneous liver biopsy after exclusion of medical causes of cholestatic jaundice (eg. Alpha 1-antitrypsin deficiency, Alagille's syndrome, and neonatal hepatitis) is a helpful investigation in diagnosis, but relies upon expert pathological interpretation. Negative ultrasonography and positive histology results should be able to establish the correct preoperative diagnosis in about 85% cases of BA [74]. In a series, an incorrect (typically giant-cell hepatitis) or non-specific biopsy diagnosis was reported in about 15% of those eventually shown to have BA [74]. Sensitivity and specificity of percutaneous liver biopsy for diagnosing BA has been reported as 88.2% each.⁷⁵

Duodenal drainage test

A 4 hourly duodenal aspiration is done to confirm the presence of bile in it. Again, the test may be false-

negative in patients of neonatal hepatitis with severe cholestasis. Among tests to confirm patency of the bile ducts, duodenal fluid aspiration is recommended by some authors as an easy, inexpensive and rapid method for detecting complete obstruction of the bile flow^{76,77}. Sensitivity and specificity have been reported as 100% and 85% respectively. The procedure has been described very reliable in the clinical practice⁷⁸, however, it is not frequently practiced.

Operative cholangiogram

A newborn with jaundice that has shown no excretion of radioisotope within 24 hours, even after phenobarbitone therapy, demands the benefit of operative cholangiogram without further delay. In our experience, nothing short of an operative cholangiogram and an open liver wedge biopsy has given the definite clue to the diagnosis in a jaundiced infant. Presence of golden yellow bile in the gall bladder confirms cholestasis and flushing of the biliary tree with the saline is all that is required. In the presence of bile, apart from the rare type 1 cases, then BA can be excluded. A free flow of the dye, from the gall bladder to the intestine, shows the patency of the distal tract. Cholangiogram through the gallbladder should demonstrate the entire biliary tree, but in those cases, where only the distal common bile duct (CBD) opacifies an attempt should be made to delineate the proximal intrahepatic tree by application of a distal vascular clamp. If the dye study shows no bile ducts or if there is no gallbladder, then the diagnosis of biliary atresia is made. This dye study provides a sharper image of the bile ducts than does the HIDA scan. On occasions, it is impossible to perform the operative cholangiogram as the extrahepatic biliary tree is completely atretic (Type III biliary atresia).

Recent Advances

Positive lipoprotein-X has been found in all cases of biliary atresia while a negative test does not necessarily mean a neonatal hepatitis. This test has been done quite frequently in Japan but is not much in use elsewhere. New modalities such as ERCP and MRCP have been used at times, although the former is clearly highly operator-dependent and the latter not sufficiently precise in its delineation of infantile biliary anatomy to offer real advantage⁷⁹⁻⁸¹. A laparotomy could be prevented in 12% of children with suspicion of biliary atresia⁸⁰.

Percutaneous transhepatic cholangiography may occasionally be used if dilated intrahepatic bile ducts are a feature as in the inspissated bile syndrome group, when not only can the diagnosis be established but an attempt at therapeutic saline lavage also can be made.

There are many instances when a definite diagnosis cannot be established without an operative cholangiogram. In these cases, one cannot procrastinate too long in the hope that the patient's condition will improve spontaneously, because the surgical results are much better when the operation is performed before the patient is 10 weeks old [3]. Even in Japan, although patients who were operated on between 30 days and 60 days gradually increased in number, still more than 40% of patients underwent surgical treatment over 61 days after birth⁸². Thus one should proceed for an operative cholangiogram to be followed by the definite procedure in the same sitting.

Surgical procedure

Surgical management is indispensable, but the damage of the intrahepatic biliary system is responsible for much of the morbidity after surgery. Now it is established with biliary atresia should be detected early and operated upon, preferably before 60 days of age, before the irreversible liver damage takes place. The treatment of EHBA is surgical, with anastomosis between the biliary tree and the intestine in the correctable type and a hepatic porto-enterostomy for the noncorrectable group⁶⁷. HPE is a temporizing treatment allowing the infant to develop and grow, followed in the majority of the patients by liver transplantation.

Hepatic duct-enterostomy and hepatic porto-enterostomy are the treatment of choice for 5% of correctable and for 95% of non-correctable type of patients, respectively. For patients with failed hepatic porto-enterostomy and for patients with decompensated liver cirrhosis at the time of definitive diagnosis, liver replacement should be considered.

The main aim of surgery is to perform a dissection at the porta hepatis, transaction of the portal mound to achieve flow of bile and then maintain it effectively in the postoperative period with the use of cholretics (steroids, phenobarbitone and decholin or UDCA). A major breakthrough in the surgery for biliary atresia was seen in 1968, Professor Morio Kasai reported

the operative relief of biliary obstruction in infants traditionally considered to have non-correctable biliary atresia¹⁶. The procedure has been modified subsequently by many others¹⁵. It is a routine practice in Japan to keep these patients in the postoperative period in the hospital for months, induce choleresis, evaluate for the postoperative cholangitis and manage the complications, if any.

There is still ample discussion regarding which procedure, hepatic porto-enterostomy or primary liver transplantation, should be taken as the initial surgical management for biliary atresia⁸³. The consensus among pediatric surgeons all over the world is that hepatic porto-enterostomy is still a reasonable first choice as far as it is performed in the early stage of the disease, with the hope some patients (5-10%) may not require transplantation at all. The main problem confronted with Liver transplantation is the nonavailability of a suitable donor, smaller size of the recipient abdomen, immunosuppression, cost, and a significant postoperative morbidity and even mortality following the major procedure. Probably biliary atresia is more in need of preventive or prophylactic measures than of new surgical procedures². Children with an advanced disease (age more than 120 days, liver firm with portal hypertension, bilirubin more than 10 mg%), require serious considerations if a major surgery like HPE should at all be performed in them. It is the considered opinion of the authors to give the benefit of exploration in such patients and in the absence of bile flow at the porta hepatis, a sump drain is left for about a week. Choleresis is induced and then a repeat HIDA scan is performed, to monitor the bile output if any. In absence of that, the drain is simply pulled out and in this way, the problems related to HPE can be avoided.

Factors affecting Prognosis

Biliary atresia is a rare disease and surgical outcome following biliary atresia depends upon adequate dissection and restoration of bile flow, together with effective treatment of the two major complications (cholangitis and portal hypertension). Of utmost importance towards the final prognosis is early detection, prompt confirmation and surgical treatment before 2 months of age. Even with early treatment the result of bilioenteric drainage procedures have been discouraging in the long term whereas porto-enterostomy (PE) done in older children has been largely unsuccessful all over the world^{84,85}.

Need for alternative management

At present, there is no specific therapy for BA; however, sequential surgical therapy begins with creation of a hepatopertoenterostomy (HPE); in those with end-stage liver disease, liver transplantation is indicated [86]. Since most candidates are young children of small size, there is a shortage of size-matched donors for liver transplantation. At present, an increased awareness to ensure early diagnosis and development of methods to prevent progressive fibrosis are needed. These considerations are dependent on detailed studies of the pathogenesis of BA.

Discussion:

The reasons to consider neonatal hepatitis and Biliary atresia in one spectrum include

1. Common Etiological hypothesis – Viral, toxic, Infectious, genetic. Recent studies have focused on normal and altered bile duct morphogenesis and the role of various factors (infectious or toxic agents and metabolic insults) in isolation or in combination with a genetic or immunologic susceptibility in the etiology of biliary Atresia⁸⁶.
2. No definitive cause of Biliary Atresia identified till date. The search for the etiopathogenesis or mechanism leading to progressive hepatic fibrosis despite establishing a good bile flow in some cases of biliary atresia is still in the primitive stages. Therapies will not improve outcomes until novel treatments are introduced, which may intervene in the inflammatory or fibrotic steps of the disease process⁸⁷.
3. Overlapping diagnostic modalities. Even tests considered reliable as HIDA after priming and liver biopsy are overlapping. There are cases where over time the liver biopsy consistent with neonatal hepatitis becomes suggestive of biliary atresia.
4. Timing of surgery in biliary atresia having a great impact on the surgery. There are many reports that accept the fact universally that increasing the age at surgery has a negative impact on the results of the Kasai operation for biliary atresia in infancy and early childhood. The porto-enterostomy should be done before there is irreversible sclerosis of the intrahepatic bile ducts⁶¹. Consequently, a prompt evaluation is indicated for any infant older than 14 days with jaundice to determine if conjugated hyperbilirubinemia is present⁶¹

5. The timing of onset of liver injury in biliary atresia is not known, although in approximately 10% of cases, biliary pathologic condition associated with the biliary atresia splenic malformation syndrome must begin well before birth [88]. In a recent study Makin E et al, 2009 reported three infants who had occlusive BA evident on the first day of life and underwent laparotomy within first week of life. In all cases, their liver was grossly normal, and histologic changes were trivial. Thus they suggested that the detrimental cholestatic liver injury, later characteristic of BA, only begins from the time of birth despite a prenatal occlusive biliary pathology. It may be that tissue injury only occurs with the onset of the perinatal bile surge initiating periductal bile leakage and the triggering of an inflammatory and ultimately fibrotic response.

Conclusion

A goal in early diagnosis and operation may result success in variable number of children with biliary atresia. The surgery is very specialized and should be performed only in few well established major institutions. Presently, Liver transplantation is the only hope of cure in patients with failed bilioenteric drainage procedure for established biliary atresia and it constitutes about 80% workload. This review article is an attempt to consolidate evidence on review of literature pointing towards a common etiopathological process leading to neonatal cholestasis that may begin with neonatal hepatitis and end with biliary atresia depending upon the concentration, amount and the timing of the inciting agent. It also highlights the importance of early referral of any case with neonatal jaundice in a full term neonate, preferably at 2 weeks age. An early HIDA, preferably after priming with phenobarbitone and steroids for 7 days, followed by an operative cholangiogram within a week should be planned for all suspicious cases of EHBA, based on clinical examination, dark urine and presence of pale stools. A flushing for cases of neonatal cholestasis due to neonatal hepatitis with a patent biliary tract during the operative cholangiogram should be looked upon as a therapeutic modality simulating lavage for meconium ileus. This will help to treat more cases within the correctable range and prevent the disease from progressing to a life threatening situation. "*Treat every case of dark urine, as biliary atresia until proved otherwise*" should be the mandate to tackle this intractable disease.

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