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Neonatal Liver Biopsy- Experience from a Tertiary Care Centre

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Abstract

Objectives: *To clinch the diagnosis of complex neonatal liver diseases (where all other diagnostic modalities fail) this study was conducted in a Tertiary Care Centre of Northern India.*

Materials and Methods: *The neonates who attended pediatric Gastroenterology Clinic of PGIMER – Chandigarh from July 2000 to June 2003 having history of liver disease (i.e. Jaundice , clay colored stool, high colored urine, hepatosplenomegaloy, syndromic features, sibling history of liver disease etc) were subjected to liver biopsy when history, clinical examination, USG abdomen, LFT, HIDA Scan, per operative cholangiogram, enzyme study of metabolic disease) fail to establish diagnosis. Liver biopsy was done as per standard protocol considering all safety measures.*

Result: *Out of total 50 neonates (who had liver biopsy), 15 (30%) had biliary atresia (bile duct proliferation, bile plugs , portal fibrosis, normal lobular architecture), 30 (60%) had ideopathic neonatal hepatitis (multi nucleated giant cells, pseudoglandular transformation, dilated canaliculi, inflammatory infiltrates in heaptocellular lobules with necrosis, mild portal tract fibrosis, bile duct proliferation), One (2%) had galactosemia (diffuse hepatocellural damage, marked steatosis, cholestasis, pseudoacinar transformation), one (2%) had alfa one antitrypsin deficiency (PAS positive Diastase resistant alfa one antitrypsin inclusion in peripheral hepatocytes, bile stasis, minimal inflammation), one (2%) had non syndromic paucity of intrahepatic bile ducts having low ratio of <.9 of intra lobular ducts to portal tracts).*

Conclusion: *Neonatal liver biopsy is an important investigation for making accurate diagnosis of complex liver disease*

Keywords: *neonatal liver biopsy, complex liver disease.*

Introduction

Neonatal Liver biopsy is very important investigation for complex liver disease .It is very important for making correct diagnosis of neonatal cholestasis, abnormal LFT of unknown origin, metabolic liver disease, alpha- 1 – anti trypsin deficiency, neonatal haemochromatosis, sclerosing cholangitis, galactosemia, biliary atresia, ideopathic bile ductopenia [(1)]

Liver biopsy is very important investigation for extra hepatic biliary atresia (EHBA).[(2)]

Contraindication of liver biopsy are increased prothrombin time, thrombocytopenia, ascites (transjugular biopsy is preferred), haemangioma, uncooperative patient[(3)]

While differentiating EHBA from neonatal hepatitis diagnostic accuracy of liver histology was 96 %, peak radio isotope content in duodenal

juice was 84%, ultra sonagraphic examination of hepatobiliary system was 80%, presence of clay colored stool was 80%[4]

The present study was done in a tertiary care centre where various cases of neonatal liver disease are found, a liver biopsy is done to solve diagnostic problem.

Materials and Method

The neonates who attended pediatric gastroenterology clinic, PGIMER – Chandigarh from July 2000 – June 2003, having a history of liver disease (jaundice , clay colored stool, high colored urine, hepatosplenomegaly, syndromic features , history of liver disease in siblings were subjected to liver biopsy where history ,clinical examination, USG abdomen , LFT, HIDA Scan, per operative Cholangiogram, enzyme study for metabolic diseases fail to established diagnosis

Liver biopsy was done as per protocol[5]

The baby was placed on table, antiseptic lotion was given on local area, small hollow needle was used.

After collection of specimen, the local area was covered with bandage and the baby was rolled on right side and kept for few hours for observation. The baby was observed for local bleeding, vomiting, crying or baby looking pale or not.

Results

Out of 50 neonates (who had liver biopsy) 15 (30%) had biliary atresia, (bile ductular proliferation, bile plug, portal fibrosis, normal lobular architecture), 30 (60%) had neonatal hepatitis (multi nucleated giant cell, pseudo galandular transformation, dialated canaliculi, inflammatory infiltrates with necrosis in hepato cellular lobules with mild portal tract fibrosis , bile duct proliferation) one (2%) had galactosemia (hepato cellular damage, marked statosis, cholestasis, pseudoacinar formation) one (2%) had alpha- 1 – anti trypsin deficiency (PAS positive diastac resistant alpha –I anti trypsin inclusion body in peripheral hepatocytes, bile stasis, minimum inflammation), one (2%) had non syndromic paucity of intra hepatic bile ducts with ratio less than 0.9 of inter lobular ducts to portal tracts.

Discussion

In 25 to 50 percent cases of neonatal cholestasis, where no causes are found after extensive search for EHBA, (viral, genetic, metabolic causes)– this group is called ideopathic neonatal hepatitis (INH) and liver biopsy help to establish diagnosis in this cases.[6] In our study we got ideopathic neonatal hepatitis in 30 (60%) cases .Out of 50 cases of neonatal cholestasis, multi nucleated giant cells, pseudogalandular transformation, dialated canaliculi, inflammatory infiltrates in hepato cellural lobules with necrosis, mild portal tract fibrosis, bile ducts proliferation were found in these cases of ideopathic neonatal hepatitis.

Out of 50 cases, we got 15 (30%) cases of biliary atresia. Liver biopsy showed bile duct proliferation, bile plug, portal fibrosis, normal lobular architecture as seen by other research workers[4]

In alpha one anti trypsin deficiency, liver biopsy shows characteristic changes of alpha one anti trypsin granules (AAT granules).[7]

Alpha one anti trypsin deficiency may show various histological picture from normal liver, various forms of choronic hepatitis, to cirrhosis. Positive hepatocyte staning for AAT granules are seen in all cases of alpha one anti trypsin deficiency. Thus immunostaining of AAT granules are much superior to PAS – distase staining to identify homo or heterozygotes of alpha one anti trypsin deficiency [8]

AAT granules are seen in hepatocytes as well as in bile ducts in alpha one anti trypsin deficiency. It has much more diagnostic value in liver biopsy[9]. Alpha one anti trypsin deficiency requires thorough investigation because it can cause micro nodular cirrhosis, hepato cellular carcinoma, pulmonary emphysema[10]

Unexplained paucity of intra hepatic bile duct (PIBD) is seen in some cases of neonatal cholestasis. Intra hepatic intra lobular bile duct

has low ratio (less than 0.9 compared to portal tracts.)

It may be syndromic variety (Alagille's syndrome having cardiac, vertebral, facial anomalies, posterior embryotoxin etc) or non syndromic variety [11]

Some researchers think that ideopathic adulthood ductopenia may be a late onset of non syndromic paucity of intra hepatic bile duct. Both may be spectrum of same disease [12]

Non syndromic PIBD presents with jaundice, intense pruritus, xanthoma, abnormal LFT. Liver transplantation is only treatment for neonatal PIBD[11]

We got one case (2%) of non syndromic paucity of intra hepatic bile duct in our study

In galactosemia, typical liver biopsy shows extensive periportal and intra lobular fibrosis, ductular cysplasia, pseudo glandular transformation and distortation of periportal vasculature[13]

We got similar picture in one (2%) case of galactosemia

There is complete reversibility of histology after galactose withdrawl in follow up biopsy at five months of age [13]

Early diagnosis and treatment is a must for galactosemia, probably within one to two weeks of life. Otherwise child may have cognitive dysfunction, language delay, speech problem in long run[14]

Duarte variety of galactosemia can consume breast milk, milk formula and may be asymptomic. When they develop symptoms like jaundice, they respond rapidly to galactose withdrawl. There is controversy regarding management of Duarte galactosemia. If galactose 1 phosphate level is more than 1mg %, galactose is withdrawn.[15]

Electron microscopy of liver in galactosemia shows extensive fatty change and fibrosis, cholestasis, lipid droplet, increased endoplasmic reticulum, abnormal mitochondria.[18]

Histologic picture of galactosemia shows hepato cellural degeneration, with focal fatty changes, particularly in regenerative nodules, pseudo rosette, cholestasis, fibrosis, cirrhosis[16]

JH Teckman observed that in alpha 1 antitrypsin deficiency, large quantity of mutant Z protein is accumulated by mutant Z gene. This triggers hepatocellular injury and fibrosis. [17]

In those liver biopsy of galactosemia, researcher observed that majority had cirrhosis or bridging fibrosis. Those patients who were compliant with diet, majority of the cases survived. Follow up of at least 6 months showed good liver function[19]

Lee et al observed that preoperative biopsy is highly specific and sensitive in diagnosis of EHBA. It is a highly reliable test that affects prognosis of EHBA babies after surgery[20]

Ideopathic neonatal hepatitis should be included in differential diagnosis of infant with cholestatic jaundice. Liver biopsy is most reliable method to differentiates INH from EHBA[21]

Shibuya T et al observed that liver biopsy is very important to diagnose and prognosticate in case of neonatal hepatitis [22]

Lucky Gupta et al observed that preoperative histopathological features have better correlation with surgical outcome rather than age of baby when surgery is done in case of EHBA. Surgery should be offered to those who are beyond currently accepted cut off age for good prognosis in EHBA provided liver histology shows lesser degree of liver damage. Higher degree of cholestasis, hepatic architectural alternation, bile ductular proliferation, portal edema, higher grades of fibrosis shows bad prognosis even if surgery is done before 60 days[23]

de carvalho E et al described etiopathogenesis of EHBA and postulated that immune response specially interferon gamma response, genetic susceptibility, disordered embryonic development of biliary tract may play big role in biliary atresia . They concluded that interferon gamma and other cytokines may be potential target for therapeutic intervention [24]

Steven M Schwarz et all observed that biliary atresia has two groups – those with isolated biliary atresia (postnatal group) which accounts for 65 to

90 percent of case and those who have congenital anomaly comprises 10 to 35 percent of cases.[25]

Correa KK et all reported a male infant with fulminant hepatic failure on day one,(congenital infection metabolic disorder etc were excluded). Liver biopsy shows neonatal giants cell hepatitis with unusual degree of fibrosis[26]

Some researchers reviewed histopathology of liver in various 'vanishing bile duct disease. 'These are progressive disappearance of intra hepatic bile duct branches. This so called disappearance of inter lobular bile ducts (syndromic and non syndromic) may be caused by immune mediated obliterative cholangiopathy[27-28]

Krantz et al postulated JAG- 1 gene mutation having important role in bile duct paucity in causing cardiac skeletal, ocular, facial abnormality. JAG-1 mutation was found in 70% case of AGS (Alagille syndrome) [29]

SC Ling et al observed that survivals of cholestatic syndromes (biliary atresia, alagille syndrome, caroli's disease, congenital hepatic fibrosis) who received appropriate treatment showed cirrhosis, portal hypertension nutritional deficiency, congenital heart disease of AGS, progressive encephalopathy, intractable pruritus, recurrent biliary sepsis, complication of portal hypertension[30]

De Bruyne R et al suggested that neonate presenting with acholic stool must be referred to pediatric hepatology unit in order to rule out biliary atresia as prognosis after proto enterostmy correlate with younger age at time of surgery[31]

Some researchers observed that biliary atresia, syndromic and non syndromic paucity of intra lobular bile duct, choledochal cyst can present with cholestasis during early life. These conditions have to be differentiated from congenital infection, in born error of metabolism which can affect liver function[32]

Conclusion

Neonatal liver biopsy is an important investigation which can save life by making a correct diagnosis and proper treatment of the cause.

Conflict of interest: Nil

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