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A Study of Extrahepatic Biliary Atresia from a Tertiary Care Centre

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Abstract

Objectives: *Extrahepatic Biliary atresia is a surgically correctable congenital anomaly in infants. As the surgical success of Kasai procedure depends upon early operation (i.e within 60 days of life), the dynamic changes of clinical profile of EHBA need to be studied. Early detection of EHBA is of paramount importance for ultimate survival of patients.*

Method: *Twenty- Six infants of EHBA who were admitted in pediatric Gastroenterology ward of PGIMER from Jan 1996 to June 2001 were taken for study. The clinical profile, ultrasonogram, hepatobiliary scintigraphy (HIDA Scan), POC (Peroperative Cholangiogram), liver biopsy, LFT, routine blood test etc. were studied.*

Results: *Out of 26 cases, 18 were male and 8 were female. Age of infants varied from 1 month to 9 month. Onset of jaundice and clay coloured stool was variable, ranging from day 1 to day 21 after birth. Twenty out of 26 (76%) infants showed jaundice and clay coloured stool before 2 weeks of life. This is contrary to age old observation that jaundice of EHBA usually appears after 2 weeks of life. Out of 26 cases, 9 patients (34%) attended hospital for the first time before 2 months of age. Congenital anomaly was seen in one infant who had Dextrocardia with situs inversus. Only one infant was preterm and 25 were full term. Findings of ultrasonogram and HIDA scan were in concordance with POC findings. Kasai operation was done on 21 (9 infants before 2 months and 12 infants between 2-3 months). On 5 patients, Kasai was not done- their ages were 6 month, 7 months, 8 months, 8.5 months, 9 months. Three post operative patients who had cholangitis before one year of age were successfully treated. Those who were operated before 60 days of life were healthy at one year of age. Those who were not operated or operated after 60 days of life died before one year of age. Liver Biopsies of all infants were consistent with EHBA. Biopsy of infants who were more than 6 months of age had findings of EHBA with predominant portal fibrosis and early cirrhotic changes.*

Conclusion: *Jaundice can appear before 2 weeks of age in EHBA. Kasai operation before 60 days have good survival at 1 year of age. Early detection and surgical intervention (less than 60 days) is mandatory.*

Introduction

Biliary Atresia is an important cause of neonatal cholestasis but evidence for strict mandelian inheritance is lacking. It is an aggressive form of neonatal cholestasis caused by distruction and obliteration of extrahepatic bile ducts- leading to rapid progressive biliary fibrosis and cirrhosis.

Combination of exome sequencing and large population studies are expected to reveal modifier gene relavent to biliary atresia[1]

Many prenatal and perinatal insults are suspected to have a role in pathogenesis of biliary atresia. Two viruses, Reo virus and Rota virus are suspected to have a role in immune mediated injury to biliary tract.

Fas Ligand up regulation and apoptosis of bile duct epithelia have been demonstrated in T lymphocyte and macrophage activation in portal tract.

It is proposed that virally induced neoantigen displaced in biliary epithelia may play a role in initiating immune mediated biliary tract destruction and ongoing injury in perinatal form of biliary atresia.

Potential etiologies for perinatal factors include viral infection resulting in biliary tract obstruction. Prenatal and perinatal factors result in complete obliteration of extrahepatic biliary tree. Even continued injury and intrahepatic sclerosis of bile duct persist after successful portoenterostomy.[2]

Bates et al observed that biliary atresia has a perinatal origin because it is rarely seen in preterm baby. Biliary atresia is 50% cases of pediatric liver transplantation.[3]

Lugo Vicente et al think that biliary atresia must be diagnosed and operated by kasai procedure within eight weeks of life. Hepatic transplantation is reserved for those children with failed portoenterostomy, progressive liver failure or late referral to surgery.[4]

Middlesworth et al think that biliary atresia is a progressive obliterative process involving biliary tract caused by severe cholestasis, progressive fibrosis and cirrhosis leading to portal hypertension. Kasai operation is standard treatment of biliary atresia. Liver transplantation is done for those whose Kasai operation fails.[5]

Devenport et al described syndromic biliary atresia group which include biliary atresia with splenic malformation or cystic biliary atresia or CMV IgM positivity associated with biliary atresia.

The remaining largest group is isolated biliary atresia.

Kasai portoenterostomy is primary treatment with expected five year native liver survival.[6]

Tagge et al conclude that portoenterostomy offers reasonable chance for success for biliary atresia.[7]

A longer duration of jaundice before Kasai operation, failure to extrahepatic bile flow, ductules less than 200 micron are associated with need for liver transplantation after Kasai procedure.[8]

Materials and Method

Twenty- Six infants of EHBA who were admitted in pediatric Gastroenterology ward of PGIMER from Jan 1996 to June 2001 were taken for study. The clinical profile, ultrasonogram, hepatobiliary scintigraphy (HIDA Scan) , POC (Peroperative Cholangiogram), liver biopsy, LFT, routine blood test etc. were studied.

Results

Out of 26 cases, 18 were male and 8 were female. Age of infants varied from 1 month to 9 month. Onset of jaundice and clay coloured stool was variable, ranging from day 1 to day 21 after birth. Twenty out of 26 (76%) infants showed jaundice and clay coloured stool before 2 weeks of life. This is contrary to age old observation that jaundice of EHBA usually appears after 2 weeks of life. Out of 26 cases, 9 patients (34%) attended hospital for the first time begore 2 months of age. Congenital anomaly was seen in one infant who had Dextrocardia with situs inversus. Only one infant was preterm and 25 were full term. Findings of ultrasonogram and HIDA scan were in concordance with POC findings. Kasai operation was done on 21 (9 infants before 2 months and 12 infants between 2-3 months). On 5 patients, Kasai was not done- their ages were 6 month, 7 months, 8 months, 8.5 months, 9 months. Three post operative patients who had cholangitis before one year of age were successfully treated. Those who were operated before 60 days of life were healthy at one year of age. Those who were not operated

or operated after 60 days of life died before one year of age. Liver Biopsies of all infants were consistent with EHBA. Biopsy of infants who were more than 6 months of age had findings of EHBA with predominant portal fibrosis and early cirrhotic changes.

Discussion

Sangkhathat S et al observed that age of infant less than 60 days, type one of biliary atresia are key determinant of successful Kasai. Early cholangitis is an accletor of progressive cirrhosis . stool colour and billirubin level at one month after surgery is predicator of jaundice clearance.[9]

Om H et al observed that Kasai procedure continue to offer palliation if not long term success, in a large percentage of patients with extrahepatic biliary atresia. Out of 47 Kasai patient – 11 required liver transplant. Long term complication of Kasai patients are cholangitis, portal hypertension, variceal bleed, growth failure.[10]

Chittmittrapap S et al observed that age at operation, portal and parenchymal inflammation , presence of cholangitis are significant factors for poor prognosis of biliary atresia.[11]

Ryckman et al observed that primary transplantation should be offered as initial surgical treatment when biliary atresia is not recognized in infancy and established cirrhosis has resulted.

Sequential surgical treatment, early Kasai in infancy followed by selective transplantation for children with progressive hepatic failure showed improved results.

At present the surgical procedure (Kasai VS transplantation) should be used as sequential and complementary rather than competitive procedures.[12]

Rodeck et al observed that early predictor of success of Kasai are free tracer execration as shown by HBSS and serum billirubin less than 57 micro mole 6 weeks after operation. These children are monitored for future transplantation.[13]

Batinica S et al observed mitochondrial dysfunction in pathogenesis of biliary atresia they determine 40 mitochondrial single nucleotide polymorphism in 15 major mitochondrial haplotypes. Three years survival of native liver with haplotype E was significantly lower than other haplotypes.

Mitochondrial DNA haplo groups B 4 and E 4 are associated with lower and higher prevalence of biliary atresia respectively.[14]

Shinkai M et al followed up 20 years of post Kasai children. Survival depends on type of biliary atresia, age at initial Kasai, Era of surgery, surgical method. By age 20, 50 % developed cirrhosis. cholangitis and GI bleed occur in 37% and 70% cases after 20 years post Kasai children. [15] [18]

A longer duration of jaundice before Kasai, failure to established bile flow, requirement for phototherapy in neonatal period , ductules smaller than 200 micron are associated with liver transplantation after Kasai procedure.[16]

Jaundice clearance and cholangitis at first year following Kasai procedure is a good prognostic factor of survival.[17]

Ramm GA et al found that a longer duration of jaundice before Kasai, failure to establish bile flow, requirement for phototherapy in neonatal period, cholangitis of one month after Kasai will be predictor for failed Kasai and future liver transplantation.[19]

Some observers found TGF beta 2 as most actively transcribed TGF beta gene during process of liver fibrosis in biliary atresia.[20]

Nakanuma Y et al observed that in biliary atresia both ductular metaplasia and ductular proliferation are obscure. Biliary atresia with ductopenia showed narrowing of intralobullar ducts as consequence of degeneration with atrophy and fibrosis.[21]

Some observers believe that ductal plate malformation is responsible for biliary atresia.[22]

Tan CE et al observed that there is considerable overlap between various types of infantile cholangiopathy- which include EHBA , paucity of intrahepatic bile ducts, persistence of fetal biliary structure – so called ductal plate malformation.

Tan CE et al observed that proximal portion of Hilar bile ducts derived from intrahepatic biliary ductal plate. Furthermore, the developing intraheptic bile ducts maintain luminal continuity with common bile duct from start of organization. Biliary atresia may result from: (a) failure to establish a definite type of bile duct (b) leakage of bile from primitive bile ducts – resulting in an interstitial inflammatory reaction in adjacent mesenchyme. (c) continuous proliferation of primitive bile ducts at level of portahepatis beyond 25th week of gestation, a failed compensatory mechanism.(23)

Some observers found that normally at porta hepatis level, primary biliary ductal plate undergoes specific sequence of remodelling, resulting in formation of large tubular bile ducts surrounded by thick mesenchyme, between 11 to 13 weeks post fertilization. These developing bile ducts are in luminal continuity with extrahepatic biliary tree throughout gestation. Contratry to old belief no "solid phase" was observed in development of extrahepatic bile duct.

Some observers found that hepatic stelate cells produce excessive collagen for fibrosis in biliary atresia. Hepatocyte , hepatic stelate cells, biliary epithelium all contribute to fibrosis.(24)

some observers found that in biliary atresia, virus induced apoptisis of biliary epithelium by a TNF related ligand produce progressive obliteration of bile ducts .

Viral infection can cause a transition of mesenchymal cells for biliary epithelium - which leads to fibrosis

Vast majority of liver transplant in biliary atresia occur less than 2 years of age. Younger patients with biliary atresia had higher waiting list and post transplant mortality. There is urgent need to find method to improve bile drainage after Kasai procedure. Aggressive liver transplantation is not possible for all case of biliary atresia due to scarcity of donor liver. Pretransplant biliary drainage by Kasai , mutational care will improve liver transplant outcome.(25)(26)

Altman RP et al observed involvement of ductular reactions in ductual plate configuration- as causative factor for biliary atresia.

Extrahepatic biliary atresia is a dynamic obliteratory process. It can be favourably modified in approximately 50 % of infant by early Kasai. Despite adequate bile drainage, progressive hepatic fibrosis is confirmed by serial biopsies of same patients.(27)

Early performance of Kasai gives children best chance of survival, allowing delay of liver transplant to adulthood. Liver transplant done in adulthood gives good post transplant survival rate.(28)

Tan Kendrick et al defined gall bladder ghost triad as gall bladder length less than 1.9 cm , lack of smooth complete echogenic mucosal lining with an indistinct wall and irregular lobular contour and used it as criteria for biliary atresia. The gall bladder ghost triad is a very accurate sign of biliary atresia. Intermediate cases require close follow up.(29)

Anticytokeratin immunostaining showed similarities between abnormal ductuls with portahepatis in biliary atresia and the developing bile ducts in the first trimester. biliary atresia is caused by failure of remodeling process at hepatic hilum, with persistence of fetal bile ducts poorly supported by mesenchyme. As bile flow increases perinatally, bile leakage from this abnormal ducts may trigger an intense inflammatory reaction – which subsequent obliteration of biliary tree.

Some observers described triangular cord sign which as a triangular or tubular echogenic density seen immediately cranial to portal vein bifurcation. It represents fibrotic remnant of obliterated cord in biliary atresia. Diagnosis of biliary atresia was conformed at surgery and histology. Gall bladder length has mean of 0.52 cm in biliary atresia in comparison with a mean of 2.39 cm in non-biliary atresia infants. Triangular cord sing is a valuable non invasive and inexpensive mean of diagnosis of biliary atresia. (30) (31)

We got triangular cord sign in USG in 50% (13/26) cases. We got 100% cases (26/26) of POC positivity in biliary atresia. POC and histology were correlated in all cases.

Katherina et al observed that complete visualization of extrahepatic biliary system by MRCP excludes biliary atresia whereas non visualization of CBD or hepatic bile ducts suggest disease. Sensivity and specificity are 90 % and 77 % respectively. sensivity of triangular cord sign in biliary atresia diagnosis is 77%, specificity 97% , PPV 95 %. The degree of hepatomegaly and heterogenous echogenesity is propositional to liver fibrosis and indicates duration of course and prognosis.[32]

Out of 26 cases of biliary atresia, we got 5 cases where Kasai procedure was not done due to delay in appearance of patients in hospital. All of them progressed to cirrhosis.

Lap Kasai is feasible but outcome in term of native liver survival rate and actuarial survival rates are unfavourable compared to conventional surgery. Lap Kasai does not cause fewer additions at subsequent liver transplant.[33]

Conclusion

Biliary atresia is difficult challenge to pediatrician and pediatric surgeon. Jaundice can appear even before 2 weeks of age in biliary atresia. Kasai procedure is still helpful to improve survival rate of biliary atresia. But golden period of 60 days is most important for Kasai procedure. Early diagnosis is mandatory for improve survival.

Conflict of interest – Nil

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