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Medical Science

# CIRRHOSIS IN CHILDREN- EXPERIENCE FROM A TERTIARY CARE CENTRE

**Sujay Chaudhuri** Division of Pediatric Gastroenterology, Department of Gastroenterology, PGIMER Chandigarh

**ABSTRACT**

**Objectives-** To evaluate incidence, etiology and clinical profile of cirrhosis in children in a northern city of India. This study was conducted.

**Methods:-** The children (less than 12 years) who attended pediatric gastroenterology OPD in PGIMER Chandigarh from July 2000- June 2003 with symptom of chronic liver disease (abdominal swelling, pedal edema, jaundice, high colored urine , clay colored stool, GI bleed , encephalopaphy, family history of liver disease in siblings etc.) were enrolled for the study. Detailed history , clinical examination , investigation (USG whole abdomen, LFT, PTI,HIDA scan , per operative cholangiogram, TORCH infection profile, enzyme study for metabolic disease like galactosemia, alfa one antitrypsin deficiency , glycogen storage disease , serum cerulospasmin , urinary copper, slit lamp examination for KF ring, auto immune marker like ANA, SMA,LKM, viral marker , UGI endoscopy, liver biopsy , liver copper estimation , ultrasound Doppler examination of hepatic veins etc.) were done.

**Results:-** Out of 50 total cases of cirrhosis , 10 (20%) were biliary atresia who came late for surgery , 5 (10%) had galactosemia, 1(2%) had alfa one antitrypsin deficiency , 1 (2%) had glycogen storage disease, 10(20%)had Wilson's disease , 10 (20%)had auto immune hepatitis , 7(14%) had Indian childhood cirrhosis, 1(2%) had neonatal hepatitis , 5 (10%) had Budd Chiari syndrome. Out of 50 cases , 25 (50%) had esophageal varices in UGI endoscopy. Out of 10 Wilson's disease 3(30%) came with fulminant condition where postmortem liver biopsy was done.

**Conclusion:-** Cirrhosis in children is an important problem. Etiological diagnosis is important to prevent its progress.

**KEYWORDS :** Chronic Liver Disease , Cirrhosis In Children

**Introduction:-** cirrhosis in children is an important problem. It is a condition of diffuse liver fibrosis with nodule formation and hepatic architectural change is irreversible resulting in portal hypertension and hepato celular failure.

Etiologies of cirrhosis in children are variable from biliary atresia and genetic disease in infancy to auto immune hepatitis , Wilson's disease , alfa one antitrypsin deficiency , sclerosing cholangitis (in adolescents) (1)

In clinical practice mortality risk of pediatric cirrhosis is estimated by PELD (pediatric end stage liver disease ) score where albumin , bilirubin, age, INR , degree of growth failure are considered. (2)

Five to fifteen percent of childhood cirrhosis is cryptogenic where no apparent cause is known. They are presumed to be due to fatty liver disease or mitochrondiopathy of liver. Liver mitochrondrial failure in health and disease are easily tested by breath test with novel 13 C substance ( alfa keto isocaproic acid and methionine) which signify liver mitochrondrial function. (3) (4)

20 percent case of biliary atresia is "fetal" origin and 80 percent is due to perinatal or "acquired origin" Garcia – Barcelo MM et al made a genome wide association study and indentifies susceptibility locus for biliary atresia in $10_q24.2$

"Fetal" form of biliary atresia is manifested as jaundice at birth , extra hepatic anomalies (vascular malformation, variant abdominal organ position and heart disease)

In acquired biliary atresia jaundice occurs 2 weeks after birth. (5)

Alfa one antitrypsin deficiency is an important cause of pediatric cirrhosis . The classic form of disease is homozygosity of two mutation ($p_i$zz genotype for SERPINA 1).

More than 100 mutations are found in alfa one antitrypsin gene but Z mutant is mainly related to liver disease . In alfa one antitrypsin deficiency neonatal cholestasis , liver dysfunction , cirrhosis are natural and liver transplantation is often required (6).

Auto immune liver disease include auto immune hepatitis (AIH) , sclerosing cholangitis , primary biliary cirrhosis (PBC) while AIH is most common in children but incidence of sclerosing cholangitis is also raised specially in adolescent with IBD . (1)

Duarte Rey C et al found that HLA class II was associated with AIH in latin America . The serologic group DQ2 was a risk factor for AIH while DR5 and DQ3 were protective factors in Latin American population (7)

Roberts EA et al observed that AIH often was present in acute disease in children. Some children have sclerosing cholangitis which may have clinical manifestation resembling AIH. This AIH like PSC (primary sclerosing chloangitis ) is termed auto immune sclerosing cholangitis (8).

In our study we got 10 (20%) auto immune hepatitis out of 50 total case of cirrhosis.

Amedee Manesme O et al observed cholestasis in 8 children with cholestasis appearing in first week of life followed by cirrhosis , portal hypertension. Percutanuous cholecystography (USG guided )showed abnormal intra hepatic bile ducts with rarefaction of segmental branches , stenosis , focal dialatation. Histology shows absence of interlobular bile ducts in early cholestasis phase and biliary cirrhosis in all patients later on. (9)

In our series we did not get sclerosing cholangitis as a cause of cirrhosis.

Roberts EA et al described pediatric fatty liver disease as an important cause of cryptogenic cirrhosis . Epidemic of pediatric obesity is most important cause of fatty liver disease. Hyperinsulinemia , inslulin resistance are pathogenic mechanism. It is more prevalent during active growth (infancy , mid childhood , puberty ) due to deranged hepatic metabolic function. (10)

In our series we did not get any case of cirrhosis due to fatty liver disease caused by obesity .

Nobiliv Valerio et al described pediatric NAFLD (non alcoholic fatty liver disease) as multifaceted disorder , ranging from simple steatosis to non alcoholic steatohepatitis (NASH) with or without fibrosis. Obesity, sedentary ,lifestyle, genetic predisposition leads to pediatric NAFLD. Pathogenesis involve liver cross talk with gut , adipose tissue . (11)

Suskind DL et al observed presence of female cells in liver of male patients with biliary atresia than in males with other liver disease . Maternal microchimerism is therefore suggested to contribute to pathogenesis of biliary atresia.(12)

In our study of 50 cases of cirrhosis we got 10 (20%) biliary atresia who came late for surgery.

Alagille D et al described hepatic ductular hypoplasia with chronic cholestasis , systolic murmur, characteristic facies , vertebral arch defect , growth retardation , mental retardation , hypogonadism(13).

In our study we did not get single case of alagille syndrome .

**Material and method:-**

The children (<12 years) who attended pediatric Gastroenterology OPD in PGIMER from July 2000 to June 2003 with symptoms of chronic liver disease (abdominal swelling , pedal edema Jaundice , high colored urine clay colored stool, GI Bleed, encephalopathy, family history of liver disease in siblings etc.) were enrolled for the study. Detailed history , clinical examination, investigation (USG abdomen, LFT, PTI, HIDA Scan, per operative cholangiogram, TORCH infection profile, enzyme study for metabolic disease like galactosemia, alfa one antitrypsin deficiency, glycogen storage disease serum cerulospasmin, urinary copper, slit lamp examination , auto immune marker like ANA, SMA, LKM, viral marker UGI endoscopy, liver biopsy, liver copper estimation,ultra sound Doppler examination of hepatic veins etc.) were noted.

**Result:-**

Out of 50 total cases of cirrhosis, 10 (20%) had biliary atresia who came late for surgery, 5 (10%) had galactosemia, 1 (2%) had alfa one antitrypsin deficiency, one (2%) had glycogen storage disease, 10 (20%) had wilson's disease, 10(20%) had auto immune hepatitis, 7 (14%) had Indian child hood cirrhosis, one (2%) had neonatal hepatitis, 5 (10%) had Budd Chiari syndrome. Out of 50 cases , 25(50%) had esophageal varices in UGI endoscopy. Out of 10 wilson's disease 3(30%) came with fulminant condition and postmortem liver biopsy was done.

**Discussion :-**

Cirrhosis in children is an important issue in child health.

Raquel Borges Pinto et al observed that biliary atresia is commonest cause of infantile cirrhosis (1)

In our study we got 10 (20%) case of cirrhosis with biliary atresia origin who were too late for Kasai operation. They were advised for liver transplantation.

We got one case (2%) of alfa one antitrypsin deficiency in our series.

We got seven cases (14%) of Indian childhood cirrhosis (ICC).

ICC is now rare but awareness of ICC started 25 years back.

We got 10 cases (20%) Wilson's disease in our series of cirrhosis. They had biochemical and clinical features of wilson's disease. Three cases (6%) had fulminant Wilson's disease who died in hospital. Rest 7 cases had compensated cirrhosis.

We got 5 cases (10%) of Budd Chiary syndrome . All of them had IVC obstruction due to thrombosis.

5 cases (10%) had idiopathic neonatal hepatitis leading to chronic liver disease and cirrhosis in our series.

One (2%) had glycogen storage disease with chronic liver disease.

We got 10(20%) cases of auto immune hepatitis. All of them were SMA and ANA positive.

We got 5 (10%) cases of galactosemia. They presented late (more than 5 months of age) having jaundice ,cholestatic hepatitis , splenomegaly , features of chronic liver disease. One had cataract. Liver biopsy showed cirrhosis in all of them.

Forty percent cases of cirrhotic children had esophageal varices which were treated according to their grading. GI bleeding , hepatocellular dysfunction , ascites , anasarca were presentation of decompensated cirrhosis.

Karen F et al observed that HCV have an accelerated course and early development of cirrhosis in children requiring liver transplant. HCV recurs universally after transplant. Chronic HCV has 0.3% incidence in children of USA.(14)

Bortolotti F et al observed that cirrhosis is an early and rare complication and a risk factor of HCC in chronic hepatitis B infected children. Those who have experienced reactivation or maintained liver damage after HBeAg clearance seems to be at a greater risk for disease progression in adult life(15)

Guido et al observed that childhood HCV is mild disease in most cases of children . Fibrosis increases with duration of disease, suggesting end stage liver disease. Liver biopsy is very important in chronic HCV infected children(16).

Goodman ZD et al observed that steatosis correlated with ALT level , BMI index Z score , in chronic HCV infected children. Positive correlation of liver fibrosis is with obesity , duration of infection, HCV genotype. (17)

Cuthbert JA et al observed that wilson's disease in an important cause of chronic liver disease and cirrhosis in children . ATP 7 B gene ( located at chromosome 13) is related to copper metabolism. Due to its mutation , WD ( wilson's disease) protein is not produced and copper is deposited in liver instead of being excreted in faeces or converted to cerulospsmin (18)

NC Nayak et al observed that Indian childhood cirrhosis ,a definite entity of chronic liver disease in children less than 6 years of age, having copper containing orcein staining in liver biopsy , prevalent is very much reduced now a days. This disease is associated with copper containing vessel in utensils. (19)

Portmann B et al observed that orcein positive granules deposits attributed to excess copper binding protein in liver biopsy specimen in Indian childhood cirrhosis. A comparable picture was seen in Wilson's disease liver biopsy. 20% of 270 cases of control group which had prolonged cholestasis were seen to have orcein positive deposits.(20)
Bhave SA et al observed that excess copper accumulation in cytoplasm of hepatocytes which disturbs microtubular system, causes hydropic swelling, Malory's Hyalin body in ICC . This pattern differs from copper deposition of wilson's disease or prolonged cholestasis-indicating different mechanism of ICC.(21)

Some observers report that infants of ICC had an appearance of clinical manifestation less than 3 months of age in 57% cases, milk boiling in copper vessel in 67 % cases , milk storage in brass in 90% cases, animal milk intake from copper vessel in 97% cases(22)

Baertling F et al reported liver cirrhosis in glycogen storage disease in 16 cases who had hypoglycemia , lactic acidosis and hepatomegaly as initial presentation .(23)

Cauchi JA et al reported 3 cases of Budd Chiari syndrome induced cirrhosis caused by hepatic vein outflow tract obstruction. He showed importance of high index of suspicion.(24)

Negral et al observed that radiological therapeutic intervention by stenting in BCS ( Budd Chiari syndrome) has better effect than angioplasty .(25)

In our study we got five (10%) cases of Budd Chiari syndrome. All of them had IVC obstruction . They were treated both medically as well as radiologically.

Laurie A et al reported two cases of patient with glycogen storage disease who had fibrosis at time of diagnosis. Both improved in growth velocity, biochemical parameter , well being and even fibrosis in histology after aggressive dietetic therapy . Both were treated with uncooked cornstarch, protein supplementation . (26)

MM Thaler et al observed that neonatal hepatitis may lead to cirrhosis were male is five times more common than female. With GI distension failure to thrive , hepatomegaly , early ascites , anasarca , bleeding , dyselectrolemia and frequent complication. (27)

Applebaun MN et al reported an infant with galactosemia in whom intensive liver damage occurred in one month. Liver biopsy shows extensive periportal and intralobular fibrosis , ductular cysplasia , “pseudo glandular” transformation and distortion of periportal vasculature. Three months after galactose free diet , clinical biochemical and histological picture completely disappeared. This

shows that functional and histological abnormalities associated with cirrhosis can be completely reversed (28).

Out of 50 cases of cirrhosis , we got 10 (20%) case of biliary atresia origin who came late for surgery.

Chen SM et al observed an universal screening system using an infant stool color card to promote early diagnosis and treatment of biliary atresia (29).

Hartley JL et al think that genetic predisposition and dysregulation of immunity are responsible for pathogenesis of biliary atresia. Obliterative extra hepatic cholangiopathy is the end product. (30)

Teckman JH et al observed that intracelular accumulation of AAT (alfa one antitrypsin deficiency) mutant Z protein within hepatocytes can cause liver injury , cirrhosis ,HCC(hepatocelular carcinoma) by triggering chronic hepatocelular apoptysis , regeneration and end organ injury. Supportive care and liver transplantation is only treatment. (31)

Inherited syndrome of intrahepatic cholestasis and biliary atresia are most common cause of chronic liver disease and prime indication of liver transplantation in children. Some patients may develop recurrences of cholestasis due to emergence of auto antibodies that disrupt canalicular function in new graft. There is a genotype – phenotype relationship. Mutation can alter bile composition and produce cholestasis. (32)

**conclusion:-**

Cirrhosis in children is very important problem. Various etiologies show that majority of them are preventable (eg. galactosemia, Indian childhood cirrhosis , biliary atresia , Wilson's disease etc.).Early detection and high index of suspicion is a must for this disease.

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