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Pattern of Persistent Liver Disorders in Children

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Abstract:-
Introduction: Liver diseases significantly impact children's morbidity and mortality, with non-alcoholic fatty liver disease (NAFLD) becoming more prevalent. Geographical heterogeneity in etiology varies, with hepatitis virus being the primary cause in South East Asia. Biliary abnormalities like biliary atresia can manifest as chronic liver disease in children with cirrhosis and portal hypertension. In developing countries, metabolic illnesses causing chronic liver disease have not been thoroughly studied.

Methods: Our hospital is a tertiary care facility in a large urban centre and serves as the referral centre. Cases admitted from August 2006 to August 2008 were analyzed and follow up was done. The dates of the onset of illness, fulfillment of diagnostic criteria, diagnosis and treatment all were noted.

Results: A study of 65 children with chronic liver disease at Manipal Hospital found 1.1% had jaundice, biliary atresia, and neonatal hepatitis, with males more prevalent. Common symptoms included fever, vomiting, altered sensorium, diarrhea, and haematemesis. Physical examination revealed anemia in 61%, clubbing in 23%, and palmar erythema in 10%. Hyperbilirubinemia was found in 63% of children, with biliary atresia in 60%. Special investigations, biochemical tests, and liver biopsy confirmed the diagnosis.

Conclusion: Chronic liver disease is suspected in children with persistent jaundice, abdominal distension, and hepatomegaly, with high risk groups being infants and older children. High incidence of metabolic liver diseases in children is due to referrals from smaller hospitals. Early diagnosis, genetic counseling, and non-transplant options are crucial for better treatment.

Keywords:- *Disease, Chronic, Jaundice, Diagnosis, Treatmnent.*

I. INTRODUCTION

Children frequently experience liver diseases, which account for a sizable share of hospital admissions. One of the major causes of morbidity and mortality in this age group is liver disease, which encompasses a wide range of conditions including infections, aberrant development, hereditary, and metabolic conditions that ultimately lead to cirrhosis and hepatic dysfunction. Children's liver illnesses are under a separate category than adult liver disorders and include both acute and chronic conditions. The pattern of liver illnesses, particularly those with hereditary and metabolic bases, varies across different geographies. These reported discrepancies can be attributed to a variety of factors, including socioeconomic, dietary, and other factors. NAFLD (non-alcoholic fatty liver disease), which was formerly uncommon in our subcontinent, is becoming more prevalent in children. (1)

The majority of liver illnesses in children are acute and chronic liver diseases. Chronic liver disease aetiology also exhibits geographic heterogeneity. Hepatitis virus is the primary cause of chronic liver disease in South East Asia, the Middle East, and certain other Asian nations. (2) It is mostly caused by the high frequency of hepatitis in these countries' general populations. In areas where diagnosis is delayed for more than twelve weeks, some biliary abnormalities, like biliary atresia, manifest as chronic liver disease. These kids frequently have cirrhosis and portal hypertension. (3)

Similar to this, in some parts of the world where oriental cholangiohepatitis (OCH) is endemic, untreated cases can lead to secondary biliary cirrhosis and portal hypertension in youngsters. Due to a lack of diagnostic resources in developing and poor nations, the profile of metabolic illnesses causing chronic liver disease has not been thoroughly studied in these areas. Therefore, the research published from these developing nations do not adequately account for the metabolic disorders that cause chronic liver disease. A chronic liver condition known as Indian childhood cirrhosis, which was a common illness in children in the Indian subcontinent, has been declining as a result of the adoption of preventive measures. This disease used to kill affected children before the age of five.(4)

Some parasitic liver diseases, such schistosomiasis and ashydatid, are still prevalent in areas where they are endemic. Non-alcoholic steatohepatitis (NASH), which has been linked to obesity, hyperinsulinemia, insulin resistance, and liver cell damage from free fatty acid toxicity or other oxidative stress, has been recently recognised as a common cause of liver disease in children. (5) 2.6–12.5% of children have fatty livers on average.

A. Objectives:

To evaluate the clinical spectrum of chronic liver diseases in Tertiary level referral hospitalised children.

ISSN No:-2456-2165

II. MATERIAL

All the patients who presented with symptoms suggestive of chronic liver diseases in Manipal hospital, Bangalore constituted the material for the study. Total of 65 children were included in the study. This was a study conducted at the Department of Paediatrics, Manipal hospital, Bangalore. The patient selection for the study was based on age, presenting symptoms suggestive of chronic liver disease.

III. METHODS

Our hospital is a tertiary care facility in a large urban centre and serves as the referral centre. Cases admitted from August 2006 to August 2008 were analyzed and follow up was done. The dates of the onset of illness, fulfillment of diagnostic criteria, diagnosis and treatment all were noted.

IV. DIAGNOSTIC EVALUATION OF CHILDREN WITH CLD

The initial evaluation must include a thorough history and physical exam. The presence of jaundice during infancy, a history of acute hepatitis, exposure to hepatotoxins, and a family history of liver disease are all pertinent historical details. Other pertinent information includes maternal and patient risk factors for hepatitis (transfusion, intravenous drug use, and ethnic background). The physical symptoms of jaundice, dark urine, and clay-colored faeces may be preceded by symptoms including weariness, malaise, abdominal pain, and weight loss. The prevalence of physical symptoms including palmar erythema, spider angiomata, muscle wasting, ascites, and an enlarged hard liver and spleen indicate chronic liver disease even if it may be challenging to determine the length of the illness. (6)

The existence of portal hypertension and the potential for gastro-oesophageal varices are both indicated by splenomegaly in this situation6. An erythrocyte sedimentation rate, platelet count, and total blood count should be part of the initial laboratory tests. Alkaline phosphatase, 5' nucleotidase or gamma-glutamyl transferase (GGT), total and fractionated bilirubin levels, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and should all be measured. It is crucial6 to assess the hepatocellular synthesis function by measuring serum albumin and prothrombin time. It is important to assess serologic indicators of HBV infection, such as HBsAg and anti-HBcAb (IgM and IgG). If these come back negative, relevant serologic tests should be run to look for signs of additional illnesses such hepatitis C, cytomegalovirus, and Epstein-Barr virus .(7) Serum alpha-1-antitrypsin concentration measurements and phenotyping are used to rule out alpha-1-antitrypsin deficiency. By assessing the serum ceruloplasmin level and 24-hour urinary copper excretion Wilson's disease should be ruled out. In each situation where Wilson's disease is suspected, the eyes should be checked under a slit light for the presence of the Kayser-Fleischer ring and sunflower cataract. Cystic fibrosis will be ruled out by a typical sweat chloride test. A diagnosis of autoimmune chronic active hepatitis is supported by the presence of autoimmune markers such as antinuclear antibody, anti-smooth muscle antibody, anti-mitochondrial antibody, and anti-liver-kidney microsomal antibody. Fasting ultrasonography will rule out anatomic anomalies such choledochal cysts and enable for the discovery of cholelithiasis or choledocholithiasis in the hepatobiliary tree. (8) using colour flow The direction of flow within the portal vein can be identified using Doppler ultrasonography. The flow is reversed when portal hypertension is present. An estimation of the severity of portal hypertension may be given via radionuclide scanning. In the majority of cases, a histological study of liver tissue will enable the distinction between chronic persistent hepatitis, chronic active hepatitis, and cirrhosis. The diagnosis is typically made based on the histological image and the use of specific staining techniques. Occasionally, to make a certain diagnosis, liver tissue must be examined under an electron microscope and the iron and copper concentrations in the biopsy sample must be measured. Some percutaneous liver biopsies may be constrained by sampling mistakes. (9)

V. RESULTS

This is a Prospective observational descriptive clinical study consisting of 65 children with chronic liver disease. There were total of 65 patients of chronic liver disease diagnosed from 2006 to 2008 at Manipal Hospital, Bangalore.

- Out of 5544 total paediatric admissions, the number of chronic liver disease cases is 65 (1.1%). 31 cases fulfilled case definitions of classical chronic liver disease (48%), 21 cases of biliary atresia (32%) and 13 cases of neonatal hepatitis (20%) were diagnosed. Out of 65children studied, 15 were less than 1month, 32 were less than 1year, 4 between 1 to 5 years, 8 were between 5 to 10 years and 6 were between 10 to 16 years. Out of the 65 children in the study group, maximum (32) were less than 1 year of age.

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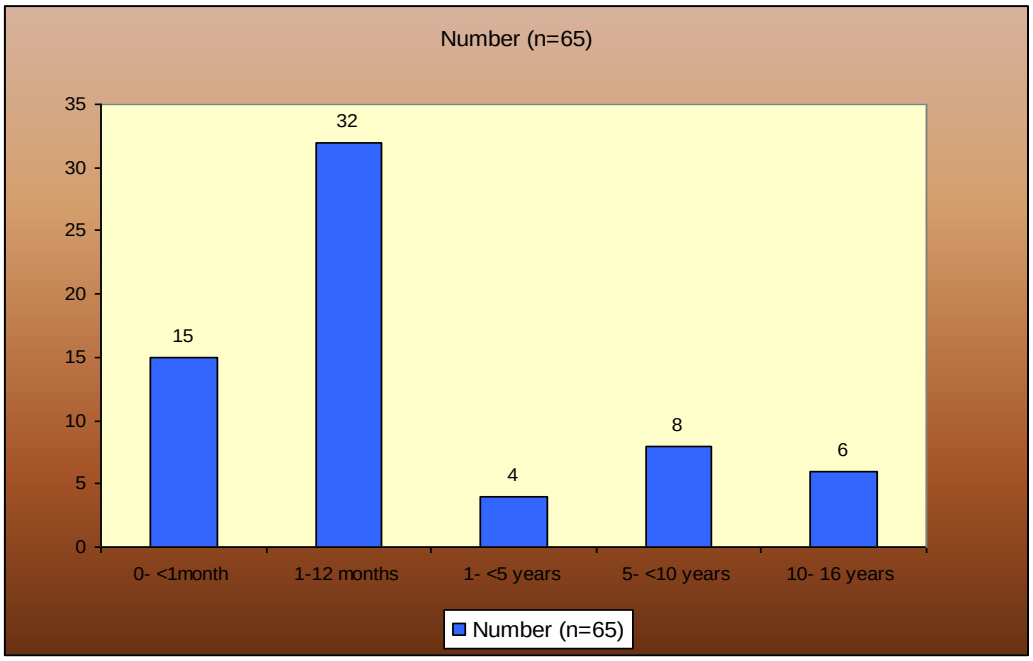

Fig. 1: Graphical representation of Liver diseases diagnosed based on age

- There were 40 male (61%) and 25 female (39%) children. Male: Female ratio 3:2. So the prevalence of the disease was more in males than females.
- Jaundice was present in all cases (97%) and the duration of jaundice ranges from 1day – 6months. Jaundice was associated with pruritis in 14 cases (21.5%). It is mainly seen in older children of 5-16 years.
- Failure to thrive was present in 52 cases (80%). Distension of Abdomen was present in 34 cases (52%). Typical moderate to high grade fever was present in 17 cases (26%) with duration of fever ranges from 6 – 20days.
- Vomiting was present in 32 cases (49%) and altered sensorium was seen in 22 cases (34%). Other symptoms were vomiting, pruritis, pain abdomen, seizures, swelling of feet, diarrhea and haematemesis. Haematemesis was seen in least number of cases (6%).
- In our study group we observed hepatomegaly in 64children (99%), splenomegaly in 20children (31%) and hepato splenomegaly in 20children (31%). Hepatomegaly observed in 64children was of two categories i.e., < 2 cms and > 2 cms. 8 children presented with ascites (12%). 8 children presented with pain abdomen (12%). 11children had generalized tonic clonic seizures (17%) and among them 5 children belong to metabolic liver diseases (46%).

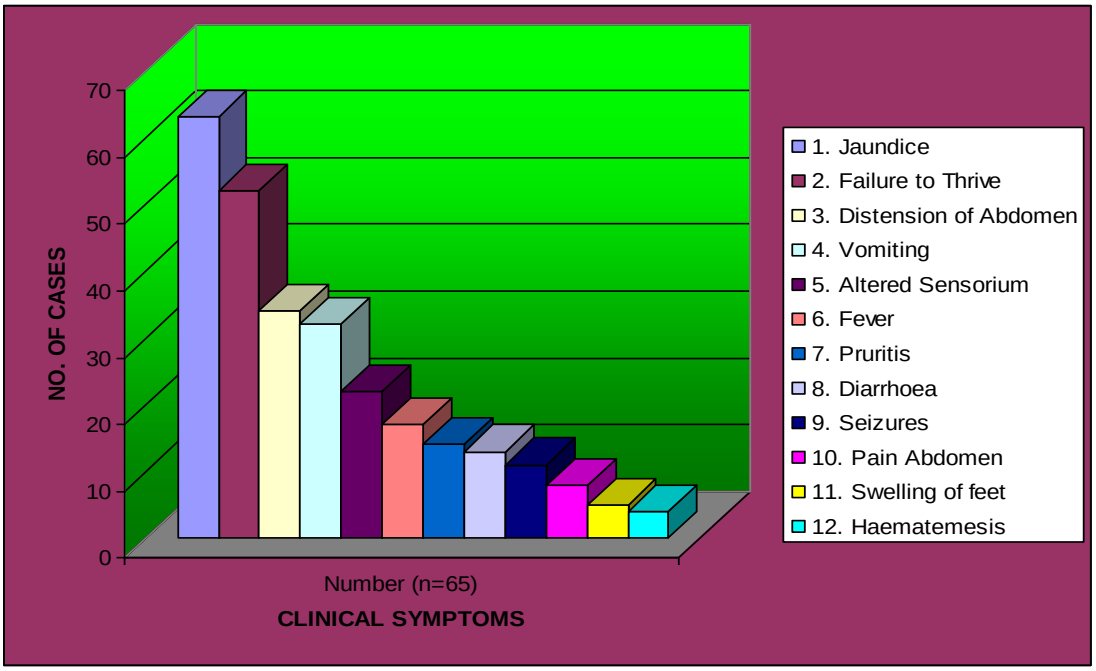

Fig. 2: Graphical representation of Number of cases and clinical symptoms

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- The spectrum of the presenting symptoms in the study population was analyzed and concluded that out of the 65 children studied, 97% (63) presented with jaundice, 26% (17) presented with fever, 80% (52) presented with failure to thrive, 52% (34) presented with abdominal distension, 49% (32) presented with vomiting, 22% (14) presented with pruritis, 17% (11) presented with seizures, 34% (22) presented with altered sensorium and other symptoms include pain abdomen, swelling of feet, diarrhea and haematemesis.
- Past history of blood transfusions was noticed in 6 cases (9%). Umbilical catheterizations and sepsis during the new born period was noticed in 10 cases (15%).
- Physical examination revealed anemia in 40(61%), clubbing in 15(23%), palmar erythema in 6(10%). No patient had spider naevi or testicular atrophy. Altered sensorium was noticed in 22 cases (34%). Liver was not palpable below the costal margin in 1(1.5%), was <2cms in 8(12%) and >2 cms enlarged in 56(88%). The surface of the liver was smooth in 58(91%) while nodularity was felt in only six cases (9%). Left lobe of the liver was palpated in only one case (1.5%).

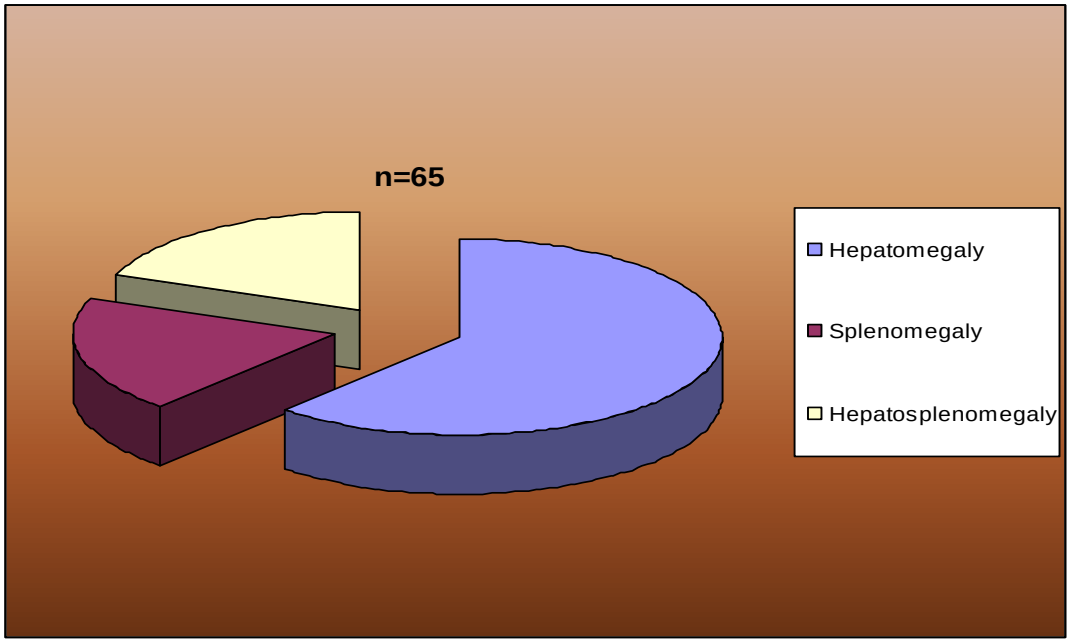

Fig. 3: Graphical representation of Hepatomegaly, Splenomegaly, Hepatosplenomegaly percentage

- Haemoglobin (gm/dl) was 5.9 to 16.8 in all children at the time of presentation. After 2 weeks it was 8.6 gm/dl to 13.1 gm/dl. Three children required 10 ml/kg of irradiated packed red blood cells transfusion, they presented with bleeding manifestations at the time of admission.
- Total Leukocyte count (TC /cu. mm) was elevated in 55 children with a range of 4500/cu.mm to 30050/cu.mm and was predominantly polymorphs at initial presentation. At 2 weeks it returned to normal in 20 children.
- Abnormal urine examination in the form of traces of protein and 10 to 30 pus cells per high power field were present in 5 children (8%), renal parameters were normal in all five children. But one child revealed multicystic left dysplastic kidney by ultrasonography of abdomen (coincidental finding).
- 56 children (86%) showed abnormally raised serum bilirubin values, among them 35 children (63%) showed the elevation of direct bilirubin fraction, suggesting further evaluation because of conjugate hyperbilirubinemia. Further, investigation like HIDA scan was done to rule out the obstructive causes of hyperbilirubinemia, most commonly Biliary Atresia.
- Among 35 children with direct hyperbilirubinemia, 21 children (60%) of that group diagnosed to have features of biliary atresia on HIDA scan. All the children were presented with clay coloured stools. Remaining 13 children (38%) were diagnosed as neonatal hepatitis, based on poor uptake in HIDA scan.
- 55 children (85%) had elevated SGOT/AST with a range of 112 to 3022 IU/L and 49 children (75%) had elevated SGPT/ALT with a range of 108 to 2012 IU/L. Among those children, more than 3 folds raise of SGOT was seen in 42 children (76%) and SGPT was seen in 28 children (57%).
- Prothrombin time was elevated in 47 children (72%) and among that mild elevation was seen in 23 children (49%). Gross elevation of Prothrombin time was seen in 24 children (51%) indicate severity of hepatocellular damage. Among them 3 children were presented with haematemesis at the time of admission and which was resolved after transfusion of blood products.
- USG Abdomen evaluation has been performed in all children (100%) at the time of presentation. It showed features of hepatomegaly, splenomegaly and hepato splenomegaly in 60 children (92%) and was showed normal study in 5 children (8%).

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- HIDA scan was done for all the cases with direct hyperbilirubinemia and it showed features of biliary atresia in 21 children (32% of total) and the features of neonatal hepatitis in 13 children (20% of total).
- Viral markers were done for all the cases of chronic hepatitis and autoimmune hepatitis and wherever they are indicated. All cases of chronic hepatitis are of Hepatitis-B induced chronic liver disease. 4 (6.1%) cases of chronic hepatitis were noticed.
- Special investigations were done in 37 cases (56%) apart from HIDA scan. HIDA scan was done in 30 cases. Muscle biopsy and lip biopsy was done in one case.
- Slit lamp examination was done in 2 cases (3%) with the help of paediatric ophthalmologist revealed K-F Ring. To confirm the diagnosis biochemical investigations like serum ceruloplasmin, urinary copper levels were done. The serum ceruloplasmin levels were 0.07 and 0.04 (normal range 0.15-0.60), serum copper levels were 17 and 25 (normal range 70-140 gm/dl) and urinary copper levels were 17 and 26 (normal range 72-140mgm/dl).
- Alpha-1-antitrypsin levels were done in 11 cases (16%) showed abnormal value of 0.3 gm/l (normal range 1-1.6 gm/l) in one case (1.5%), hence diagnosis of alpha-1-antitrypsin deficiency was made and in all other 10 cases the value was within normal limits.
- In 5 cases (7.6%) of cirrhosis with portal hypertension, apart from routine investigations, ascitic fluid analysis, serum Iron levels was done. Among those, 3 cases died due to the complications like portal hypertension, oesophageal varices, spontaneous bacterial peritonitis, fulminant hepatic failure and encephalopathy.
- Serum ferritin, iron and transferrin levels were done in 3 cases, showed abnormal raise of serum ferritin (report-7487). Based on abnormal raise of serum ferritin levels the diagnosis of neonatal haemochromatosis was made and the lip biopsy done to confirm the diagnosis and which showed equivocal result.
- In 14 cases (22%) liver biopsy was done to confirm the diagnosis. It revealed 11 cases of glycogen storage disorders (along with type 1 & 2) and one case of allagille's syndrome (paucity of intralobular ducts).
- In 11 cases of glycogen storage disorders, 5 cases (7.6%) were of unclassified variety, 3 cases (4.6%) were Type-1A variety and 3 cases (4.6%) were Type-2 variety (pompe's disease).
- One case had both features of glycogen storage disorder and niemann pick's disease. To confirm the diagnosis of niemann pick's bone marrow aspiration and biopsy was done and which confirmed the diagnosis.
- Type-2 glycogen storage disease also called pompe's disease, among three cases, one child had severe respiratory complications like ventilator dependent recurrent pneumonia with recurrent failed extubations. Hence this child underwent tracheostomy and kept on non-invasive ventilator (BiPAP) in paediatric intensive care unit. The child was discharged with non-invasive home ventilator (BiPAP). In subsequent follow ups the child was started on enzyme replacement therapy and she is showing good response.
- Two cases (3%) had indirect hyperbilirubinemia without any haemolysis and after complete special investigations like TORCH screening, alpha-1-antitrypsin levels, alpha fetoprotein levels, urine aminoacidogram, tandem mass spectrometry and liver biopsy, the child was diagnosed as criggler-najjar syndrome.
- In Two children (5%), special tests like anti liver kidney mitochondrial auto antibodies, anti-SMA auto antibodies were done. It showed positive result; hence they are diagnosed as auto immune hepatitis group.
- In all 13 cases (20%) of neonatal hepatitis, after routine investigations, HIDA scan, tandem mass spectrometry, urine aminoacidogram was done.
- Among 21 cases (32%) of biliary atresia, Kasai's Porto-enterostomy was done in 15 cases. Post operatively and on follow up, these children were showing good response.
- One case of allagille's syndrome was diagnosed and this case was followed up and after long discussion with surgical gastroenterologists the child was taken for liver transplantation, because the mother agreed to be the living donor transplant. Liver transplantation was done successfully by our surgical team. This was the first living donor-liver transplantation in paediatric age group done in southern India. The child was followed for next 6 months, presently no complications and the child is on Immunosuppressant Therapy.
- One case (1.5%) of undifferentiated embryonal sarcoma of liver was diagnosed in 10 years old female child and started on chemotherapy. Child underwent complete resection of the tumour and on chemotherapy. The child was followed for next 6 months, presently no further complications and metastasis was noticed.
- One case (1.5%) after complete extensive special investigations, the probable diagnosis was not made; opinion from paediatric gastroenterologist was taken and finally put in an undiagnosed type of chronic liver disorder (most probably metabolic liver disorder).
- Epidemiology out of 65 children with chronic liver disease, youngest was 1 day old male baby and oldest was 16-years. 23.1% of children were < 1 month, 49.2% in the age group of <1 year, 6.2% of children were between 1 and 5 years, 12.3% of children were between 5 and 10 years and 9.2% beyond 10 years of age.
- The higher incidence in our study is similar to the American study[11] done by W. Ray and Robert S. Brown et al, other Indian studies including Yachha S.K[12] et al, Sharma B.C et al and Rajeshwari K[13] et al studies. The prevalence of the disease was more in males than females (3:2) in present study and is similar to Yachha S.K et al, Sharma B.C et al and Rajeshwari K et al studies. (14)
- Two (3%) of our children had autoimmune liver disease (type 1 in 1 and type 2in 1)[15] which is similar to 4.5% frequency in adults with chronic liver diseases in India[16]. However, this frequency is lower as compared to Western and European countries[17-20].

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Table 1: Frequency in adults with chronic liver diseases

Diagnosis	n=65	%
Biliary Atresia	21	32.2
Neonatal hepatitis	13	20
Cirrhosis with Portal HTN	5	7.6
GSD	5	7.6
Chronic hepatitis	4	6.1
GSD-Type 1	3	4.6
GSD-Type2(Pompe's)	3	4.6
Autoimmune hepatitis	2	3.1
Wilson's disease	2	3.1
Criggler najjar syndrome	2	3.1
Neonatal haemochromatosis	1	1.6
Allagille's Syndrome	1	1.6
Alpha-1-antitrypsin Deficiency	1	1.6
Undifferentiated Embryonal Sarcoma-liver	1	1.6
Undiagnosed CLD	1	1.6

VI. CONCLUSIONS

- Chronic liver disease should be suspected in children with persistent jaundice, abdominal distension, failure to thrive and hepatomegaly.
- The high risk groups as per present study for chronic liver disorders and related complications are infants of 1 month to 1 year of age (49.2%) and older children of 5 to 10 years age group (12.3%).
- Present study has shown male sex preponderance for chronic liver disorders. The male to female ratio is 3:2.
- Neonatal cholestatic syndrome is one of the major subgroups in our study and it comprises of biliary atresia (32.2%) and Neonatal hepatitis (20%).
- The percentage of metabolic liver disorders out of total chronic liver disorders in present study was 21.5%. The incidence of Neonatal hepatitis syndrome was the most common cause after biliary atresia in the present study.
- The certain unusual and rare types of chronic liver disorders like undifferentiated embryonal sarcoma of liver, Allagille's syndrome, alpha-1-antitrypsin deficiency, neonatal haemochromatosis and criggler najjar syndrome are seen in present study.
- Interestingly, the incidence of hepatic malignancies has been very less (1.6%). Not encountered any cases of Hepatoma, hepatoblastoma and hepatocellular carcinoma. The Undiagnosed chronic liver disorders constituted 1.6% of total chronic liver disorders when compared to other studies.
- Early recognition of babies who have biliary atresia is critical for optimal medical or surgical interventions.
- The high incidence of biliary atresia, neonatal hepatitis and glycogen storage disorders may be due to referrals from various smaller hospitals because of availability of various investigation modalities.
- Defining the type of chronic liver disease, especially metabolic variety is of immense clinical significance as it helps in genetic counselling and early treatment.
- Metabolic liver diseases in children are now being increasingly diagnosed in our country and Wilson's disease was the most frequently diagnosed metabolic liver disease (3.1%).
- The regional hospitals and labs should be well equipped to diagnose these cases. Metabolic liver diseases can be screened in a cost effective manner to allow earlier more effective therapy.
- Despite the numerous efforts to improve the early diagnosis, chronic liver diseases remains a disease at risk to be under recognized or misdiagnosed with other intestinal illnesses in young children.
- Identifying the presence of chronic liver disease in a paediatric patient at the initial presentation is of cardinal importance to prevent the complications of chronic liver diseases.
- An exciting recent development is the availability of multiple non-transplant options for the treatment of chronic liver diseases.
- The definitive therapy, such as targeted enzyme replacement or gene therapy is available for certain metabolic liver disorders.
- Availability of liver transplantation has improved the outcome and survival in certain chronic liver diseases. A better understanding of aetiological agents and genetic predisposition is required in order to improve the quality of life of children with chronic liver disorders.

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