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Spectrum of paediatric liver diseases in tertiary health care centre

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Abstract
Introduction: The spectrum of liver diseases is different in children and adults. Development of non-invasive diagnostic methods and advanced hepatic imaging has changed the role of liver biopsy, it is still important in evaluation of paediatric liver disease.
Material and Method: This is an observational, hospital-based study of 32 liver biopsies received during period of 5 years (January 2014-October 2019), comprising cases upto 12 years of age.
Results: In the 32 liver biopsies studied, male to female ratio was 0.68, extrahepatic biliary atresia was commonest histological finding followed by glycogen storage disorder and neonatal hepatitis. Common presentation was Jaundice and hepatomegaly. Clinical and biochemical investigation correlation among biliary atresia and non-biliary atresia group was done.
Conclusion: Liver biopsy assisted by a good clinical examination, radiology and laboratory evaluation can succeed in diagnosis of majority of liver diseases where clinical and laboratory parameters overlap.

Keywords: Liver biopsy, children, metabolic liver disease, indications

Introduction
The spectrum of liver diseases are different in children and adults. In paediatric age group, liver suffers from metabolic, infective, cholestatic and neoplastic disorders resulting in abnormal liver function tests, jaundice and hepatomegaly. [1] Diseases of the liver contribute significantly to childhood morbidity and mortality [2]. Histological assessment of the liver remains an essential tool in establishing, diagnosis in numerous paediatric diseases in correlation with clinical and laboratory data. A liver biopsy may serve as a significant method in assisting clinicians in therapeutic management decisions There is a great emphasis for development of non-invasive methods to replace liver biopsy for evaluation of liver diseases [3] Advances in serologic testing, enzyme analysis, DNA sequencing, and developed imaging techniques have reduced the need for liver biopsy

Aims and Objectives
1. To study the spectrum of liver diseases in children.
2. To correlate clinical and laboratory investigation with histopathological findings

Material and Methods
- Nature of study- Hospital based observation study
- Sample size- 32 cases
- Duration 5 years
- Inclusion criteria- all consecutive liver biopsies of age upto 12 years
- Exclusion criteria- inadequate biopsies

Methods
Histopathological examination
Specimen of liver biopsies along with complete requisition form received in department were given a histopathological number Biopsy received was gently expelled onto a piece of filter paper, gross findings like number of biopsies, length and colour was noted.. Biopsies were wrapped in filter paper and were placed into plastic cassettes. Biopsy tissue was fixed in formalin and processed routinely. These tissues were dehydrated with ascending grades of alcohol, cleared with xylene and embedded in paraffin to prepare blocks.

These blocks were then sectioned into 4-5 micrometre using rotatory microtome. These sections were then stained with Haematoxylin and Eosin (H & E) were examined under microscope.
Special stains were used in selective cases. Reticulin was used in cases to assess cirrhosis, Periodic acid Schiff was used for cases of glycogen storage disorder
The histopathological findings were correlated with the clinical history and investigations obtained.

Biochemical Investigation
Evaluation was done by Erba Manheim XL 640 automated analyser by the principle of spectrophotometry.

Results
Data collected was entered in Microsoft excel and Statistical analysis was done using SPSS (Statistical Package for Social Sciences) for Windows version 20.0. Categorial variables are expressed as frequency, percentage and continuous in terms of mean, standard deviation. Comparison of variables between two groups performed with Chi square for variables. The p values < 0.05 were considered statically significant.

Observations
Total 32 liver biopsies were studied over a period of 5 years. 17 cases were less than 1 year of age. 13 were male and 19 were female with male to female ratio of 0.68
The spectrum of liver disease found were secondary biliary cirrhosis due to biliary atresia which was commonest followed by extrahepatic biliary atresia, neonatal hepatitis, glycogen storage disorder, wilson disease, intrahepatic cholestatasis and hepatoblastoma
Clinical presentation was in the form of jaundice (87.5%), acholic stools (71.8%) hepatomegaly (81.25%) and splenomegaly (56.25%) pain abdomen (50.0%)
On comparison of clinical features among biliary atresia and non- biliary atresia group statistically significant association was seen in jaundice and acholic stools
On comparison of LFT parameters among biliary atresia and non- biliary atresia group total bilirubin levels show statistically significant association whereas no significant difference was found in liver enzymes.

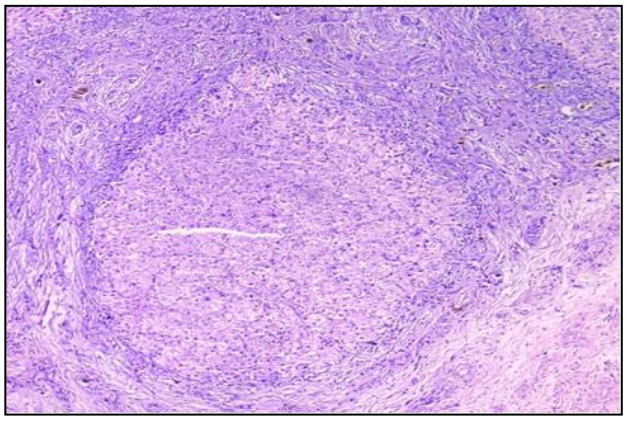

Fig 1: Photomicrograph of biliary atresia cases showing bile duct proliferation with fibrosis (a H & E,40x)

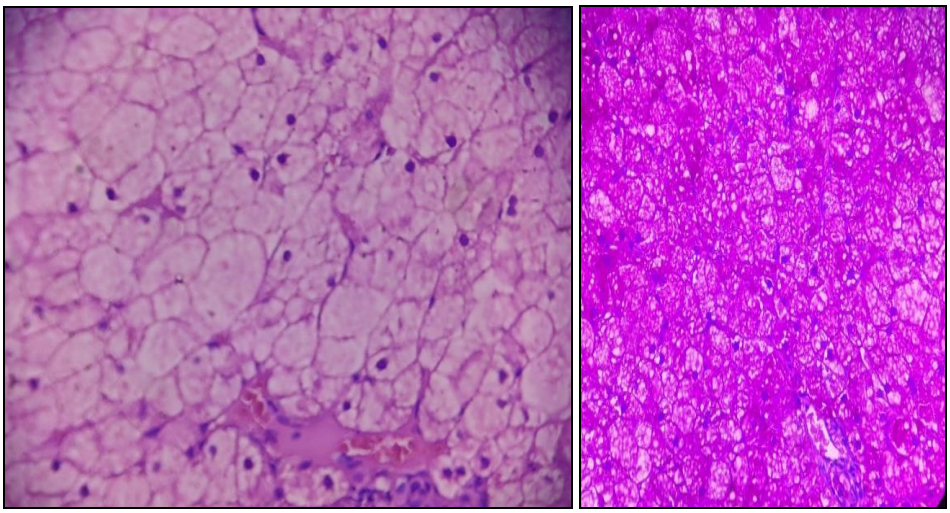

Fig 2: Photomicrograph of case of glycogen storage disorder showing swollen hepatocytes in mosaic pattern with compressed sinusoid (a; H&E 10x), PAS stain showing pas + hepatocyte containing glycogen (b; 40x)

Discussion
Liver biopsy is traditionally the 'gold standard' for the evaluation of liver disease P. Bedossa *et al*. consider that when it comes to liver biopsy the term ‘‘best” standard is more appropriate than ‘‘gold” standard [4].
There are many biochemical, immunological, and radiographic techniques which have facilitated the diagnosis and management of liver disease, but liver biopsy is still note obsolete. Clinicians still rely on information derived from the liver biopsy to inform patients and to make their therapeutic decisions as in case of biliary atresia.

Table 1: Comparison of histological diagnosis with other studies

	Dhole SD *et al*. [5]	**Shahraki T *et al*.** [6]	**Our study**
Total number of cases	55	45	32
Biliary atresia	7.27%	30.4%	18.7%
Secondary biliary cirrhosis	-	2.2%	34.7%
Glycogen storage disorder	3.63%	4.3%	12.5%
Neonatal hepatitis	9.09%	4.3%	12.5%

The two most common causes of infant cholestasis are biliary atresia (BA) and idiopathic neonatal hepatitis (INH) which is also comparable to study by pragati AS *et al*. [7] and which showed EHBA in 38.46% and neonatal hepatitis 24.61%.

Table 2: Comparison of clinical manifestation with other studies

	Dhole SD *et al*. [5]	Shahraki T *et al*. [6]	Qureshi H *et al*. [7].	Malik M *et al*. [8]	Mehnaz A *et al*. [9]	Our study
Total cases	55	46	55	30	80	32
jaundice	73%	100%	49%	73%	50%	87.5%
Acholic stools	-	37%	-	-	-	71.8%
Hepatomegaly	63%	78%	63%	66%	55%	81.2%
Spleenomegaly	60%	52%	76%	63%	50%	56.2%

Finding in our study were similar to study by shahraki T *et al*. [6].

Table 3: Comparison of Clinical Findings of Biliary Atresia and Non-Biliary Atresia Groups with other study

	Shahraki T *et al*. [6].			Our study		
	BA group	Non BA group	P value	BA group	Non BA group	P value
Jaundice	100%	96%	0.5	61.9%	38.1%	0.01
Acholic stools	64%	25%	.01	68.4%	31.6%	.001
Hepatomegaly	85%	80%	.60	82.8%	17.2%	0.48
Spleenomegaly	71%	50%	.30	66.6%	33.4%	0.42
Total bilirubin	4.5±8.8	6.6±12.7	.06	11.07+3.1	5.93+7.41	.029
Direct bilirubin	2.8±6	4.5±7	.40	8.03+3.11	3.66+4.72	.09
AST	142±367	137±234	.01	207.46+110.021	176.64+117.39	0.48
ALT	125±216	86±122	.005	103.46+46.1	103.79+46.9	0.98
ALP	237±1394	1752±1923	.60	910.69+429.6	813.64+604.3	0.63
PT	15±7.5	12.7±1.4	.20	13.76+1.56	12.82+1.47	0.11

In our study difference in biliary atresia(BA) and non-biliary atresia (non BA) group show significance in presenation of jaundice and acholic stool (p value <.05) while no significant difference was found in liver enzymes in our study as compared to study by Shahraki T *et al.* [6] which show p value <0.05 in case of ALT. Another study conducted by Wang H *et al.* [10] also showed no significant difference among liver enzymes. Thus liver function test does not significantly contribute to diagnosis of biliary atresia from other causes of neonatal cholestasis, definitive diagnosis depends on cholangiogram and liver biopsy. Many non- invasive biomarkers like serum apolipoprotein C-II and transthyretin are used but no single biomarker or imaging test can adequately distinguishes biliary atresia from other types of neonatal cholestasis, combinations of biomarkers, imaging tests and clinical and pathological correlation is required for rapid and accurate diagnosis of biliary atresia.

Conclusion

- Histologic assessment of liver tissue is cornerstone for evaluation and management of liver disease in children, although the indications for performing a liver biopsy have undergone substantial changes in the last decade
- Paediatric liver biopsy is of value in diagnosis of disorders where clinical and laboratory parameters overlap,
- Novel imaging modalities, biomarkers, proteomics are likely to further change the role of liver biopsy

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