ORIGINAL ARTICLE

Histopathologic Spectrum of Childhood Liver Diseases in a Tertiary Hospital in North-western Nigeria.

Usman Bello[1], Samaila Moodupeola Omotara[1] , Yawale Iliyasu[2]

ABSTRACT

Background: Diseases of the liver are a significant cause of morbidity and mortality in children. The patterns of hepatic disorders in this age group differ greatly from adults and show marked regional variations. The objective of this study is to document the histopathologicpattern of liver disorders in children at a major referral laboratory in Northern Nigeria.
Materials and Method: Consecutive liver biopsies received in the department of pathology, Ahmadu Bello University Teaching Hospital Zaria over a fifteen year period (2001-2015) were processed accordingly. Information on age, sex and duration of disease was retrieved from request cards. Diagnosis was made based on morphological criteria. Collected data were analyzed and presented in frequency distribution table, figures and photomicrographs.
Results: Forty seven cases were analyzed comprising 27 (57.4%) males and 20 (42.6%) females with male to female ratio of 1.3: 1. Their ages ranged from two months to 15 years with mean age of 7.5 years Children aged five years and below accounted for 44.7% of cases and of these, ten cases (47.6%) had neonatal hepatitis. Children aged 11-15 years accounted for 42.5% of cases with chronic viral hepatitis being the predominant disease occurring in 15 cases in this age group. All the chronic hepatitis cases were of hepatitis B virus (HBV) infection. Children aged 6-10 years were the least affected and constituted 12.8% (6 cases) only with hepatic schistosomiasis accounting for half of their liver pathologies. Five of the cases were neoplastic; 4 cases (8.5%) of hepatoblastoma and 1 case (2.1%) of hepatocellular carcinoma (HCC).
Conclusion: Liver disorders in children were age specific; the most common disease in this study was chronic HBV hepatitis seen in older age group while neonatal hepatitis and biliary atresia predominates in younger children.

KEYWORDS: Liver Pathology, Children, Neonatal hepatitis, Hepatoblastoma.

Introduction

Hepatic disorders are relatively common; however, most cases of liver diseases requiring histopathologic assessment are due to chronic liver diseases (CLD). Liver biopsy plays a pivotal role in the specific management of these disorders from diagnosis, monitoring disease progression to the final outcome of these groups of disorders.[1,2] Liver biopsy though an invasive procedure still remain the gold standard for diagnosis of CLD.[3]

The clinicopathologic categories of liver diseases in children ranges from congenital, infectious, metabolic, cholestatic to neoplastic transformation of the chronic form of some these disorders in some cases through a precancerous processes of cirrhosis.[4] However, in children neoplastic diseases of the liver may not follow this format instead

Department of [1]Morbid Anatomy and Forensic Medicine, College of Health Sciences, Usmanu Danfodio University, Sokoto. Nigeria, [1]Pathology, Ahmadu Bello University Teaching Hospital Zaria, Kaduna State.

Correspondence to:
DR USMAN BELLO
Department of Morbid Anatomy and Forensic Medicine, College of Health Sciences, Usmanu Danfodio University, Sokoto. Nigeria,
eMail: bbusman55@yahoo.com

the processes of carcinogenesis follow a complex largely obscured mechanism.[5]

Epidemiologically, the patterns of hepatic disorders in this age group differ greatly from adults. Biliary atresia and neonatal hepatitis predominates in some series.[6,7] The incidence of biliary atresia is between 1: 8,000 and 1: 17,000 live births with an overall female preponderance. The incidence is higher in Japan and China(1 in 9,600) than in Europe and the UK (1 in 16,000).[8] In most of Africa including Nigeria, the incidence data are not available, though individual institutional reports suggest that up to five children with this disorder are encountered yearly in many centres.[9,10] Other documented diseases are secondary haemochromatosis, storage disorders, fatty liver and cirrhosis.[11,12] In Jos, North-Central Nigeria, Obafunwa *et al* documented hepatic schistosomiasis as the most common liver disease in children.[13] Non alcoholic fatty liver disease (NAFLD) is also a leading cause of CLD in children and its increasing prevalence can be predicted by obesity and the male sex. Progression of NAFLD to non alcoholic steatohepatitis (NASH), cirrhosis and HCC in this group is well documented.[14] Neoplastic diseases of the liver are not uncommon and include hepatoblastoma and HCC.[15]

This study seeks to document the histopathologic pattern of liver disorders in children at a major referral laboratory in the Northern Nigeria.

Materials and Method

Consecutive liver biopsy specimens received in the pathology department of Ahmadu Bello University Teaching Hospital (ABUTH) Zaria over a fifteen year period (2001-2015) were fixed in 10% formal saline, processed in paraffin wax and tissue slides stained with haematoxylin and eosin. Other used stains include reticulin, masson trichome, periodic acid schiff (PAS) with and without diastase digestion, Shikata orcein and Prussian blue.

The PAS-diastase demonstrated **glycoproteins**, accentuated hypertrophied Kupffer cells filled with ceroid pigment in cholestasis. Reticulin stain was used for accurate assessment of structural changes, to highlight hepatic plate architecture and thin layers of connective tissue in early cirrhosis. Trichome stain highlighted extent of fibrosis and cirrhosis. Perls' stain demonstrated stainable iron while Orcein stain demonstrated hepatitis B viral surface material (HBsAg) within hepatocytes.

Information on age, sex and duration of disease, relevant clinical history and ancilliary investigations were retrieved from individual case cards. Microscopic features detailing different pathologies were analysed. Histological diagnosis was made based on morphological criteria. The study is hospital based and collected data were analyzed and presented in frequency distribution tables and figures including photomicrographs and legends.

Results

There were 438 liver biopsy specimens received during the study period and of these 47 (10.7%) were for children aged 15 years and below with the mean age of 7.5 years. There were 27 (57.5%) males and 20 (42.5%) females with male to female ratio of 1.3:1. Children aged five years and below formed 48.8% (21 cases) with 10 (47.6%) cases of neonatal hepatitis and 7 (33.3%) cases with biliary atresia comprising bulk of the diseases in this age group. Children aged 11-15 years constituted 42.5% of cases with chronic viral hepatitis having 34.9% of the total number of cases in this study. Children aged 6-10 years were the least affected by the diseases of the liver with only 5 (11.6%) of the total number of cases

Table 1: Age and Sex Distributions of Pathologic Causes of Liver Disease in Children

Pathologic disorder	Age group (in years)						Total (%)
	0-5		6-10		11-15		
	Male	Female	Male	Female	Male	Female	
Chronic hepatitis	0	0	1	0	12	2	15 (31.9)
Hepatic schistosomiasis	0	0	2	1	0	1	4 (8.5)
Neonatal hepatitis	3	7	0	0	0	0	10(21.3)
Biliary atresia	4	3	0	0	0	0	7 (14.9)
Cirrhosis	1	1	0	2	1	1	6 (12.8)
Hepatoblastoma	1	1	0	0	2	0	4 (8.5)
HCC	0	0	0	0	0	1	1 (2.1)
Total	9	12	3	3	15	5	47 (100)
Group total (%)	21(44.7)		6 (12.8)		20 (42.5)		

Key:- HCC= Hepatocellular carcinoma

The diseases were histopatholgically categorized into: infectious; 19 (40%) cases, cholestatic; 17 (36%) cases, cirrhosis; 6 (13%) cases and neoplastic; 5 (11%) cases.

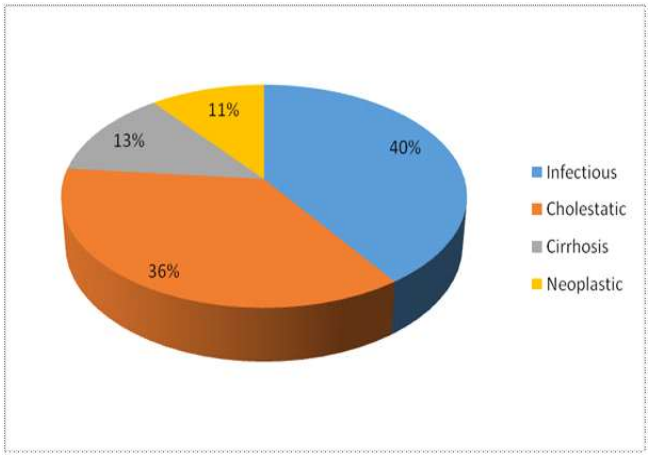

Figure 1: Pie Chart Showing Categorical Distribution of Liver Diseases in Children

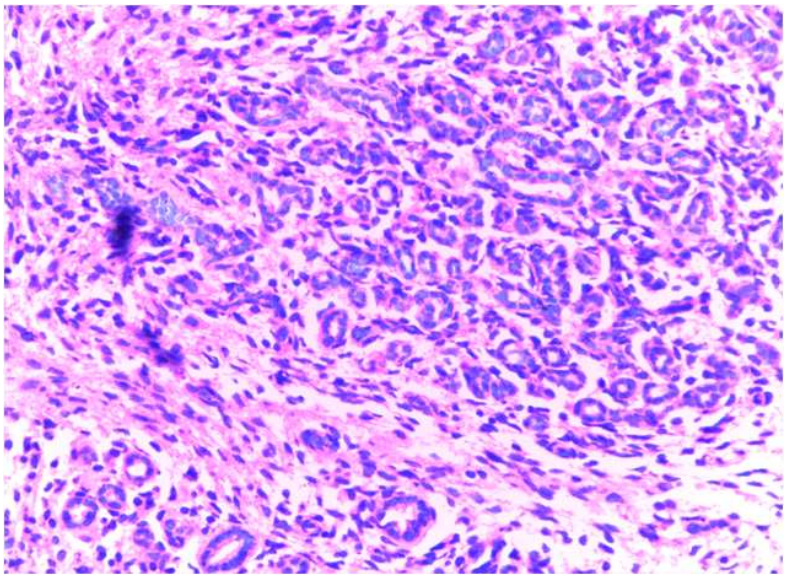

Figure 2a: Hepatoblastoma; epithelial type showing small polygonal foetal cells forming acini and tubules (H &E X100)

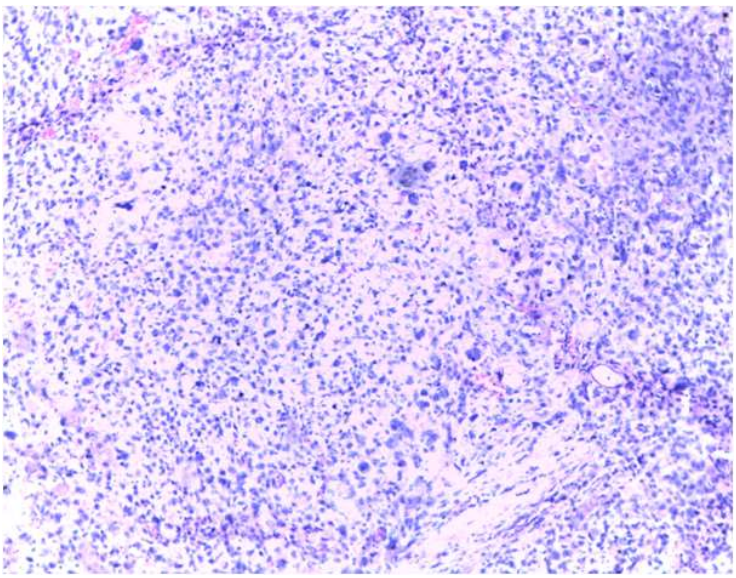

Figure 2b: Hepatoblasma; epithelial type showing more primitive embryonal cells forming few tubules (H &E X100)

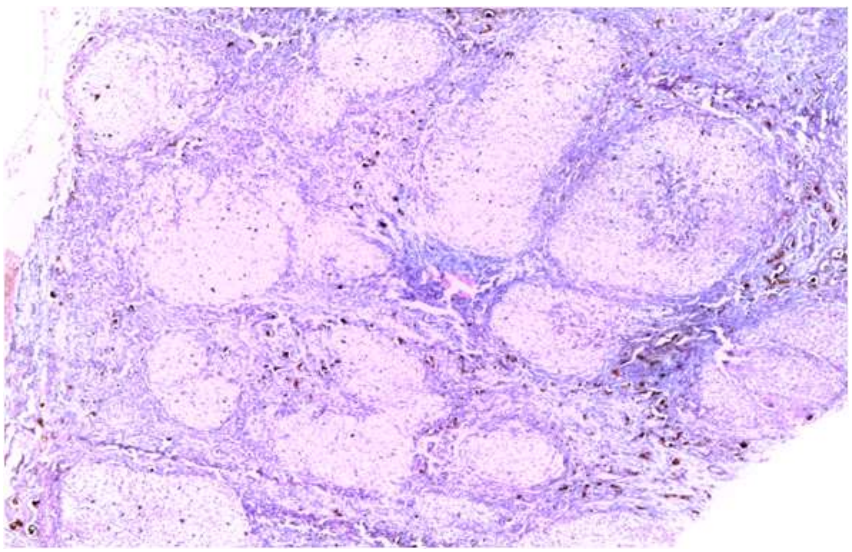

Figure 3: Secondary biliary cirrhosis with irregular nodules and proliferating bile ductules (Haematoxylin and Eosin X 100)

Overall, chronic viral hepatitis (31.9%), neonatal hepatitis (21.3%) and biliary atresia (14.7%) were the predominant diseases. Six cases (12.8%) of liver cirrhosis and 4 (8.5%) cases each of hepatic schistosomiasis and hepatoblastoma were also recorded. One case of hepatocellular carcinoma was seen in a 15year old male child.

The infectious diseases accounted for 19 cases (40.4%) and include 15 cases of chronic viral hepatitis seen in 13 male and 2 female patients in the ages of between 9 to 15 years and 4 cases of hepatic schistosomal fibrosis with equal sex distribution. All the cases of chronic hepatitis had serological markers and histological features of HBV infection. There were 2 cholestatic diseases recorded in this report; neonatal hepatitis and biliary atresia, both of which were seen in children below two years. Neonatal hepatitis showed a female predilection while biliary atresia showed a slight male preponderance.

Cirrhosis accounted for 6 cases (12.8%) of this series with male to female ratio of 1:2. The five neoplastic lesions recorded were all malignant and included four cases of hepatoblastoma in a 19month old female and three males aged two years, 12 years and 12years old respectively and a case of hepatocellular carcinoma in a 15year old male child. The four cases of hepatoblastoma were of the epithelial type (figure 2) composed of both small polygonal foetal cells and smaller embryonal cells forming acini, and tubules.

Discussion

The predominant childhood liver diseases in this report were chronic viral hepatitis, neonatal hepatitis and biliary atresia. Chronic viral hepatitis affected children aged ten years and above. This high figure may be explained by the high level of foeto-maternal transmission during childbirth in our environment which has been reported to account for 90% of cases.[16] Neonatal hepatitis was seen in the first few weeks of life while all the cases of biliary atresia were seen in children less than two years. In a comparable study in Abuja; North-central Nigeria, Ahmed et al reported chronic viral hepatitis (57.1%), neonatal hepatitis and biliary atresia as the most common hepatic disorders in children.[17] However, an earlier study by Obafunwa et al in Jos, North-Central Nigeria documented schistosomal hepatic fibrosis as the commonest disease in paediatric liver biopsies.[13] The proportion of hepatic schistosomiasis in this study is comparable to other reports.[18,19] Our 31.9% of chronic viral hepatitis is lower than a report by Dar et al in Kashmir (39.2%) [20] and higher than Seyed et al in Iran (23.1%) though commonest disease in all.[11] In the latter report metabolic disorders including hereditary tyrosinaemia type 1, glycogen and lipid storage diseases contributed significantly (12.1%). No case of metabolic liver disorder was recorded in our study. Arif et al in Iraq reported that 41% of chronic liver diseases in children were clinico-pathologically due to inborn errors of metabolism.[21] These disorders may not necessarily be uncommon in our setting but misdiagnosed due to lack of ancillary diagnostic techniques such as tandem mass spectrometry analysis which is required for the diagnosis of some of these disorders.

Neonatal hepatitis formed 21.3% of our series comparable to the 20% reported in a study of Sudanese children from North-eastern Africa[19] and 19.4% in Ga-Rankuwa, South Africa.[6] In these reports liver cirrhosis (26%) and biliary atresia (20.8%) were the predominant diagnoses respectively. Cheema et al[18] also reported similar prevalence (20.3%) of neonatal hepatitis in their review of 768 liver biopsies in Pakistan's children as the most common diagnosis. However, Akinbami et al[7] in their study of 67 paediatric liver biopsies recorded a higher prevalence (28.9%) of neonatal hepatitis as the predominant liver pathology among the Omani children. On the other hand, a study in Iraq reported a lower prevalence (12.5%) of

neonatal hepatitis as compared to our study.[21] This lower prevalence may be explained by the fact that there were marked geographical variation, racial differences and other environmental and maternal factors peculiar to each of the study areas.

Another important cholestatic disease recorded in this series was biliary atresia and constituted 14.9%. Muthuphei in Pretoria, South Africa reports that biliary atresia was the most common paediatric liver disorder accounting for 20.8% of their cases.[6] Biliary atresia and neonatal hepatitis constituted 81% of chronic liver diseases in children less than two years in this report and showed similar trend with Akinbami's report.[7] These two disorders in addition to biliary hypoplasia are termed neonatal hepatitis syndrome and are the most common hepatic disorder in the first few weeks to two years of life. Biliary atresia is the single most common structural cause of neonatal cholestatic jaundice and is the most frequent cause of death from liver disease in early childhood accounting for 50% to 60% of liver transplants in children due to the rapid progression to secondary biliary cirrhosis in areas where this service is feasible.[8] Three of our cases had established secondary biliary cirrhosis (figure 3). The 12.8% prevalence of cryptogenic liver cirrhosis found in this study concurs with the 13.2% prevalence documented by Dehghani et al[22] elsewhere. A prevalence of 16.3% was, on the other hand, reported in another study among South African children[6] and liver cirrhosis was found to be the predominant liver pathology in a study of Sudanese children.[19]

The prevalence of NAFLD in paediatric population is estimated to be between 3% and 10% depending on the characteristic of the population especially lifestyles.[23] Huang et al in a study of 219 schoolchildren, aged 6 to 12 years reported the rates of NAFLD of 3% in the normal-weight range, 25% in the overweight range, and 76% in obese children.[24] We did not record any fatty liver disorder in this study. The relative absence of this disease in this environment is probably due to malnutrition in form of protein and calories deficiency due to the low and poor socio economic environment. The neoplastic diseases seen were all hepatoblastoma except for a single case of HCC. Hepatoblastoma is the most common primary liver cancer in children and usually occur at a very young age of three years and below, and are of embryonal or congenital origin.[25] It has been associated with some congenital abnormalities such as hemi-hypertrophy, nephroblastoma, glycogen storage disease, and familial colonic polyposis.[26] In this study, we recorded 2 cases below 2 years and the other two cases were 12years each. This finding is comparable to reports of three cases aged 2months, 14months and 10year old by Sinniah et al from Malaysia.[27] Atimati et al also reported a 16year old girl with hepatoblastoma from Benin city, Nigeria.[28] Hepatocellular carcinoma is relatively a common malignancy in our environment in adult but very infrequent in the paediatric age group. We recorded a single case and similar to this, Sinniah and Sumithra also reported five primary liver cancers in children and in their report three cases were hepatoblastoma with a single case each of HCC and cholangiocarcinoma. Akinyinka et al in Ibadan reported 19 cases spanning 35 year period and all of the cases were associated with hepatitis B viral (HBV) infection.[29] Chronic HBV infection is the most common aetiologic factor associated with HCC development especially in sub Saharan Africa and Asia.

Conclusion

Evaluating paediatric patients with chronic liver disease require liver biopsy and histopathologic assessment. The diseases were age specific as shown in this study; the most common disease was chronic HBV hepatitis seen in older age group while neonatal hepatitis and biliary atresia predominated in younger children.

References

1. Grant A, Neuberger J. Guidelines on the use of liver biopsy in clinical practice. Gut 1999; 45:1-11
2. Ahmad M, Afzal S, Roshan E, Mubarik A, Bano S, Khan SA, et al. Usefulness of needle biopsy in the diagnosis of paediatric liver disorders. *J Pak Med Assoc.* 2005; 55(1): 24-8
3. Bravo AA, Sheth SG, Chopra S. Liver Biopsy. N Eng J Med 2001; 344(7):495- 500.
4. Antal D, Valerie M, Nedim H. Hepatic neoplasms in children: A focus on differential diagnosis. Clin Res Hepatol Gastroenterol, 2014; 38(4): 399-402
5. Morales-Romero J, Vargas G and García-Román R. Occult HBV Infection: A Faceless Enemy in Liver Cancer Development. *Viruses* 2014; *6*: 1590-1611
6. Muthuphei M. N. Childhood Liver Diseases in Ga-Rankuwa Hospital, South Africa, East Afr Med J 2000; 77(9):508-509
7. Akinbami FO, Venugopalan P, Nirmala V, Suresh J, Abiodun P. Pattern of chronic liver disease in Omani children--a clinicopathological review. *West Afr J Med.* 2004;23(2):162-6
8. Sinha C. K., Davenport M. Biliary atresia, Review. J Indian Assoc Pediatr Surg 2008; 13(2): 49-56
9. Akang EE, Osinusi KO, Pindiga HU, Okpala JU, Aghadiuno PU Congenital malformations: a review of 672 autopsies in Ibadan, Nigeria Pediatr Pathol. 1993: 13(5):659-70.
10. Mabogunje OA. Biliary atresia in Zaria, Nigeria: a review. Ann Trop Paediatr 1987; 7:200–204
11. Dehghani S M, Haghigha M, Imanieh M H, Geramizadeh B, Eskandari Z, Erfanifar F, Malekpour A. Percutaneous Needle Biopsy in the Diagnosis of Liver Diseases in Children. Journal of Comprehensive Pediatrics. 2013; 3(5):184-8
12. Monajemzadeh M, Tabriz HM, Mahjoub F, Fallahi G, Farahmand F. Liver needle biopsy in Iraninan pediatric patients: Diagnostic significance and pattern of liver diseases. Indian J Pathol Microbiol 2009;52:10-3
13. Obafunwa JO, Elesha SO. Childhood liver diseases in Jos, Nigeria: A retrospective histopathological study. East Afr Med J 1991; 68: 702-6
14. Giorgio V, Prono F, Graziano F, Nobili V. Pediatric non alcoholic fatty liver disease: old and new concepts on development, progression, metabolic insight and potential treatment targets. *BMC Pediatr.* 2013;13:40
15. Zaman S, Hanif G, Hussain M, Basit Z, Khan S, Rathore Z, et al. Hepatic tumours in childhood: an experience at the Children Hospital and Institute of Child Health, Lahore. *J Pak Med Assoc.* 2011; 61(11): 1079-82
16. Mihigo R, Deo N, Andrew H, Michael K, Steven W, John C C. Control of viral hepatitis infection in Africa: Are we dreaming? Vaccine *2013; (31): 341– 346*
17. Ahmed PA, Ulonnam CC, Mohammed-Nafiu R, Ballong J, Nwankwo G. Pattern of liver diseases among children attending the National Hospital Abuja, Nigeria. Niger J Paed 2016; 43 (1): 46 - 50
18. Huma A C, Arit P, Hassan S M, *Zafar F.* Safety of Outpatient Blind Percutaneous Liver Biopsy in Children and to Document the Spectrum of Pediatric Liver Disease. Pak Pediatr J 2015; 39(1): 12-18
19. Sabir O M. Pathologic causes of liver disease in Sudanese children: Results of 450 liver needle biopsies at a single children hospital. Sudan J Paediatr 2011; 11(1): 38-41.
20. Dar G A, Zarger S A, Jan K, Malik M I, Mir T A, Dar M A. Spectrum of Liver Diseases among Children in Kashmir Valley. Academic Med J India. 2014; 2(3): 80–6
21. Arif HS, Thejeal RF. Etiology of chronic liver disease in Iraqi children, with special emphasis on the role of liver biopsy. Pak J Med Sci 2011;27(4):870-873
22. Dehghani SM, Imanieh MH, Haghighat M, Malekpour A, Falizkar Z. Etiology and

Complications of Liver Cirrhosis in Children: Report of a Single Center from Southern Iran. *Middle East J Dig Dis* 2013;5:41-6
23. Giorgio V, Prono F, Graziano F, Nobili V. Pediatric non alcoholic fatty liver disease: old and new concepts on development, progression, metabolic insight and potential treatment targets. *BMC Pediatr.* 2013;13:40
24. Huang SC, Yang YJ: Serum retinol-binding protein 4 is independently associated with pediatric NAFLD and fasting triglyceride level. J Pediatr Gastroenterol Nutr 2013, 56:145–150
25. Neil N D, Liver and Gallbladder. In: Kumar V, Abbas AK, Aster JC (Eds.) Robbins and Cotran Pathologic Basis of Disease, 9th ed. Elsevier Saunders Co. 2015; pp. 867-875
26. Desmet V.J, Rosai J. The Liver. In; Rosai and Ackerman's Surgical Pathology, 10th ed, Juan Rosai(ed). Elsevier Inc. 2011: pp858-980
27. Sinniah D, Sumithran E, Lin Hp, Chan L L and Toh C K. Primary Liver Cancer in Malaysian Children. Med. J. Malaysia 1980; 36(3) : 265-268
28. Atimati AO, Abiodun PO, Obaseki DE, Olubor OO. Hepatoblastoma in an adolescent girl: A case report. Niger J Paed 2014; 41 (4): 383 – 385
29. Akinyinka O O, Falade, A. G, Ogunbiyi O, Johnson A. O. Hepatocellular carcinoma in Nigerian children. International Child Health, Annals Trop Paediatr 2001; 21(2): 165-168

Cite this article as: Usman B, Samaila M O, Yawale I Histopathologic Spectrum of Childhood Liver Diseases in A Tertiary Hospital in North-Western Nigeria. Bo Med J 2017; 14(1): 47-54 **Source of Support:** Nil,
Conflict of Interest: None declared.