Etiology and clinical pattern of liver diseases in children

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Abstract:

Background: liver diseases may not be recognized by clinicians, who can lead to a subsequent delay in the initiation of effective therapies, the commonest presenting signs and symptoms of pediatric liver diseases include hepatomegaly, jaundice, coagulopathy or elevation of the liver enzymes or waste products as ammonia.

Objectives: To highlight the etiologies, pattern of presentations and the route of diagnosis of all liver diseases in children less than 10 years referred to the Gastroenterology and Hepatology Unit in Children Welfare Teaching Hospital over a six months period.

Patients and methods: A prospective study was conducted in the Gastroenterology and Hepatology Unit in the Children Welfare Teaching Hospital / Baghdad Medical City hospital during the period from first of December 2016 to the end of thirty first of May 2017.

Forty patients aged below 10 years were thoroughly assessed for possible causes of liver disease and the severity of liver damage. These patients were subjected to a detailed history, thorough physical examination and a list of investigations

Results: forty patients their age less than 10 years, the most common age group in this study was from 1 year to 5 years was 17(40%), males are more affected than females in the ratio of 1.5:1, it was found that the mean age of onset is the biliary atresia and Galactosemia cases were within the first week of life, congenital infection cases presented earlier than the two above groups. In this study most of the cases were diagnosed clinically and by available investigations and only cases of biliary atresia and glycogen storage diseases were diagnosed by liver biopsy.

Conclusion: All patients presented late with complications, biliary atresia cases were very late in presentation, all with fibrosis. Family history usually very important in hereditary liver diseases as galactosemia and glycogen storage disease a careful physical examination in addition to previous medical history most of the time gives a clue to the final diagnosis.

Keywords: liver diseases, clinical aspects, children less than 10 years.

Introduction:

The precise documentation of liver disease, often not recognized by clinician, which can lead to a subsequent delay in the initiation of effective therapies (1). Unfortunately, the sensitivity and specificity of many clinical symptoms and signs in liver disease are low, so the disease may be present without detectable signs or symptoms and those present may not be specific to liver disease. Thus, for example, it is possible to have chronic viral hepatitis B for decades proceeding to cirrhosis without any external or even biochemical evidence due to the liver's limited response to injury (2, 3). The commonest presenting signs and symptoms of pediatric liver disease include hepatomegaly, jaundice, coagulopathy or elevation of liver enzymes or waste products as ammonia (4). The causes of pediatric hepatic disease hugely vary with age. Some conditions such as biliary atresia and idiopathic neonatal hepatitis are observed only at birth or shortly thereafter. On the other hand, acetaminophen poisoning and Wilson disease are typical of older children, especially adolescents on the other hand, viral hepatitis may occur at any age (5). Some cases of glycogen storage disorders may present with chronic liver disease, and many patients with the autosomal recessive liver-specific type may develop cirrhosis. In Wilson disease the hepatic insult is believed to be caused by excess copper, which acts as a pro-oxidant and promotes the generation of free annoying radicals (6).

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Materials and Methods:

A prospective study was conducted in the Gastroenterology and Hepatology Unit in the Children Welfare Teaching Hospital / Baghdad Medical City complex during the period from first of December 2016 up to the end of thirty first of May 2017. Forty patients aged less than 10 years were referred to the unit with liver problems because of unknown diagnosis. Cases of breast milk jaundice, Kalaazar, hemolytic causes of jaundice and tumors were excluded. All patients were thoroughly assessed for possible causes of liver disease and severity of liver damage. Prolonged neonatal

jaundice is defined as jaundice lasting for longer than 14 days in term infants or longer than 21 days in preterm infants. Those were 16 cases (7). Acute hepatitis: any patient presented with acute jaundice, fever, abdominal pain and vomiting of few days duration. Chronic liver disease is defined as liver disease continuing without improvement for at least 6 months excluding tumors (7, 8). From each patient, a detailed history was taken concerning the illness, time of the onset of the symptoms, time of presentation, complications of the disease, other associated disease, residency and family history of the same illness. These patients were subjected to a detailed history, thorough physical examination and a list of investigation that includes:

A. Basic investigations:

Complete blood count, ESR and blood film. Liver enzymes, including SGOT, SGPT, alkaline phosphatase, total serum bilirubin. Prothrombin time and partial thromboplastin time. Blood sugar and blood urea. Copper studies including: serum copper, ceruloplasmin, 24 hour urinary copper value and ophthalmological search for Kayser Fleischer ring. Iron studies: serum iron, iron binding capacity and serum ferritin level. Alpha-1-antitrypsin level in the blood. Serum protein electrophoresis. Liver immunological markers (ANA, ASA and AMA). Viral markers of chronic liver disease for hepatitis A, B and C viruses. Radiology including abdominal ultrasound examination and Doppler study of the portal system and inferior vena cava. Endoscopic examination of the upper GIT for 6 patients. Liver biopsy examination using menghini needle in addition to routine staining, staining for iron and PAS stain for alpha-1 antitrypsin carried in suspicious cases. Ascetic fluid analysis including biochemical, cytological and microbiological that includes culture and sensitivity (in patients with ascites). TORCH: the diagnosis is demonstrated of specific (IgM) antibodies by indirect fluorescence.

B. Additional investigations:

These include Hb-electrophoresis, urine and blood for reducing substances, serological tests for VDRL and other connective tissue test.

Results:

The most common age group in this study was from more than 1 year to 5 years 17(40%) and more than one month to 6 months 13(32.5%) ,males are more affected than females in the ratio of 1.5:1, but the ratio varies in between different diseases as shown in (table -1). It was found that the mean age of onset in the biliary atresia and Galactosemia cases were within the first week of life, but the mean age of presentation was as late as 4 months and 5 months respectively and males are more affected than females in both conditions. The mean age of onset and presentation is earlier in congenital infection than the two above groups. Acute hepatitis cases and metabolic liver diseases presented later than the first year of life, especially Wilson disease, where the age of onset was beyond 5 years and the mean age of presentation was 6.5 years and it was more common in males rather than females. In contrary, immune hepatitis cases which were more common in females rather than males as shown in (table -2). Most cases presented with jaundice, while cases of glycogen storage disease presented commonly with hepatomegaly, hypotonia and delayed milestones. All cases of acute hepatitis A virus presented with jaundice and neurological manifestations as tremor, disturbed consciousness or even coma and one of the cases was recurrent hepatitis as shown in (table -3). In this study most of the cases were diagnosed clinically and by available investigation and only cases of biliary atresia and glycogen storage diseases were diagnosed by liver biopsy as shown in (table -4).

Table (1): Age & gender distribution of the study

Age	Gender				Total	
	Male		Female			
	No.	%	No.	%	No.	%
0-1 months	0	0	2	5	2	5
>1-6 months	11	23	2	5	13	32.5
>6months–1 year	1	2.5	1	2.5	2	5
> 1-5 years	7	17.5	9	22.5	16	40
> 5-10 years	5	12.5	2	5	7	17.5
Total	24	60	16	40	40	100

Table (2): Causes of liver disease in this study in relation to the age of onset, presentation and sex distribution

Disease entity	Mean age of onset	Mean age of presentation	Gender		Total (%)
			Male	Female	
Biliary atresia	4 days	4 months	5	2	7 (17.5%)
Galactosemia	5 days	5.5 months	5	1	6 (15%)
Glycogen storage disease	14 months	30 months	3	3	6 (15%)
Autoimmune hepatitis	33 months (2.7 years)	50 months (4.5 years)	2	4	6 (15%)
Wilson's disease	5.6 years	6.5 years	5	1	6 (15%)
Hepatitis A	4.6 years	4.4 years	4	1	5 (12.5%)
Congenital infection	7 days	50 days	1	1	2 (5%)
α1-antitrypsin deficiency	10 months	16 months	0	1	1 (2.5%)
Unknown diagnosis	2.11 months	3 years	1	0	1 (2.5%)

Table (3): Clinical presentation in different diseases in this study group

Cause (no.)	Jaundice	Hepato-megaly	Hepatospleno-megaly	Oesophageal varices (haematemsis)	Hypotonia	Neurological symptoms	+ve Family history
Biliary atresia (7)	100%	-ve	100%	-ve	-ve	-ve	-ve
Galactosemia (6)	100%	33.3%	66.6%	-ve	-ve	-ve	+ve
Glycogen storage disease (6)	16.6%	33.3%	66.6%	16.6%	50%	50%	+ve
Immune hepatitis (6)	66.6%	-ve	100%	33.3%	-ve	-ve	+ve
Wilson's disease (6)	100%	-ve	100%	33.3%	-ve	33.3%	+ve
Hepatitis A (5)	100%	100%	-ve	-ve	-ve	100%	+ve
Congenital infection (2)	100%	50%	50%	-ve	-ve	-ve	-ve
α-1 antitrypsin (1)	-ve	-ve	100%	100%	-ve	-ve	-ve

Table (4): Methods of diagnosis

Disease entity	Diagnosis clinically and by investigation	Diagnosis by liver biopsy
Biliary atresia	-	+ve
Galactosemia	+ve	-
Congenital infection	+ve	-
Hepatitis A	+ve	-
Glycogen storage disease	-ve	+ve
Immune hepatitis	+ve	-
Wilson's disease	+ve	-
α -1 antitrypsin	+ve	-

Discussion:

In this study it was found that male: female ratio 3:2 which is in accordance with result obtained by Arif H S et al (16) in Iraq 1.4:1, and El-Defrawy M S. (17) in Egypt 2.5:1, and Dhole S D et al in India. (18) in Sudan 1.4:1. The most common age group affected between 1-5 years (40%) and it is quite higher than the result found by Dhole S D et al in India. (18) (32.88%) and in Pakistan by Tahir A. (19) and this may be explained by differences in diseases distribution according to geographic habitant. The most common cause of liver diseases in this study was biliary atresia (17.5%) followed by other causes which disagrees with result found in Dhole S D et al in India. (18) (10%), and in Pakistan by Tahir A. (19) (6.7%) and this large number of cases is unfortunately related to delay in seeking medical advice and usually beyond any surgical intervention, cirrhosis was already shown on liver biopsy, and fibrosis might start as early as 8 weeks of life, at the same time galactosemia was found among (15%) while it is much lower by Bhatia V et al in India (20) (4%). Glycogen storage disease also found among (15%) of patients and it was found among (7.3%) by Shah S Z et al in Pakistan (21) and (3.6%) by ARYA G in USA (22). The mean age of presentation for biliary atresia was four months which was longer than what was found in other studies in Brazil by Bezerra about 82.6 days (23) and in Colombo by Infaq M. et al about 81.8 days (24) and this may be explained by low index of suspicion and delay seeking medical advice. utoimmune hepatitis found among (15%) in this study but it was (3.3%) by Shah S Z et al in Pakistan (21) and (4.4%) by ARYA G in USA (22). Wilson's disease was discovered among (15%) of patients and it was (8.66%) by Shah S Z et al in Pakistan (21) and (9.4 %) by ARYA G in USA (22) and all of these differences may be explained by small sample size. Hepatitis A present in (12.5%) of patients (3.4%) by ARYA G in USA (22) and this may be explained by differences in sterilization and sanitation. Alpha 1-AT deficiency was found in (2.5%) but it was much higher (39.2%) by ARYA G in USA (22) and this may explained by the availability of sophisticated investigation assisting in reaching the diagnosis. In this study it was found that the most clinical presentation was jaundice, hepatosplenomegaly and to lesser extent esophageal varices and this nearly similar to results obtained by Hanif et al (25) and Dangwal et al (26). Although a liver biopsy is obtained only after a thorough noninvasive clinical investigation in patients with persistent abnormal liver enzyme elevation, but it plays a vital role in the precise diagnosis in cases of hepatosplenomegaly, cholestatic jaundice, pyrexia of unknown origin, neoplastic and metabolic liver disorders. Histopathological evaluation of the liver can provide unavailable information regarding its structure as well as the type and severity of damage or fibrosis that involve the liver. Percutaneous liver biopsy in children is a procedure with a low rate of major complications and a high rate of minor bleeding as well as no need for intervention and is considered as a safe procedure even in infancy (27, 28). It was found that in this study that liver biopsy was diagnostic in biliary atresia and glycogen storage diseases and this agree with results obtained by Arif H S et al (16) and Dangwal et al (26).

Conclusions:

All patients presented late with complications.

Biliary atresia cases were very late in presentation, all with fibrosis. Early diagnosis carry better prognosis. Family history usually very important in hereditary liver diseases as galactosemia and

glycogen storage disease. Careful physical examination in addition to previous medical history most of the time gives a clue to the final diagnosis.
Hepatitis A virus presented in this series in different pattern. Cases of recurrent hepatitis and persistent cholestasis were presented all with neurological manifestations.

References:

1. *D'Agata I D., Balistreri William F. Evaluation of Liver Disease in the Pediatric Patient. Pediatrics in Review1999; 20(11):376-389.*
2. Nelson S P, Jonas M. Clinical features of liver disease. Walker - Smith, Hamilton; Practical pediatric gastroenterology. 2nd ed. B.C. Decker Inc.1996: 107-116.
3. Bisset W M, Beath S V, Jenkins H R, et al. Disorders of the alimentary tract and liver. In: McIntosh N, Helms P, Smyth R (eds). Forfar and Arneil textbook of pediatrics. 7th ed. Philadelphia. Churchill Livingstone CO 2008: 642-643.
4. Karpen S J. Acquired mechanisms of cholestasis. In: SUCHY F J., SOKOL R J., BALI STRERI W F. editors. LIVER DISEASE IN CHILDREN. Third Edition. Cambridge University Press 2007: 30-33.
5. Hanif M, Raza J, Qureshi H, Issani Z. Etiology of Chronic Liver Disease in Children. J Pak Med Assoc 2004;54:119–22.
6. Ahmad Dar G., Malik M. I., Ganie F. A.,et al. Chronic Liver Diseases in Children: Clinical Spectrum and Etiology. BBB 2014;2(2):406-4116. Dhawan A. Etiology and Prognosis of Acute Liver Failure in Children. Liver Transplantation 2008; 14(10): 80-84.
7. Hassan H. H A, Balistreri W F. Neonatal Cholestasis. In: Behrman RE, Kliegman RM, Jenson HB, Stanton BF. Nelson Textbook of Pediatrics. 20th ed, Philadelphia. WB Saunders CO. 2016: 1928-1035.
8. Squires R, Teitelbaum J E. APPROACH TO THE PATIENT WITH HEPATOBILIARY SYMPTOMS OR SIGNS. Rudolph C D., Rudolph A M., Hostetter M K., Lister G, Siegel N J. .Rudolph's Pediatrics, 21st Edition. McGraw-Hill.2003:1477-1481.
9. Leyva-Vega M, Haber B A. Biliary Atresia. Bishop W P. PEDIATRIC PRACTICE Gastroenterology. McGraw-Hill Companies.2010:330-340.
10. Choi SO; Park WH; Lee HJ. Ultrasonographic "triangular cord": the most definite finding for non-invasive diagnosis of extrahepatic biliary atresia. Eur J Pediatr Surg, 1988; 8(1): 12-6.
11. MCKIERNAN P J. The Acutely Ill Baby. KELLY D A. Diseases of the Liver and Biliary System in Children, SECOND EDITION. Blackwell Publishing 2004:74-90.
12. DAVISON S. Acute Hepatitis. KELLY D A. Diseases of the Liver and Biliary System in Children, SECOND EDITION. Blackwell Publishing 2004:92-103.
13. Odieure M. Clinical presentation of metabolic liver disease. Journal of inherited metabolic liver disease, 1991; 14: 526-530.
14. Gill HH, Shankaran K et al. Wilson's disease varied presentation. Indian J Gastroenterology, 1994; 13(3): 95-8.
15. Sawada A; Tajiri H et al. Favorable response to lymphoblastoid interferon alpha in children with chronic hepatitis. CJ Hepatol, 1998; 28(2): 184-8.
16. Arif H S et al. 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.
17. El-Defrawy M S., Abd El-Motaleb G S., El-Hennawy A. SPECTRUM OF CHRONIC LIVER DISEASES IN EGYPTIAN CHILDREN IN BENHA. Benha M. J. 2004; 21(3):673-678.
18. Dhole S D, Kher A S. , Ghildiyal R G, et al. Chronic Liver Diseases in Children: Clinical Profile and Histology. Journal of Clinical and Diagnostic Research. 2015; 9(7): 4-7.
19. Tahir A, Malik F R, Ahmad I, Krishin J , et al. AETIOLOGICAL FACTORS OF CHRONIC LIVER DISEASE IN CHILDREN. J Ayub Med Coll Abbottabad 2011; 23(2):12-14.
20. Bhatia V, Bavdekar A, Matthai J, Waikar Y, Sibal A. Management of neonatal cholestasis: consensus statement of the Pediatric Gastroenterology Chapter of Indian Academy of Pediatrics. Indian Pediatr. 2014; 51:203-10.
21. Shah S Z, Malik R, Shah S F, et al FREQUENCY OF CAUSES OF CHRONIC LIVER DISEASE IN CHILDREN. Pak Armed Forces Med J 2017; 67 (5): 762-67.
22. ARYA G, BALISTRERI W F. Pediatric liver disease in the United States: Epidemiology and impact Journal of Gastroenterology and Hepatology 2002; 17: 521–525
23. Bezerra A. Biliary atresia in Brazil: where we are and where we are going
Jorge . Jornal de Pediatria 2010; 86(6):445-447.
24. Infaq M., Waidyanatha S. A study on cholestasis in infants less than six months of age presenting to Lady Ridgeway Hospital for Children, Colombo. Sri Lanka Journal of Child Health, 2016; 45(1): 34-37.
25. Hanif M, Raza J, Qureshi H, Issani Z. Etiology of chronic liver disease in children. J Pak Med Assoc 2004; 54:119-22.
26. Dangwal T.R, Agrwal V, Malhotra V, Bavaga V and Mittal S.K. Clinical spectrum of chronic liver diseases in North India. Trop. Gastroenterol. 1997; 18 (4):184.
27. Westheim BH, Ostensen AB, Aagenaes I, Sanengen T, Almaas R. Evaluation of risk factors for bleeding after liver biopsy in children. J Pediatr Gastroenterol Nutr. 2012; 55(1):82-7.
28. Matos H, Noruegas MJ, Goncalves I, Sanches C. Effectiveness and safety of ultrasound-guided percutaneous liver biopsy in children. Pediatr Radiol. 2012; 42(11):1322-5.