Research Journal of Microbiology

ISSN 1816-4935

Academic Journals Inc.

www.academicjournals.com

Research Journal of Microbiology 3 (3): 187-192, 2008
ISSN 1816-4935

Etiology of Acute Hepatitis in Pediatric Patients Referring to a Major City Hospital, Shiraz, Iran

[1]Seddiqe Amini-Ranjbar, [2]Mohammad-Hadi Imanieh,
[2]Mahmoud Haghighat and [2]Bita Geramizadeh,
[1]Neuroscience Research Center, Kerman University of Medical Sciences, Iran
[2]Shiraz University of Medical Sciences, Iran

Abstract: On-time diagnosis and consequently early treatment of acute hepatitis have important role in its long-term prognosis. This prospective study was done from November 2002 to January 2004 in Shiraz in order to find the etiology of acute hepatitis in children of Fars Province. For this purpose, 75 children with median age of 8.2 years and the clinical picture of acute hepatitis referring to the Outpatient Clinic and Emergency Room of Namazi Hospital (Shiraz/ Iran) were studied. After taking history, physical examination and recording the pertinent information in a questionnaire, CBC and LFT were requested. In the case of liver enzymes of higher than two times as much as the normal range, IgM HAV, HBsAg, HCVPCR, ANA, AsMAb, urinary copper and serum ceruloplasmin tests and eye examination for KF ring were performed. Ascitic fluid was sent for culture, cytology and further analysis. In some cases, based on the necessity, abdominal sonography and biopsy were performed as well. Fifty five percent were female and 65% gave the history of disease from one week prior to the appearance of icterus. The first leading causes of acute hepatitis were found to be, respectively hepatitis A (45.3%), Wilson disease (17.3%) and autoimmune hepatitis (12%). In 8% of the cases, in spite of extensive work up no cause was found (unknown cases). Tea color urine (84%), abdominal pain (82%) and anorexia (81%) were the most prevalent complaints. The most common signs were hepatomegaly (90%), icterus (89%) and tender liver (64%), respectively. Ascites (77%) and splenomegaly (61%) were observed more frequently in patients with Wilson disease comparing to other patients. AST and ALT rising to more than 10 times the normal range were more frequently seen in autoimmune hepatitis (89 and 100%) and hepatitis A (62 and 68%) patients, respectively. Considering the relatively high prevalence of treatable causes of acute hepatitis (Wilson, autoimmune hepatitis), attention to the mentioned diseases in facing childhood acute hepatitis is highly recommended.

Key words: Acute hepatitis, Wilson disease, hepatitis A, autoimmune hepatitis

INTRODUCTION

Hepatitis or the inflammation of liver parenchyma is one of the common diseases of childhood. It has various etiologies based on age, geographical area, cultural and health conditions. Some of its etiologies such as Wilson disease and autoimmune hepatitis would be treatable provided that they are diagnosed and treated at early stages (Karim *et al*., 2007). According to Rendi-Wagner *et al*. (2007) even in areas of low hepatitis A endemicity such as developed countries, hospitalization incidence of children is still at a considerable level so considering hepatitis A in pediatric patients presenting with jaundice is important. As most cases of hepatitis, especially in children, are considered as a benign and transient disease by clinicians, there may be no adequate follow up attempt by both the patient and the clinician (Whitehead *et al*., 2001).

Corresponding Author: Seddiqe Amini-Ranjbar, Afzalipour Hospital, Kerman, Iran

It has been documented that jaundice is often wrongly attributed in primary care and in hospital settings outside gastroenterology (Whitehead *et al*., 2001) owing to lack of practical knowledge regarding the epidemiology of the etiological factors of jaundice. Considering the importance of long-term complications of hepatitis (Hahn *et al*., 2002) and lack of any study about the causative factors of childhood acute hepatitis in our region, the present study was designed to survey the etiologies of acute hepatitis in 1-16 years old patients referring to the Outpatient Clinic and Emergency Room of Nemazi Hospital (Shiraz/Iran) with the clinical picture of acute hepatitis during a 15 months period. The general objectives of the present study were to identify the etiological spectrum and clinical profile of pediatric patients with acute hepatitis.

MATERIALS AND METHODS

This prospective descriptive study was done on 75 consecutive children (outpatients or hospitalized) from November 2002 to January 2004 in Shiraz, Iran with a median age of 8.2 years with the clinical picture of acute hepatitis (icter with or without hepatomegaly or right upper quadrant tenderness and liver enzymes level more than 2 times as much as the normal value).

First the researcher visited the patient and the intended points in relation to the history and the result of physical examination were recorded in a questionnaire. Then CBC and LFT were performed and in the case of being more than 2 times of the normal value and based on the necessity and the age of child, urinary copper, ceruloplasmin, ANA, AsMAb, HCVPCR, HbsAg and HAV IgG, IgM were measured. In children with urinary copper of 40-100 μg 24 h^{-1} D-Penicillamine test was performed. Meanwhile, eye examination was performed for all children over 4 years old.

In the case of persistent clinical symptoms or abnormal LFT for more than 12 weeks or aggravating symptoms with passing time and negative results in the mentioned tests, liver biopsy was performed. In the event of ascites, abdominal sonography was done and the liquid was sent for cytology, analysis and culture.

In subjects with Wilson and hepatitis B and C the screening of first-degree relatives was done. Approval from the local ethics committee was obtained for present study. After gathering the information that had been recorded in the questionnaires, data were summarized by SPSS 12.

RESULTS AND DISCUSSION

The most common cause of acute hepatitis in our patients whether hospitalized (n = 58) or outpatients (n = 17) were hepatitis A, Wilson and autoimmune hepatitis, respectively (Table 1).

Among our subjects, 86% were from Fars Province and 55% were girls. Most subjects were over 6 years old and 65% gave the history of disease from one week prior to the appearance of icter. From all patients, 41% had history of using drugs such as aspirin, acetaminophen, antibiotics or cold syrup. There was no history of traveling during one month prior to the disease and 78% had no contact with icteric cases. The most common complaint was tea color urine (Table 2).

Ascites was more frequent in patients with Wilson and autoimmune hepatitis (Table 3). Liver transaminases in hepatitis A, autoimmune hepatitis and the unknown group showed considerable increase (up to higher than 20 times as much as the normal value) (Table 4).

Among all children, 23% had anemia and its most common reason was hemolysis due to Wilson and G6PD deficiency. From all subjects, 8% died of acute hepatic failure and the highest rate of mortality was in Wilson disease (4 from 6).

In the screening of families, in patients with Wilson, at least one case and in patients with hepatitis B at least three cases had asymptomatic disease.

Table 1: Absolute and relative frequency of patients with final diagnosis of Acute hepatitis

Final diagnosis	Frequency	Percentage
Hepatitis A*	34	45.3
Wilson disease	13	17.3
Autoimmune Hepatitis	9	12.0
Hepatitis B	5	6.7
Hepatitis C	1	1.3
Lymphoma	2	2.7
Sickle cell disease	2	2.7
Reye syndrome	1	1.3
Cholangitis	1	1.3
Scorpion bite	1	1.3
Hemochromatosis	1	1.3
UTI	1	1.3
Storage disease	1	1.3
Unknown	6	8.0
Total	75	100.0

*: Three pts had hepatitis A and autoimmune hepatitis simultaneously, In 23 pts who were certain to have Wilson, hepatitis B, hepatitis C and IgM HAV were not measured, Group of unknown was the patients whom in spite of extensive workup, certain diagnosis was not detected

Table 2: Absolute and relative frequency of complaints of 75 children presenting with clinical picture of acute hepatitis*

Final diagnosis complaints	Hepatitis A (n = 34)	Wilson disease (n = 13)	Autoimmune Hepatitis (n = 9)	Hepatitis B (n = 5)	Hepatitis C (n = 1)	Others** (n = 10)	Unknown (n = 6)	Total (n = 75)
Tea color urine	28 (90)	10 (77)	8 (88)	3 (60)	0 (0)	8 (80)	6 (100)	63 (84)
Abdominal pain	27 (87)	11 (85)	7 (77)	3 (60)	0 (0)	8 (80)	6 (100)	62 (82)
Anorexia	28 (90)	9 (69)	7 (77)	3 (60)	0 (0)	8 (80)	6 (100)	61 (81)
fever	24 (77)	6 (46)	9 (100)	2 (40)	1 (100)	8 (80)	6 (100)	56 (75)
Fatigue	22 (71)	10 (77)	7 (77)	3 (60)	0 (0)	4 (40)	5 (83)	51 (68)
vomiting	25 (80)	5 (38)	5 (55)	3 (60)	0 (0)	4 (40)	6 (100)	48 (64)
Pale stool	21 (67)	6 (46)	4 (44)	1 (20)	0 (0)	5 (50)	4 (66)	41 (54)
Constipation	17 (54)	4 (31)	4 (44)	3 (60)	0 (0)	1 (10)	3 (50)	32 (42)
Coryza	14 (45)	3 (23)	3 (33)	1 (20)	0 (0)	2 (20)	4 (66)	27 (36)
Arthralgia	6 (19)	5 (38)	5 (55)	3 (60)	0 (0)	1 (10)	2 (33)	22 (29)
Diarrhea	4 (13)	1 (8)	4 (44)	2 (40)	0 (0)	1 (10)	0 (0)	12 (16)
Rash	3 (8)	0 (0)	1 (11)	0 (0)	0 (0)	0 (0)	1 (16)	5 (6)

*: Values in parentheses show percents, **: Others consists of: lymphoma, sickle cell disease, Reye`s syndrome and

Table 3: Absolute and relative frequency of clinical findings of 75 children presenting with clinical picture of acute hepatitis*

Final diagnosis findings	Hepatitis A (n = 34)	Wilson (n = 13)	AIH (n = 9)	Hepatitis B (n = 5)	Hepatitis C (n = 1)	Others (n = 10)	Unknown (n = 6)	Total (n = 75)
Hepatomegaly	29 (93)	12 (92)	8 (88)	4 (80)	1 (100)	10 (100)	6(100)	68 (90)
Icterus	28 (90)	13(100)	7 (77)	3 (60)	1 (100)	9 (90)	6 (100)	67 (89)
Tender liver	22 (71)	6 (46)	5 (55)	1 (20)	1 (100)	8 (80)	6 (100)	48 (64)
Splenomegaly	10 (32)	8 (61)	4 (44)	0 (0)	0 (0)	4 (40)	3 (50)	29 (38)
Ascites	4 (13)	10 (77)	5 (55)	0 (0)	0 (0)	3 (30)	1 (16)	24 (32)
Decreased level of consciousness	8 (20)	6 (46)	2 (22)	1 (20)	0 (0)	0 (0)	2 (33)	18 (24)
Gibleeding	1 (31)	1 (8)	0 (0)	0 (0)	0 (0)	3 (30)	0 (0)	5 (10)
Rash	2 (6)	1 (8)	2 (22)	0 (0)	0 (0)	1 (10)	0 (0)	8 (9)

*: Values in parentheses show percents, **: Others consists of: lymphoma, sickle cell disease, Reye`s syndrome and

Understanding the causes of jaundice and the history and physical examination hallmarks provide the basis for choosing the most efficacious diagnostic and management plan in pediatric patients. To the best of our knowledge few studies have investigated prospectively the causes of acute hepatitis in a group of pediatric patients (Bryan *et al*., 2001; Whitehead *et al*., 2001) but rather they have reported the profile of only a specific type of hepatitis patientssuch as autoimmune hepatitis (Baranov *et al*., 2003), Wilson disease (Karim *et al*., 2007) and viral hepatitis (Abe *et al*., 2004).

Table 4: Absolute and relative frequency of transaminase levels of 75 children presenting with clinical picture of acute hepatitis*

Final diagnosis level of enzyme	Hepatitis A (n = 34)	Wilson (n = 13)	AIH (n = 9)	Hepatitis B (n = 5)	Hepatitis C (n = 1)	Others (n = 10)	Unknown (n = 6)	Total (n = 75)
ALT								
2> time	1 (3)	2 (15)	0 (0)	0 (0)	0 (0)	2 (20)	0 (0)	4 (5)
2-9 time	9 (29)	7 (54)	0 (0)	3 (60)	1 (100)	5 (50)	3 (50)	28 (37)
10-19 time	1 (3)	1 (8)	3 (33)	1 (20)	0 (0)	1 (10)	1 (16)	9 (12)
20-100 time	12 (39)	3 (23)	5 (56)	0 (0)	0 (0)	1 (10)	1 (16)	22 (29)
100> time								
AST	8 (26)	0 (0)	1 (11)	1 (20)	0 (0)	1 (10)	1 (16)	12 (16)
2> time	2(7)	0(0)	0 (0)	0 (0)	0 (0)	6 (60)	0 (0)	8 (10)
2-9 time	12 (38)	9 (69)	1 (11)	3 (60)	1 (100)	1 (10)	3 (50)	30 (40)
10-19 time	2 (7)	1 (8)	2 (22)	1 (20)	0 (0)	2 (20)	1 (16)	9 (12)
20-100 time	10 (32)	3 (23)	5 (56)	0 (0)	0 (0)	0 (00)	2 (33)	20 (26)
100> time	5 (16)	0 (0)	1 (11)	1 (20)	0 (0)	1 (10)	0 (0)	8 (10)

*: Values in parentheses show percents, **: Others consists of: lymphoma, sickle cell disease, Reye`s syndrome and

Based on present findings, the most common cause of acute hepatitis (HAV) in the studied children in Fars was endemic hepatitis, while it is rare in Central America (Bryan *et al*., 2001) but common in Taiwan (50%) (Wang *et al*., 2001), since none of the patients gave the history of traveling out of Fars during one month prior to their disease and all of them except three cases used filtered water. Moreover most of them (78%) had no contact with icteric patients. The high prevalence of hepatitis A in one hand and the presence of an unknown group (with unknown etiology) accounting for 8% of the whole population shows that viruses whether hepatotropic or non-hepatotropic have been the common reasons of acute hepatitis in the studied children. Even in nonendemic countries it has been proposed that hepatitis A is one of the main causes of jaundice in hospital admitted pediatric patients (Rendi-Wagner *et al*., 2007).

In a study done in Laos, leptospirosis had been the most common cause of hepatitis and hepatitis A had been reported only in 14% of the cases (Bounlu *et al*., 1998). In Wales, viral hepatitis has been reported rarely (Whitehead *et al*., 2001). In studies done in India, hepatitis E has been the most common cause of acute hepatitis and hepatitis A has been observed only in 5% of the cases (Das *et al*., 2000). In Stann Creek (79%) and Russia (65.6%), hepatitis B has been reported as the most common cause of acute hepatitis (Bryan *et al*., 2001; Abe *et al*., 2004) but in Canada hepatitis C is common hepatitis (ElSaadany *et al*., 2002). The difference between the results of the present study and the results of the above mentioned studies could be due to different geographical, social, cultural and health conditions. There was no similar study in agreement with the present study.

The difference between the rate of undetermined cases in our study (8%) and that of India study done on 75 cases (23%) may be due to not considering Wilson, autoimmune hepatitis and others in India study (Das *et al*., 2000).

Non-specific common complaints prior to the appearance of icter should bring differential diagnoses in the mind of clinicians, so that lead them to a careful physical examination and consequently prevent them from unnecessary prescriptions such as aspirin. In the present study, at least in one case unnecessary prescribed drug lead to acute liver failure and Reye syndrome was confirmed by autopsy.

Wilson disease was found as the second common cause of acute hepatitis in this study, while the prevalence of Wilson in Michigan University study (29 in 40000) (Brewer *et al*., 2000) and Korea (1 in 3667) (Hahn *et al*., 2002) and in Rochester (El-Youssef, 2003) was rare. This difference may be due to the high prevalence of consanguinity marriage in Fars or generally in Iran, since all parents of children with Wilson except one had a close family relationship.

Autoimmune hepatitis was the third common cause of acute hepatitis of childhood in the present study (12%) that is significantly different from the results of studies in European countries (0.69/100000), London College Hospital (1.2/822)), Russia (1.2%) (Baranov *et al*., 2003) and German (rare) (Strassburg and Manss, 2003). This difference can be related to hepatitis A as the accompanying disease as trigger agent in the present study, because 3 cases of our subjects had hepatitis A simultaneously.

Regarding the high prevalence of anemia (23%) and Wilson as its most common cause, performing CBC in all patients with hepatitis seems to be necessary.

In conclusion, we have put some perspective on what causes obvious jaundice in this part of Iran. Considering the most common causes of acute hepatitis in this study, it is suggested that in hepatitis A endemic countries such as Iran in facing children with acute hepatitis, IgM HAV should be as the first laboratory work up and other surveys are done in the case of necessity. Otherwise, patients with hemolysis should be studied for Wilson disease and G6PD deficiency in acute stage and all patients with acute hepatitis should be followed at least for 3 months and in the event of persistent symptoms, they should be studied for the presence of autoimmune hepatitis and Wilson disease so regarding the relatively high prevalence of treatable causes of acute hepatitis (Wilson, autoimmune hepatitis), attention to the mentioned diseases in facing childhood acute hepatitis is highly recommended.

ACKNOWLEDGMENT

This research was funded by the Deputy for Research of Shiraz University of Medical Sciences.

REFERENCES

Abe, K., E. Hayakawa, A.V. Sminov, A.L. Rossina, X. Ding, T.T.T. Huy, T. Sata and V.F. Uchaikin, 2004. Molecular epidemiology of hepatitis B, C, D and E viruses among children in Moscow, Russia. J. Clin. Virol., 30: 57-61.

Baranov, A.A., B.S. Kaganov and O.S. Gundobina *et al*., 2003. Autoimmune hepatitis in children. Int. Pediatr., 18: 23-29.

Bounlu, K., S. Insisiengmay and K. Vanthanouvong *et al*., 1998. Acute jaundice in Vientiane, Lao Peoples Democratic Republic. Clin. Infect. Dis., 27: 717-721.

Brewer, G.J., 2000. Recognition diagnosis and management of Wilson disease. PSEBM., 223: 39-46.

Bryan, G.P., L. Reyes, S. Hakre, R. Gloria, G.M. Kishore, W. Tillett, R. Engel, D. Cruess and R.H. Purcell, 2001. Epidemiology of acute hepatitis in the Stann Creek district of Belize, Cetral America. Am. J. Trop. Med. Hyg., 65: 318-324.

Das, K., A. Agarwal and R. Andrew *et al*., 2000. Role of hepatitis E and other hepatotrpic virus in aetiology of sporadic acute viral hepatitis: A hospital based study from urban Dehli. Eur. J. Epidemiol., 16: 937-940.

El-Saadany, S., P. Gully and A. Giulivi, 2002. Hepatitis A, B and C in Canada. Results from the national sentinel health unit surveillance system. Can. J. Public Health, 93: 435-438.

El-Youssef, M., 2003. Wilson disease. Mayo. Clin. Proc., 78: 11 26-1136.

Hahn, S.H., S.Y. Lee, Y.J. Jang, S.N. Kim, H.C. Shin, S.Y. Park, H.S. Han, E.S. Yu, H.W. Yoo, J.S. Lee, C.S. Chung, S.Y. Lee and D.H. Lee, 2002. Pilot study of mass screening for Wilson's disease in Korea. Mol. Genet. Metab.,76: 1333-1336.

Karim, M.B., M.M. Rahman and M.S. Islam, 2007. Wilson's disease with hepatic presentation in childhood. Mymensingh Med. J., 16: 29-32.

Rendi-Wagner, P., M. Korinek, A. Mikolasek, A. Vécsei and H. Kollaritsch, 2007. Epidemiology of travel-associated and autochthonous hepatitis a in Austrian children, 1998 to 2005. J. Travel Med., 14: 248-253.

Strassburg, S.P. and M.P. Mains, 2003. Autoimmune hepatitis. Best Pratice and Res. Clin. Gastroenterol., pp: 291-306.

Wang, S.M., C.C. Liu, Y.S. Hung, Y.J. Yang and H.Y. Lei, 2001. Chang in hepatitis a virus seroepidemiology in southern Taiwan: A large percentage of the population lack protective antibody. J. Med. Virol., 64: 104-108.

Whitehead, M.W., I. Hainsworth and J.G.C. Kingham, 2001. The causes of obvious jaundice in South West Wales: Perceptions versus reality. Gut, 48: 409-413.