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ORIGINAL ARTICLE

Chronic hepatitis C in children: Clinical spectrum and histopathological study

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KEYWORDS

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Abstract *Introduction:* Hepatitis C virus (HCV) is a major public health problem and a leading cause of chronic liver disease. An estimated 180 million people are infected worldwide. The prevalence of hepatitis C virus (HCV) infection is relatively low in children, with an anti-HCV prevalence rate of 0.2–0.4% in the Western world. Egypt has the highest prevalence of adult HCV infection in the world, averaging 15–25% in rural communities. The main (90%) HCV genotype is type 4. The magnitude of HCV infection in children is not well studied. Asymptomatic HCV infection is detectable in 2.02% of Egyptian children.

Aim: To study the clinical presentation and histopathological features of the liver in children with chronic hepatitis C infection.

Methods: The study population included 40 children from 2 to 16 years who had been diagnosed with chronic hepatitis C (HCV-RNA positive for 6 months or more by Real-time PCR) in the liver clinic at El-Shatby Children Hospital.

Abbreviations: HCV, hepatitis C virus; RNA, ribo nucleic acid; ALT, alanine – trans ferase; AST, aspartate – trans ferase; GGT, gamma glutamyale – trans peptidase; INR, international normalization ratio.

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Results: Among the 40 patients' biopsies, 26 (65%) were stage 0, 10 (25%) were stage 1, 4 (10%) were stage 2–3 (HAI). The grades of all 40 children ranged between 0 and 1 (HAI). Developing fibrosis was significantly associated with age ($P = 0.015$).

Conclusion: Children with chronic HCV infection are generally asymptomatic. Significant hepatic fibrosis was present in 10% of children with HCV infection. Fibrosis stage was significantly higher in older age children. There was no significant association between fibrosis stage and any biochemical parameter.

1. Introduction

The hepatitis C virus (HCV) is a major public health problem and a leading cause of chronic liver disease.[1] An estimated 180 million people are infected worldwide.[1] Egypt has the highest prevalence of adult HCV infection in the world, averaging 15–25% in rural communities.[2]

The magnitude of HCV infection in children is not well studied. Asymptomatic HCV infection is detectable in 2.02% of Egyptian children.[3] In two-community based cross sectional studies, the first study from Upper Egypt, 84 (3%) out of 2967 subjects under 19 years of age screened for HCV antibody using the ELISA technique, were found to be positive.[4] In the second study from Lower Egypt, 178 (9%) out of the 2010 screened subjects under 19 years of age were found to be positive.[5]

The main (90%) HCV genotype is type 4.[6]

Although blood transfusion, vertical transmission, and living in a house with an infected family member are the established risk factors for HCV transmission, approximately 70% of acquired infections are due to unidentified risk factors.[7,8] The clinical presentation of HCV; the incubation period ranges from 6 to 12 weeks. Acute infection usually occurs without any signs or symptoms. Few patients ($< 30\%$) will experience fever, malaise, nausea, abdominal discomfort and jaundice. HCV RNA can be detected within 2 weeks, and alanine amino transferase (ALT) will increase about 1 month after infection.

Chronic infection is usually asymptomatic, but can be associated with fatigue especially in teens and adults. Patients who present with anorexia, weight loss, abdominal pain, hepatomegaly, and splenomegaly usually have advanced liver disease.[9]

Both adult and pediatric patients lack stigmata of chronic liver disease until they develop signs of decompensated liver disease. Some physical examination findings may include ascites, edema, jaundice, palmar erythema, spider nevi, caput medusa, gynecomastia, hypogonadism, hepatosplenomegaly, leuconychia, cyanosis, clubbing, fetor hepaticus, enlarged parotid gland, paraumbilical hernia, abdominal bruits, scant body hair, and other clues (e.g., excoriations, petechia, and tattoos). Patients with HCV can also demonstrate extrahepatic manifestations of infection, such as cryoglobulinemia, porphyria cutanea tarda, or necrotizing vasculitis.[10] Hepatitis C virus (HCV) progresses gradually, and can result in serious complications such as cirrhosis and hepatocellular carcinoma.[11] However, data on the natural history and histopathology of HCV-related liver disease in children are conflicting.[12–16] Studies from Japan and Europe point to a relatively benign clinical and histopathologic liver disease[17–20] whereas studies from the USA suggest a more aggressive course with development of early fibrosis.[21–25] Geographic variation in genotypes and diversity of the infected population studied may account for some of these differences, in addition to, as yet unknown viral/host factors.[26–28]

The lack of uniformity in the descriptions of the natural history, clinical presentation and histologic features of HCV infection in children prompted us to evaluate 40 HCV infected children followed in our liver unit.

1.1. Subjects

The current study was a prospective study carried out at Al-Shatby Hospital. The study population included 40 children aged from 2 to 16 years who had been diagnosed with chronic HCV infection; i.e.: having HCV-RNA positive for 6 months or more by Real-time PCR which is a molecular assay method for HCV RNA detection and quantification with detection limit = 12 IU/ml.[29] None of these patients was under treatment during the study.

1.2. Inclusion criteria

Children will be eligible for the study if they have:

- Positive anti-HCV antibody. (Axsym system HCV version 3.0 Abbott Diagnostic Division: Germany).[30]
- Positive HCV RNA in serum for 6 months or more.[29]
- Compensated liver disease (total serum bilirubin $\leqslant 1.5$ mg/dL; INR $\leqslant 1.5$; serum albumin $\geqslant 3.4$, • Acceptable hematological and biochemical indices (Hemoglobin $\geqslant 12$ g/dL; neutrophil count $\geqslant 1500$/cmm, platelet count $\geqslant 75{,}000$/cmm and serum creatinine $\leqslant 1.5$ mg/dl).

1.3. Exclusion criteria

- Evidence of hepatic decompensation (hepatic encephalopathy or ascites).
- Other liver diseases, such as hepatitis B or schistosomiasis.

2. Methods

Informed consent was obtained from the childs parents and ethical approval of the study protocol was secured from the Ethics Committee of Alexandria Faculty of Medicine.

All children were subjected to:

1. Thorough history taking
2. Full clinical examination; stressing on abdominal examination for assessment of liver span and consistency, splenic size and signs of liver disease.
3. Routine laboratory investigations including: urine analysis, complete blood picture, kidney function tests and liver function tests.
4. Abdominal ultrasound.
5. Percutaneous liver biopsy using a Menghini 14 mm or 16 mm gauge needle was performed in all children.

Histological Activity Index was used to determine the stage and grade of liver injury.[31]

All biopsy specimens were fixed in formalin and paraffin embedded. Four-um thick sections stained with hematoxylin-eosin and Masson trichrome were available for examination in all cases.

3. Results

Table 1 shows that 15% of chronic HCV children were below 5 years, 35% were from 5 to below 10 years and 50% were from 10 to 15 years old, and 71.2% of chronic HCV children were males while 28.8% were female.

Table 2 shows that only one case in the studied group had fatigue as a symptom of chronic HCV infection.

Table 3 shows that all cases had ALT serum levels within normal values (ULN = 65 IU/L)[34] and their mean was 39 ± 1.2. Also AST had normal value (ULN = 35 IU/L)[32] with a mean of 35 ± 9.9. Regarding GGT serum level, it was within normal range with a mean of 30 ± 3.3 mg/dl. Liver synthetic functions were impaired in four cases, where they had low serum albumin level (2 gm%)[34] and prolonged INR (1.6-1.9).[32]

Table 4 shows that among 40 patients' liver biopsies; 26 (65%) had no fibrosis, while only 5% showed severe fibrosis. All biopsies showed a mild degree of inflammation according to Ishak classification schemes[31] and two biopsies showed steatosis.

Table 5 shows a significant correlation between the degree of fibrosis in liver biopsies and the age of chronic HCV children.

Although there was an increase in the ALT level with an increase in the degree of fibrosis; this was not statistically significant. This is true for all other biochemical tests (Table 6).

4. Discussion

In Egypt and other developing countries, high rates of HCV infection are observed in all age groups, suggesting that an ongoing risk of HCV acquisition still exists. Egypt has one of the highest prevalence rates of HCV infection worldwide, averaging 12–24% in the general population. HCV genotype 4 is the most prevalent genotype in Egypt (90%).[3]

The prevalence of HCV infection is relatively low in children, with an anti-HCV prevalence rate of 0.2–0.4% in the Western world.[1] Few studies have evaluated the epidemiology and risk factors of HCV infection in children in Egypt. A study reported that HCV seroprevalence among Egyptian children ranges from 0.5% to 3%.[6] Age range in the present study was 2–16 years. This very young age of HCV cases was also reported by Wendy et al.[33] who reported an age range from 3 months.[33] Khalil et al.[34] in Assiut University Hospital reported 465 cases of HCV infection with an age range of 2 months to 15 years.[34] The early onset of HCV infection in the present study and other reports is explained by vertical transmission from pregnant infected mothers who are not screened for HCV and the role of transmission (use of contaminated tools during labor whether at hospitals or at home). In addition routine screening of all mothers is not yet mandatory. Current screening guidance suggests checking hepatitis C antibodies only in pregnant women with high risk factors of a

Table 1 Distribution of the chronic HCV children according to their demographic data.

	Cases (n = 40)		Test of significance	
	No.	%	t	p-Value
Age (mean ± SD)	9.2 ± 3.4		0.62	0.536
Age groups	No.	%	X2	p-Value
<5	6	15	0.355	0.837
10	14	35		
16	20	50		
Gender				
Male	27	71.2	0.318	0.573
Female	13	28.8		
Residence				
Rural	28	81.8	1.553	0.213
Urban	12	18.2		

Table 2 Distribution of the chronic HCV children according to the presence of symptoms.

	HCV symptoms		Test of significance	
	No.	%	z	p
Symptomatic	1	0.4	0.57	0.569
Asymptomatic	39	97.5		
Total	40	100		

Table 3 Distribution of the chronic HCV children according to some biochemical data.

Some biochemical data		HCV children
ALT	Rang	37–42
	Mean ± SD	39 ± 1.2
AST IU/L	Rang	18–51
	Mean ± SD	35 ± 9.9
Albumin gm%	Rang	2–4.1
	Mean ± SD	3 ± 1.1
INR	Rang	1–1.9
	Mean ± SD	0.3 ± 1.6
GGT mg/dl	Rang	23–35
	Mean ± SD	30 ± 3.3

Table 4 Distribution of the chronic HCV children according to the degree of fibrosis in their liver biopsies.

Degree of fibrosis	HCV cases	
	No.	%
No Fibrosis	26	65
Mild fibrosis	10	25
Moderate fibrosis	2	5
Severe fibrosis	2	5

No fibrosis: HAI score 0.
Mild fibrosis: HAI score 1.
Moderate fibrosis: HAI score 2–3.
Severe fibrosis: HAI score 4–6.

Table 5 Correlation between the age of the chronic HCV children and degree of fibrosis in their liver biopsies.

Degree of fibrosis	Age (years)				Test of significance	
	< 5	5–10	10–16	Total	*t*	*p*-Value
No fibrosis	5	12	9	26	1.318	0.005*
Mild fibrosis	1	1	8	10	1.210	0.340
Moderate fibrosis	0	1	1	2	1.113	0.156
Severe fibrosis	0	0	2	2	1.120	0.022*
Total	6	14	20	40	1.553	0.213

No fibrosis: HAI score 0.
Mild fibrosis: HAI score 1.
Moderate fibrosis: HAI score 2–3.
Severe fibrosis: HAI score 4–6.
* significant if p > 0.05

Table 6 Correlation between some biochemical tests of chronic HCV children and degree of fibrosis in their liver biopsies.

Biochemical tests	Degree of fibrosis				Test of significance	
	No fibrosis	Mild fibrosis	Moderate fibrosis	Severe fibrosis	*t*	*p*-Value
ALT Mean ± SD	28 ± 3	34 ± 2	37 ± 5	40 ± 2	1.327	0.432
AST Mean ± SD	18 ± 7	33 ± 4	48 ± 3	51 ± 3	1.312	0.342
GGT Mean ± SD	23 ± 4	28 ± 3	32 ± 5	35 ± 9	1.142	0.256
Albumin Mean ± SD	4.1 ± 1.2	3.8 ± 1.1	3.5 ± 1.3	2 ± 1.1	1.430	0.341
INR Mean ± SD	1 ± 0.2	1.2 ± 0.3	1.3 ± 0.3	1.9 ± 0.3	1.443	0.114

No fibrosis: HAI score 0.
Mild fibrosis: HAI score 1.
Moderate fibrosis: HAI score 2–3.
Severe fibrosis: HAI score 4–6.

current or past history of IV drug abuse, women who received clotting factor concentrates produced before 1987, or a blood transfusion or an organ transplant before 1992, women who were on chronic hemodialysis, women with persistent abnormal liver function tests and health care workers after needle sticks or mucosal exposure to HCV positive as well as infants of infected mothers. These categories of high risk patients should be tested for anti-HCV at 1 year and followed up for the development of hepatitis.[35] Chronic HCV infection is associated with numerous clinical manifestations. In our study, only one case had symptoms in the form of fatigue in agreement with El-Raziky et al. study.[3]

The use of liver biopsy to assess the degree of fibrosis in children with chronic hepatitis C infection has been discussed in many aspects; whether is is mandatory or not or the existence of other alternatives for this invasive procedure. Other queries also are as yet unanswered; should it be an initial step in deciding whether to start treatment or should we keep the candidate under strict follow up. In our practice, liver biopsy is still the gold standard in assessing fibrosis of HCV cases and for deciding the management plan. Delgado-Borrego et al.[36] stated that children with HCV should undergo liver biopsy to determine the presence and degree of fibrosis. In the absence of fibrosis, treatment may be deferred. If any degree of hepatic fibrosis is present, antiviral therapy for HCV should be considered.[36]

In our study a total 40 cases with chronic hepatitis C infection underwent liver biopsy. There was no significant correlation between the degree of fibrosis in liver biopsies and the gender of chronic HCV children.

A significant correlation between the degree of fibrosis in liver biopsies and the age of chronic HCV children was detected where 10% of our cases had a significant degree of fibrosis at the age of 10–16 years. Kamran et al.[37] reported that portal fibrosis was present in 78% of the specimens, including fibrous portal expansion (26%), bridging fibrosis (22%), bridging fibrosis with architectural distortion (22%), and cirrhosis (8%). Centrilobular pericellular fibrosis, has not been previously reported in the context of chronic hepatitis C infection in adults or children.[37] Goodman et al. added that, the positive correlation of inflammation with duration of infection and fibrosis, and of obesity with fibrosis suggests that children with chronic hepatitis C will be at risk for progressive liver disease as they age and possibly acquire other comorbid risk factors.[38] Jara et al.[39] considered liver biopsy as the accurate tool for assessment of lesions produced by chronic hepatitis. Although not performed in every affected child, it usually reveals mild lesions. They also stated that the use of non-invasive biochemical tests (Fibro-Test and Acti-Test) is being evaluated in children with hepatitis C for their correlation with histology.[39]

Chen et al.[40] also confirmed that the liver biopsy is the gold standard for the grading and staging of chronic hepatitis C. The grade is variable in chronic HCV infection.[40] In the vast majority of pediatric treatment trials of hepatitis C, patients were candidate for treatment only if liver histology was available. This point of view augments our policy in treating these children. So to prove that it is not mandatory to perform a liver biopsy, Iorio et al.[41] performed liver biopsy in 67 children with chronic hepatitis C infection before they started any treatment and it was repeated again after 5.5 years. Only one child

had micronodular cirrhosis. This finding confirms the idea that histological assessment cannot affect the management plan and that chronic hepatitis C in children seems to be a milder disease with a more favorable natural course when compared to hepatitis C virus (HCV) infection in adults.[41]

El-Hawary et al.[41] conducted a study at Fayoum University to assess hepatic fibrosis in children with chronic hepatitis C infection. They agreed that a liver biopsy provides good data. It confirms the diagnosis and excludes other liver diseases, as well as accurately assessing both grade and stage of the disease.[42]

5. Conclusion

Children with chronic HCV infection are generally asymptomatic. Significant hepatic fibrosis was present in 10% of children with HCV infection. Fibrosis stage was insignificantly higher in older age children. There was no significant association between fibrosis stage and any biochemical parameter.

Recommendation: 1-HCV is a global health problem. Patients and doctors should be aware about this virus and the ways by which it can be transmitted. 2-Patients and doctors should be aware of the nature of HCV liver disease, patients should be well educated about their disease and the importance of following up regularly. 3-Liver biopsy although it is the most important diagnostic tool used to assess the degree of inflammations and stage of fibrosis in children with chronic hepatitis C virus infection; it carries the hazards of being an invasive procedure. Searching for reliable non invasive techniques became mandatory for better management of cases.

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