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Symptomatic and Pathophysiologic Predictors of Hepatitis C Virus Progression in Children

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Abstract

BACKGROUND—The slow progression of HCV infection could ultimately negatively impact children during their lifespan. This study describes the symptomatic and pathophysiologic presentation of hepatitis C virus (HCV) infection in a cohort of pediatric outpatients.

METHODS—HCV positive children were identified by diagnosis codes from outpatient visits. Demographic and pathophysiologic indicators (co-morbidities, reported symptoms, ALT, AST, GGTP, HCV viral load, genotype, and liver biopsy results) were collected and analyzed.

RESULTS—We reviewed 62 patients with HCV infection who were from 3 months and 19 years of age ($M \pm SD$, 12.5 ± 5.8 years). Sixty percent presented with clinical symptoms of fatigue, joint-abdominal pain, bruising/bleeding or other non-specific symptoms. On liver biopsy ($n=35$) 80% had evidence of inflammation, 57% had fibrosis and 9% had steatosis. All patients with steatosis or cirrhosis reported symptoms. Males were significantly more likely than females to be symptomatic, 58.3% vs. 41.7%, $p=0.04$. Patients with symptoms were significantly older ($M=13.5 \pm 5.2$ vs. 8.9 ± 5.5 years, $p=.003$). There was a significant inverse relationship between viral load and symptoms ($\chi^2=4.75(1)$, $p=.03$). Patients with low viral load (less than 2 million copies) were 5 times more likely to have symptoms than those with high viral loads ($p=.03$). Significance was also noted between HCV genotype and ALT levels ($\chi^2=3.72(1)$, $p=.05$). There were no significant relationships between symptom status and race, co-morbidities, ALT, AST, GGTP, HCV genotype, or liver histology.

CONCLUSION—Pediatric patients with HCV can have significant symptoms and physiologic liver changes related to HCV.

Keywords

Symptoms; Fibrosis; Cirrhosis; Co-morbidity; hepatitis C

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Introduction

In 2002 the estimated number of patients under the age of 19 years living with chronic HCV infection ranged from 68,00 to 102,000 in the US (1). Several studies of pediatric HCV cohorts suggest that HCV infection follows a benign course of disease (2–4), yet other studies have shown a more aggressive clinical course in pediatric HCV populations (3,5–11). In addition, pediatric patients with HCV remain a vulnerable population because of the limited knowledge available on the progression of the disease (12).

Most previous studies indicate that significant fibrosis and cirrhosis do not develop until 20–40 years after infection with HCV and pediatric patients are often reported to be asymptomatic. However, reports indicate that small percentages (1.8–7.8%) of pediatric HCV patients do present with cirrhosis or progress to decompensated cirrhosis (13,14). Although research has advanced treatments for HCV, there are significant unmet needs for this subgroup of pediatric patients with HCV infection.

There have been significant progress in HCV treatment in recent years which allows clinicians to more accurately predict overall response to therapy using viral genotype and early changes in HCV viral load (15). However, because many pediatric patients are asymptomatic and have mild liver disease, treatment is often delayed, awaiting development of more effective, less toxic therapeutic regimens. To better understand the symptomatic and pathophysiologic presentation of HCV, 62 consecutive pediatric patients with HCV were evaluated.

Methods

We completed a retrospective cohort study of pediatric patients who were identified by diagnosis codes of HCV infection at initial outpatient visit from 2000–2005 at Nemours Children's Clinics. The study was approved by both the Institutional Review Board of the A.I. DuPont Hospital for Children/Nemours Children's Clinic and the Office of Human Subjects Research at the National Institutes of Health. This study involved the use of existing data/documents/records which were recorded by the investigator in a manner that subjects could not be identified, directly or through identifiers linked directly to the subjects. To examine the prevalence of HCV infection and the demographic and clinical factors of pediatric patients with HCV, a retrospective medical record review was performed.

The sample pool included all patients, with a diagnosis of HCV infection seen for an initial evaluation as an outpatient at urban pediatric gastroenterology and hepatology clinics in the eastern U.S. The demographic and clinical data were gathered from each subjects' initial baseline consultation from electronic databases. Demographic variables (age, gender, and race) and physiologic indicators of liver disease status (alanine transaminase [ALT], aspartate transaminase [AST], gamma glutamyl transpeptidase [GGTP], HCV genotype, HCV viral load, and liver biopsy results) were recorded. The presence and type of clinical symptoms and co-morbid conditions were collected directly from the dictated initial outpatient report. Care provider reports of symptoms in preverbal patients that were documented in the outpatient report were also included.

Demographic data were categorized as follows: age (years), gender (male/female), race (White/African-American/Hispanic/Asian/ Other/Unknown), body mass index (weight in kg/m², BMI), symptoms (fatigue/joint or abdominal pain/ bruising or bleeding/ non specific symptoms), and co-morbid conditions (absent/present). Co-morbid conditions included other medical conditions such as HIV, congenital defects, and chronic medical conditions. Clinical variables were categorized as follows: ALT, AST, GGTP (normal/abnormal according to laboratory normal standards where samples were collected), HCV viral load

(above or below 2 million copies per ml), HCV genotype (genotype 1, 2 or 3), histology (present or absent for inflammation/steatosis/fibrosis) and cirrhosis (present or absent based on biopsy/imaging) [See Table 1]. Histologic findings were not mutually exclusive, in that a patient could have more than one histologic abnormality including presence of inflammation, steatosis, fibrosis and/or cirrhosis. In addition to each individual histologic finding, histologic abnormalities were also batched into presence or absence of any histologic abnormality. The HCV genotype data was further categorized into HCV genotype 1 and non-1 [See Table 2].

The liver biopsy data for inflammation, steatosis and fibrosis were obtained from pathology reports at each institute and a single reviewer, blinded to the patients' symptoms and characteristics, coded the pathology reports. If the patient presented with significant reported symptoms for evaluation of HCV the patient was included in the symptomatic group. If there were no presenting symptoms related to HCV infection or if the patient screened positive for the virus with no symptoms of acute or chronic liver disease noted, the patient was included in the asymptomatic group.

Descriptive statistics, correlations, independent sample t-tests, and binary logistic regression were performed using SPSS version 15 software (Chicago, Illinois). An alpha value of <0.05 was used to determine statistical significance *a priori*.

Results

The overall sample consisted of 62 pediatric patients with HCV infection between the ages of 3 months and 19 years ($M \pm SD$, 12.5 ± 5.8 years). The study groups was 53% female and the majority were White (61%). Forty seven percent of the patients had an abnormal ALT and AST, and 30% had abnormal GGTP. Approximately, 75% of the patients had co-morbid conditions. All 4 patients who had evidence of cirrhosis and 3 patients with evidence of steatosis were symptomatic [Table 1]. Approximately three quarters had HCV genotype 1 of which about 41% was genotype 1a. The relationship of genotype with demographic and clinical characteristics is noted in [Table 2].

Almost 60% ($n=36$) of the patients presented with clinical symptoms of fatigue, joint or abdominal pain, bruising or bleeding, and other non specific symptoms. Twenty-five patients had no symptoms. Of those with symptoms, 15 reported fatigue, 9 abdominal pain, 6 bleeding, 4 joint pain and 2 with non specific symptoms. Biopsy reports were available for 35 patients, of which 80% showed inflammation, 57% showed some degree of fibrosis, 9% had evidence of steatosis and 5% showed cirrhosis on histology [Figure 1]. All patients with steatosis or cirrhosis reported symptoms. Two of the three steatotic patients and one of the cirrhotic patients had a body mass index of greater than 30 kg/m^2 [Table 3].

Patients with symptoms were older (13.5 ± 5.2 yrs. vs. 8.9 ± 5.5 yrs.) as evidenced by bivariate logistic regression ($CI=1.04-1.27$, $p=.003$). Males were significantly more likely than females to have symptoms 58.3% vs. 41.7%, $p=0.04$. Additionally, non-Whites were six times more likely to have fibrosis than Whites ($CI=1.3-32.1$, $p=.02$).

There was a significant correlation of viral load with symptoms ($\chi^2=4.75(1)$, $p=.03$). Pediatric patients with low viral load (less than 2 million copies) were 5 times more likely to have symptoms than those with high viral loads ($p=.03$). A significant relationship was also noted between HCV genotype and ALT values ($\chi^2=3.72(1)$, $p=.05$) [See Table 2]. There were no other significant relationships between symptom status and race, co-morbid conditions, ALT, AST, GGTP, genotype, or liver histology.

Discussion

The majority of pediatric patients with HCV infection present with significant clinical symptoms. Previous data suggest that patients with chronic HCV infection are generally asymptomatic (16). The findings reported here suggest that there is a strong justification to do a more careful clinical assessment of symptoms of patients with HCV infection at initial presentation.

Approximately 25–30% of cases are diagnosed as a result of long-term mild symptoms of chronic fatigue and joint pain (17). The majority of our patients had some degree of inflammation and 57% had fibrosis. Although a small number, all pediatric HCV patients with cirrhosis and steatosis reported symptoms. Patients with lower viral loads were more likely to be symptomatic compared with those with higher viral loads, possibly related to the presence of co-morbid conditions in 74% of the cohort. Little attention has been paid to pediatric patients with HCV because of previous perception that progression to liver fibrosis was rare (16). However, an often-missed population of pediatric patients may have a significantly higher progression rate to liver fibrosis (9). The histopathologic findings in the current study are reminiscent of the findings of Mohan and colleagues (18) who identified moderate to marked periportal inflammation in 49% of biopsies with evidence of fibrosis in 60%. However in contrast, our study revealed that pediatric patients are symptomatic.

Although this is a retrospective study with a limited sample size, these findings indicate that pediatric patients with HCV have potentially significant symptoms and pathophysiologic liver changes related to HCV infection. One potential limitation is the lack of an administered standardized measure of symptoms. In particular, documentation of young non-verbal patients' symptoms was based on care provider reports which may differ from self-reported symptoms and this may explain, in part, our observation that symptomatic patients tended to be older. The lack of a standardized histologic evaluation is another potential limitation of this study. This cohort represents patients presenting for medical care in urban pediatric medical centers, who may be more symptomatic and may not be representative of the pediatric HCV population in general. These findings, though, indicate a need for future prospective studies with a larger sample size that employ more standardized methods for symptom measurement and that are designed to assess the relationship between symptoms and pathophysiologic factors and disease progression.

Current understanding of HCV therapy allows clinicians and researchers to better predict which HCV infected patients will respond most favorably, with regard to genotype and early response to treatment (19). It remains unclear whether patient symptom status should be taken into consideration when deciding whether or not to treat HCV infection in pediatric patients. Symptom scores and studies assessing compliance or adherence in the pediatric population are rarely reported (20). Future studies are needed to better evaluate the effects of chronic diseases, such as the case with HCV, on pediatric symptoms (20).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

HCV	hepatitis C virus
ALT	alanine transaminase
AST	aspartate transaminase
GGTP	gamma glutamyl transpeptidase

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TABLE 1

Sample Demographic and Clinical Characteristics.

Demographics	Overall (N=62)/%	Symptoms Present (n=36)/%	No Symptoms (n=25)/%	p value
Age	12.5 ± 5.8	13.5 ± 5.2	8.9 ± 5.5	.003
Sex				
Male	29(46.8)	21(58.3)	8(32.0)	.04
Female	33(53.2)	15(41.7)	17(68.0)	
Race				
White	38(61.3)	20(55.6)	17(68.0)	.46 ^a
African-American	9(14.5)	5(13.9)	4(16.0)	
Hispanic	7(11.3)	4(11.1)	3(12.0)	
Asian	3(4.8)	3(8.3)	0(0)	
Unknown	2(3.2)	1(2.8)	1(4.0)	
Other	3(4.8)	3(8.3)	0(0)	
Co-morbid Conditions				
Present	46(74.2)	28(77.8)	18(72.0)	.61
Absent	16(25.8)	8(22.2)	7(28.0)	
ALT^b				
Abnormal	27(46.5)	18(50.0)	9(36.0)	.36
Normal	31(53.4)	17(47.2)	14(56.0)	
AST^c				
Abnormal	27(46.5)	18(50.0)	9(36.0)	.36
Normal	31(53.4)	17(47.2)	14(56.0)	
GGTP^d				
Abnormal	11(29.7)	8(22.2)	3(12.0)	.09
Normal	26(70.3)	11(30.6)	15(60.0)	
HCV Viral Load^e				
Low (<2 million copies/ml)	32(76.2)	22(61.1)	10(40.0)	.03
High (≥2 million copies/ml)	10(23.8)	3(8.3)	7(20.0)	
Genotype^f				
1	27(72.9)	15(41.6)	12(48.0)	.81
Non 1	10(27.0)	6(16.7)	4(16.0)	
Histologic^g				
Inflammation	28(80.0)	16(44.4)	12(48.0)	1.00
Steatosis	3(8.5)	3(8.3)	0(0)	.12
Fibrosis	20(57.1)	11(30.6)	9(36.0)	.77
Cirrhosis				
Biopsy/Imaging	4(6.5)	4(11.1)	0(0)	.08

^aStatistics for overall race.^bALT=alanine transaminase (n=58),^cAST =aspartate transaminase (n=58).

- ^dGGTP=gamma glutamyl transpeptidase(*n*=37),
- ^eHCV viral load (*n*=42),
- ^fGenotype (*n*=37), and
- ^gbiopsy histology (*n*=35).

TABLE 2

Relationship of Genotype with Demographic & Clinical Characteristics

		Genotype 1 (n=27)/%	Genotype Non 1 (n=10)/%	p value
Race	White	18(66.7)	8(80.0)	.27
	African American	2(7.4)	0(0)	
	Hispanic	5(18.5)	0(0)	
	Asian	1(3.7)	1(10.0)	
	Other	0(0)	1(10.0)	
	Unknown	1(3.7)	0(0)	
Symptom	No	12(44.4)	4(40.0)	.81
	Yes	15(55.6)	6(60.0)	
ALT^a	Abnormal	15(55.6)	2(20.0)	.05
	Normal	12(44.4)	8(80.0)	
AST^b	Abnormal	14(51.9)	2(20.0)	.08
	Normal	13(48.1)	8(80.0)	

^a ALT= alanine transaminase,^b AST= aspartate transaminase.

TABLE 3

Demographic Details of the Cirrhosis/Steatosis cases ($n=7$)

	Age(yrs)	BMI	Sex*	Race	Source	ALT	AST	Symptomatic	Biopsy Result
Steatosis	19	20.5	M	White	h/o Blood Transfusion	↑	↑	+	Prominent mid lobular macrosteatotic fatty change, focal portal lymphocytic infiltration
	15	30.3	M	White	Both parents HCV positive	n	n	+	Faint interportal bridging, mild portal lymphocytic hepatitis, mild-moderate lobular steatosis
	17	32.7	M	White	Unknown	↑	n	+	Mild-moderate fibrosis, minimal piecemeal necrosis, mild-moderate steatosis, bridging present
Cirrhosis	18	32	F	Black	h/o Blood Transfusion	↑	↑	+	Cirrhosis seen by imaging
	17	23	F	White	Adopted, parent history unknown	↑	↑	+	Severe fibrosis
	16	25	F	White	Unknown	n	↑	+	Severe fibrosis
	9	14	M	Asian	h/o Blood Transfusion	n	↑	+	Cirrhosis seen by imaging

* Sex: M= male, F= female,

↑= increased,

n= normal, Symptomatic:

+ = symptoms present.