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Impact of Hepatitis C Virus Infection on Children and Their Caregivers: Quality of Life, Cognitive, and Emotional Outcomes

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ABSTRACT

Objective: Hepatitis C virus (HCV) infection is associated with decreased quality of life (QOL) and neurocognitive dysfunction in adults, but little is known about its impact on children and their caregivers.

Patients and Methods: We studied the QOL, behavioral, emotional, and cognitive functioning of 114 treatment-naïve children with HCV enrolled in a placebo-controlled, randomized, multisite clinical trial evaluating peginterferon α-2a alone or with ribavirin. Baseline assessment included measures of children's QOL, cognitive functioning, behavioral adaptation, and depression. Caregivers' QOL also was assessed.

Results: Relative to published normative data, caregivers were more likely to believe that their children's health was poor and would likely worsen ($t = 3.93$; $P < 0.0001$), and reported higher concern about their children's health status ($t = 6.63$; $P < 0.0001$) and that this concern limited family activities ($t = 2.45$; $P < 0.01$); they also viewed their children as having more internalizing behavioral problems ($t = 1.98$; $P < 0.05$). Only 2 (2%) children had a score in the clinically depressed range. Children with HCV had worse cognitive functioning than the normative sample but significantly better functioning than children with attention-deficit/hyperactivity disorder. Caregivers' QOL scores did not differ significantly from the normative sample, but infected mothers had lower QOL than noninfected caregivers. Caregivers were highly distressed about their children's medical circumstances.

Conclusions: Although HCV infection, in its early stages, does not lead to global impairment in QOL, cognitive, behavioral, or emotional functioning in children, it is associated with higher caregiver stress and strain on the family system, and it may be associated with some cognitive changes in children. ***JPGN 48:341–347, 2009.*** **Key Words:** clinical trial—HCV—parents—quality of life. © 2009 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

The prevalence rate of hepatitis C virus (HCV) infection in children 5 to 14 years old ranges from 0.2% to 0.4% in the United States (1). Substantially higher rates of infection are observed in children who received blood products or clotting factor concentrates before the implementation of universal screening precautions (2,3). Although an asymptomatic course during childhood can be expected for most pediatric patients, some children develop progressive liver disease with fibrosis, cirrhosis, and hepatocellular carcinoma (4–7), and some will eventually need liver transplantation.

There is growing evidence that HCV in adults is strongly associated with decrements in quality of life (QOL) (5,6,8,9), cognitive performance (10,11), and psychological functioning (8,12). For instance, studies have noted lower health-related QOL, deficits in attention and higher executive functioning, and heightened levels of anxiety and depression in adults with HCV

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compared with healthy controls and patients with other types of liver disease. Despite these findings, little is known about how HCV affects children along these same parameters. Iorio et al (13) observed increased irritability, decreased QOL, and other psychosocial problems in children on interferon therapy. Similarly, in a small group of asymptomatic children who acquired HCV in the first year of life, Nydegger et al (14) found that their physical and mental QOL was significantly lower than in children without HCV.

The aim of this study was to assess the impact of HCV on the QOL, cognitive functioning, and psychological status of children who were treatment naïve. We hypothesized, based on findings in the adult HCV literature, that children with HCV would have lower QOL, more problems with executive functioning, and more psychological difficulties than children without HCV. In light of the impact of childhood chronic health conditions on adult caregivers, we also assessed the QOL of the primary caregiver for these children and its relation to that of their children. In addition, we analyzed QOL scores according to HCV status of the caregiver. Finally, we examined whether QOL, cognitive, and psychological outcomes were related to HCV duration.

PATIENTS AND METHODS

Eligible study participants were children with HCV and their parent/guardian (hereafter designated as caregiver) who were enrolled in a placebo-controlled, randomized, multisite clinical trial (15) evaluating peginterferon α-2a alone or with ribavirin/placebo. In brief, study eligibility criteria included HCV viremia on 2 tests 6 months or more apart and/or 1 positive test in a child with maternal–fetal transmission, chronic hepatitis consistent with HCV infection on liver biopsy within 36 months of screening, and compensated liver disease (Child-Pugh grade A clinical classification). Exclusion criteria included any prior treatment with interferon or ribavirin, decompensated liver disease, major depression, or history of other severe illness.

At the time of study enrollment, children underwent a baseline assessment that included measures of QOL, cognitive functioning, and behavioral and psychological functioning. All of the measures were completed by each child's parent or legal guardian. The Child Health Questionnaire-Parent Form 50 (CHQ) (16) measures functional status and well-being across several QOL domains, including physical functioning, role/social limitations, general health, bodily pain/discomfort, parent impact, self-esteem, mental health, general behavior, and family impact. The Behavior Rating Inventory of Executive Function (BRIEF) (17) measures emotional and behavioral dysregulation, difficulties with response inhibition, working memory, and the ability to quickly transition into new situations or tasks. The Child Behavior Checklist (CBCL) (18) measures behavioral and psychological functioning across multiple domains. The Children's Depression Inventory (CDI) (19) assesses affective, cognitive, and behavioral symptoms of depression in children.

The child's primary caregiver completed all questionnaires about his or her child's functioning. Primary caregivers also completed the SF-36 Health Survey (20) to assess their own QOL. None of the caregivers refused to complete the baseline measures.

Written, informed consent was obtained from the child's parent or legal guardian before participation in the study. The study protocol was approved by the institutional review boards at all of the study sites.

Descriptive statistics were calculated to summarize the medical and sociodemographic characteristics of the sample and the outcome measures. The proportion of children with clinically significant scores on each of the outcome measures was calculated. Scores on all outcome measures were compared with normative and comparison samples using *t* tests. We used the normative data, drawn from the US general population, for the CHQ (n = 391) (16), BRIEF (n = 604) (17), CBCL (n = 1753) (18), and SF-36 (n = 2474) (20), as well as available data using children with other chronic conditions. The Wilcoxon rank-sum test was used to test the difference between mothers with HCV who transmitted the virus to their enrolled child and all other caregivers. Spearman ρ correlation coefficients were calculated to assess the associations between the outcome measures and sociodemographic characteristics and HCV duration. The significance level was set at $P < 0.01$ for all analyses. Because we considered these analyses to be exploratory, we did not correct for multiple comparisons. We considered $P < 0.01$ to indicate a significant association and $P < 0.001$ to indicate strong associations.

RESULTS

Participants were 114 children who met study eligibility criteria. As noted in Table 1, the sample was predominantly

TABLE 1. *Sociodemographic and medical characteristics of study patients with hepatitis C virus (HCV)*

Characteristics	
Total no. studied	114
Sex, female (%)	51 (45)
Age, y, mean ± SD	11 ± 3
Race (%)	
White	85 (75)
Black/African American	5 (4)
Asian	5 (4)
American Indian/Alaska Native	1 (1)
More than 1 race	6 (5)
Unknown	12 (11)
HCV genotype (%)	
1	92 (81)
2	7 (6)
3	13 (11)
6	1 (1)
Unable to genotype	1 (1)
Transmission mode (%)	
Vertical/perinatal	86 (75)
Sexual contact	1 (1)
Intravenous drug use	1 (1)
Transfusion	8 (7)
Unknown	18 (16)
ALT, mean ± SD	60 ± 49
Infection duration, mo, mean ± SD	108 ± 55

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TABLE 2. *Child Health Questionnaire summary and scaled scores for study sample, normative sample, pediatric hepatitis C virus (HCV) sample, and diabetes comparison group*

	Study sample (n = 114)	Normative sample (16) (n = 391)	Pediatric HCV sample (14) (n = 19)	Diabetes sample (21) (n = 128)
Physical summary	52 ± 6	53 ± 9	45 ± 11*	49 ± 8*
Psychosocial summary	52 ± 9	51 ± 9	44 ± 12*	49 ± 10
Physical functioning	96 ± 10	96 ± 14	85 ± 20*	94 ± 11
Role/social emotional/behavioral	95 ± 16	93 ± 19	77 ± 35*	94 ± 14
Role/social physical	97 ± 10	94 ± 19	83 ± 28†	92 ± 19
Bodily pain	82 ± 19	82 ± 19	84 ± 15	73 ± 25
General behavior	79 ± 17	76 ± 17	70 ± 21	71 ± 17*
Mental health	80 ± 12	79 ± 13	72 ± 16	77 ± 13
Self-esteem	83 ± 17	80 ± 18	72 ± 19	83 ± 16
General health perceptions	66 ± 15	73 ± 17†	50 ± 17†	59 ± 16*
Parental impact–emotional	65 ± 27	80 ± 19†	46 ± 31	62 ± 27
Parental impact–time	88 ± 17	88 ± 20	78 ± 24	76 ± 23†
Family activities	85 ± 19	90 ± 19	75 ± 24	67 ± 23†
Family cohesion	75 ± 22	72 ± 22	NA	75 ± 25

Data are expressed as mean ± standard deviation. Higher scores reflect better quality of life.
* $P \leq 0.001$.
† $P \leq 0.0001$.

white, with HCV genotype 1 and perinatal transmission. Caregivers who completed the baseline assessment were predominantly white (83%) and had a mean age of 46 ± 7 years. Of the caregivers, 43 (39%) who completed the questionnaires were biological mothers with HCV infection who transmitted the virus to their child.

Quality of Life

QOL scores for the study sample did not differ significantly from the normative sample, although they were consistently higher than scores reported by another group of children with HCV (14) and children with diabetes (21) (Table 2). However, 2 of the scaled scores, General Health Perceptions ($P < 0.0001$) and Parent Impact-Emotional ($P < 0.0001$), were significantly lower in the study sample than in the normative sample. CHQ scores did not vary significantly based on the caregiver's own HCV status.

TABLE 3. *SF-36 scaled scores for caregivers in the study sample, normative sample, and comparison groups*

	Study sample (n = 114)	Normative sample (20) (n = 2474)	Adult HCV sample (22) (n = 70)
Physical functioning	82 ± 25	84 ± 23	82 ± 17
Role-physical	82 ± 26	81 ± 34	58 ± 45†
Bodily pain	75 ± 27	75 ± 24	67 ± 26
General health	69 ± 24	72 ± 20	43 ± 27†
Vitality	60 ± 20	61 ± 21	49 ± 20†
Social functioning	83 ± 24	83 ± 23	65 ± 18†
Role-emotional	84 ± 23	81 ± 33	64 ± 43†
Mental health	72 ± 19	75 ± 18	66 ± 11*

Data are expressed as mean ± standard deviation.
HCV = hepatitis C virus.
* $P \leq 0.001$.
† $P \leq 0.0001$.

Caregivers of children with HCV did not report QOL that was significantly different from the SF-36 normative sample (Table 3). Their QOL scores were significantly higher, however, than those reported by another sample of adults with newly diagnosed HCV (22). Table 4 shows that mothers with HCV who transmitted the virus to the enrolled child had QOL scores that were significantly lower than caregivers without HCV on 3 SF-36 domains: role functioning-physical, role functioning-emotional, and general health. Scores on the other SF-36 scales also trended in the same direction. Higher child QOL, both physical and psychosocial, was significantly associated with higher caregiver QOL across most domains (Table 5).

Cognitive Functioning

Children with HCV differed significantly from the normative (17) and pre–liver transplant (Rodrigue JR, Guenther R, unpublished data, 2005) samples on several

TABLE 4. *SF-36 scaled scores for hepatitis C virus (HCV)–infected mothers who transmitted virus to the enrolled child vs noninfected caregivers*

	HCV-infected mothers (n = 43)	Noninfected caregivers (n = 67)
Physical functioning	77 ± 27	86 ± 23
Role-physical	75 ± 28	87 ± 24*
Bodily pain	68 ± 29	80 ± 24
General health	57 ± 23	77 ± 21*
Vitality	56 ± 20	63 ± 20
Social functioning	77 ± 24	87 ± 23
Role-emotional	77 ± 23	90 ± 21*
Mental health	68 ± 19	75 ± 19

Data are expressed as mean ± standard deviation.
* $P < 0.006$.

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TABLE 5. *Spearman correlations between child (CHQ) and parent (SF-36) quality of life*

	Caregiver quality of life (SF-36)							
	Physical functioning	Role-physical	Bodily pain	General health	Vitality	Social functioning	Role-emotional	Mental health
CHQ physical summary	0.20*	0.27†	0.31‡	0.17	0.22*	0.27†	0.33‡	0.31†
CHQ psychosocial summary	0.03	0.18	0.16	0.31†	0.21*	0.30†	0.27†	0.35‡

CHQ = Child Health Questionnaire.
*$P < 0.05$.
†$P < 0.01$.
‡$P < 0.001$.

clinical and index scales (Table 6). Executive function ratings for the HCV study sample, however, were significantly better than those for children with attention deficit hyperactivity disorder (23). T scores of 65 or higher are considered indicative of clinical impairment in executive function. Although the study sample means were in the normal range, 18% of children showed clinically significant impairment in executive function, as defined by elevated Global Executive Composite T scores.

Behavioral/Emotional Functioning

Mean CBCL scores were within the normal range (Table 7). All of our HCV study patients' CBCL clinical scales were significantly higher than the normative sample, although they did not differ significantly from children awaiting liver transplantation (Rodrigue JR, Guenther R, unpublished data, 2005) or those with HIV infection (24). Regarding clinical significance (defined as T score $\geq$65), 13% and 9% of children had clinically significant internalizing (somatic problems, depression, anxiety) and externalizing problems (aggressive behavior, social problems), respectively; 20% reported clinical elevation on the Somatic Problems scale.

The mean CDI T score (44 ± 6) was in the normal, nondepressed range. Only 2 (2%) children had a CDI score in the clinically depressed range (defined as T score $\geq$65). Higher CDI scores were significantly associated with more behavioral problems ($\rho = 0.34$; $P = 0.0003$), more impairment in global executive function ($\rho = 0.40$; $P < 0.0001$), lower physical health–related QOL ($\rho = -0.46$; $P < 0.0001$), and higher emotional impact for parents ($\rho = -0.22$; $P = 0.02$).

HCV Duration of Infection and Outcomes

HCV duration of infection was significantly correlated with the BRIEF Metacognition score ($\rho = -0.22$; $P = 0.02$). Children with longer HCV duration had less

TABLE 6. *Behavior Rating Inventory of Executive Function (BRIEF) T scores for study sample, normative sample, and comparison groups*

	Study sample (n = 114) (%)	Normative sample (17) (n = 1078)	Pretransplant sample* (n = 67)	ADHD sample (23) (n = 130)
Behavioral regulation	52 ± 10 (13)	50 ± 10	55 ± 14	59 ± 11‡
Metacognition	54 ± 11 (18)	50 ± 10	57 ± 12	68 ± 8‡
Global executive composite	54 ± 11 (18)	50 ± 10	58 ± 13	66 ± 9‡
Inhibition	55 ± 10 (18)	50 ± 10	54 ± 11	59 ± 12
Shift	52 ± 10 (15)	50 ± 10	55 ± 15	59 ± 12‡
Emotional control	50 ± 10 (8)	50 ± 10	54 ± 15	58 ± 13‡
Initiation	53 ± 11 (18)	50 ± 10	58 ± 11†	61 ± 10‡
Working memory	54 ± 11 (19)	50 ± 10	62 ± 12‡	70 ± 9‡
Plan/organization	54 ± 11 (18)	50 ± 10	56 ± 13	67 ± 10‡
Organization of materials	52 ± 11 (15)	50 ± 10	53 ± 10	63 ± 12‡
Monitor	52 ± 10 (13)	50 ± 10	55 ± 13	63 ± 9‡

Data are expressed as mean $\pm$ standard deviation (percentage in clinical range provided for the study sample only). Higher scores reflect worse cognitive functioning. ADHD = attention-deficit/hyperactivity disorder.
* Rodrigue JR, Guenther R, unpublished data (2005) based on a comprehensive questionnaire battery completed by parents as part of the required pre–liver transplant psychological assessment at the University of Florida. This sample includes children and adolescents (mean age 9.3 ± 5; 59% female; 90% white) with different causes of liver disease who were referred, but not yet formally approved, for liver transplantation.
†$P \leq 0.001$.
‡$P \leq 0.0001$.

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TABLE 7. *Child Behavior Checklist (CBCL) T scores for study sample, normative sample, and comparison groups*

	Study sample (n = 114) (%)	Normative sample (18) (n = 1,753)	Pretransplant sample* (n = 67)	HIV sample (24) (n = 36)
Internalizing	52 ± 10 (13)	50 ± 10	53 ± 13	50 ± 11
Externalizing	50 ± 10 (9)	50 ± 10	52 ± 10	53 ± 11
Total behavior problem	51 ± 10 (10)	50 ± 10	53 ± 11	NA
Anxious/depressed	54 ± 5 (7)	50 ± 10†	55 ± 11	NA
Withdrawn/depressed	54 ± 6 (10)	50 ± 10†	52 ± 8	NA
Somatic problems	58 ± 7 (20)	50 ± 10†	57 ± 9	NA
Social problems	55 ± 6 (7)	50 ± 10†	53 ± 10	NA
Thought problems	55 ± 6 (9)	50 ± 10†	51 ± 12	NA
Attention problems	55 ± 6 (10)	50 ± 10†	54 ± 7	NA
Rule-breaking behavior	54 ± 5 (5)	50 ± 10†	52 ± 7	NA
Aggressive behavior	54 ± 7 (8)	50 ± 10†	51 ± 9	NA

Data are expressed as mean ± standard deviation (percentage in clinical range provided for the study sample only). Higher scores reflect more behavioral problems. HIV = human immunodeficiency virus.

* Rodrigue JR, Guenther, R, unpublished data (2005).

† $P \leq 0.0001$.

impairment in metacognitive processes. Illness duration was not associated with CDI or CBCL scores.

DISCUSSION

Findings from this study indicate that QOL, cognitive, behavioral, and emotional functioning are not globally impaired in children with HCV infection. As a group, the children showed no deficits in QOL, behavioral problems, or clinical depression, relative to normative samples. Furthermore, their functioning in these domains was comparable to or better than that of other children with chronic health conditions. Although HCV diagnosis appears to cause stress, depression, and anxiety in newly diagnosed adults (9–12), there is little evidence that these symptoms are pervasive in children and adolescents. When compared with rates reported in the adult HCV literature (as high as 75%) (25), relatively few children have clinical levels of depression, behavioral disturbances, or QOL impairment.

Collectively, primary caregivers also do not appear to experience any significant QOL decrements. However, mothers who vertically transmitted HCV to the enrolled child reported more compromised QOL than caregivers who did not have HCV. This finding is consistent with research showing that QOL deteriorates in the context of chronic HCV (5,6,9,25,26), although there is some evidence that QOL improves with successful antiviral therapy (8,26,27). We did not assess mothers' HCV liver disease status or treatment history, so we are unable to examine the relation between these parameters and QOL in this study. Clearly, more research is needed to better understand the psychological sequelae associated with parents who have transmitted HCV to their children. In such circumstances, mothers may be simultaneously dealing with the demands of their own illness and coping with issues of disclosing and discussing viral transmission to their child, feelings of guilt or shame, and depression. Some of these issues have been the focus of study within the HIV literature (28,29), but they have not been examined in the context of HCV.

The QOL of children with HCV who are treatment naïve does not appear to be negatively affected, relative to otherwise healthy children. Indeed, QOL in some areas is higher than that reported for children with HIV or diabetes. Moreover, as reported by their caregivers, the QOL of children in our sample was generally higher than that reported by Nydegger et al (14). The disparate QOL findings in these 2 studies may be explained, in part, by cultural factors, sample size differences, and sociodemographic and medical factors. For instance, Nydegger et al studied only 19 children (83% male) with predominantly transfusion-acquired HCV. Of particular note, Nydegger et al asked 10 adolescents to self-report on their QOL and found that their perceptions, in striking contrast to their parents' assessment, did not differ significantly from those of otherwise healthy children.

Our findings suggest that some caregivers of children with HCV are distressed about their children's medical circumstances, which tends to support Nydegger et al's recent findings. In both studies, caregivers report relatively high concern and worry about the children's current and future physical health, emotional well-being, and general behavior. Parents also may be concerned about how their child will be treated by family members, friends, and teachers because of their HCV status (14). We found that parents of children with more advanced HCV infection seem to be more stressed, which may be due to both the implications of liver disease progression and the behavioral symptoms exhibited by the children. Regardless, these findings highlight the importance of assessing parental adjustment and adaptation throughout their child's HCV management.

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Adults with HCV have been shown to experience cognitive deficits, particularly in attention and higher executive functioning (10). These deficits may be secondary to the direct effect of HCV on the central nervous system, rather than the indirect effects of fatigue or depression that often accompany HCV (30,31). Executive function in the HCV-infected children was slightly impaired relative to normative data and relative to children evaluated for liver transplantation. Those with HCV were rated as having more difficulty with planning and organizational skills, as well as inhibiting one's own behavior. However, they fare considerably better than children with attention-deficit/hyperactivity disorder, whose condition is known to significantly impair executive functioning. One fifth of the HCV study sample showed evidence of problems in executive functioning. Because we did not directly assess cognitive performance in this sample of children, it is possible that HCV contributes to more subtle neuropsychological difficulties that are not apparent to their parents and, therefore, not detected in this study. Additional research is necessary to more systematically examine whether early stage HCV infection directly affects central nervous system function and impairs academic performance.

There are only limited data on the natural history of HCV in children (32,33); however, available evidence suggests that HCV may represent a milder disease process in children than in adults (34). Therefore, HCV, especially in the early stages, may not cause any significant impairment in physical functioning, social activities, and bodily discomfort. Moreover, in the absence of functional impairment, children and adolescents may not experience any behavioral or emotional sequelae that can be linked to their medical diagnosis. Only 2 children had clinical depression, but it is important to emphasize that those with consistent mood disturbance were not enrolled in the study. Per study protocol, enrolled children with clinically high CDI scores were interviewed further by their pediatrician investigator, who initiated consultation with a mental health professional.

It is possible that introducing antiviral treatment may precipitate changes within these behavioral and emotional parameters. For instance, Iorio et al (13) reported that QOL deteriorated significantly during antiviral treatment in children. Although QOL returned to baseline within 3 months of stopping interferon, it is possible that a different clinical profile than the one found in our study will emerge for children on antiviral therapy. Notwithstanding the findings of Iorio et al (13) and Nydegger et al (14), the favorable QOL of children in our study may argue for aggressive antiviral treatment before the development of the cognitive and psychological problems seen in adults with HCV.

Study findings should be examined within the context of a few methodological limitations. First, this is a study of children in the early stages of HCV who are treatment naïve. Therefore, findings should not be generalized beyond these medical parameters. Second, we compared children with HCV to normative samples of predominantly healthy children, rather than to a matched control group. Third, we relied exclusively on the report of primary caregivers about the functioning of children in this study. Such reports can be biased for many reasons and may not accurately capture the true functional status of the child. Some studies have shown that as children age, the gap between parent and child ratings of behavior and emotional adjustment widens (35). Future studies should use multiple informants, including the children themselves, their primary caregivers, and teachers.

In conclusion, children with HCV in its early stages may not show signs of significant cognitive, behavioral, or emotional impairment. Nevertheless, we encourage the close monitoring of these children over time, especially once antiviral treatment has been initiated.

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