Chronic Hepatitis C in Childhood: An 18-Year Experience

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Background. The long-term outcome of chronic hepatitis C (CHC) has not been well studied, both for untreated and interferon-treated children. The aim of this study was to evaluate the long-term outcome of disease in a large series of children with CHC.

Methods. Clinical, biochemical, virological, and histological features were evaluated in all children (age, 2–18 years) with CHC who did not have concomitant disease and who attended at our hospital’s liver unit during the period of 1986–2004.

Results. One hundred twenty-five children with CHC were studied. All patients remained free of symptoms throughout the period of observation. On the basis of transaminase levels during the first year of positivity for antibodies to hepatitis C virus (HCV), children were divided into 2 groups: patients with hypertransaminasemia (100 patients, all of whom had detectable HCV RNA), and those with normal transaminases (25 patients; 16 had viremia and 9 did not have viremia). Sustained clearance of viremia was achieved in 38% of the patients treated with interferon, compared with 12% of untreated children (P < .05). A sustained response to therapy was obtained in 64.7% of children infected with an HCV genotype other than genotype 1 and in 24.2% of those infected with HCV genotype 1 (P < .05). Histological lesions were mild in all 64 patients who underwent liver biopsy. No linear correlation was found between duration of disease and progression of fibrosis. Examination of a follow-up liver biopsy specimen revealed cirrhosis only in 1 (4.7%) of 21 children.

Conclusions. Children with CHC were symptom free and had a morphologically mild liver disease. Interferon therapy may be effective for patients infected with HCV genotypes other than genotype 1, whereas lower response rates are expected for HCV genotype 1–infected children. The real impact of therapy on long-term outcome remains to be established.

Hepatitis C virus (HCV) infection in adults is the leading cause of chronic liver disease and cirrhosis and is the most common underlying diagnosis in patients who undergo liver transplantation [1]. On the basis of the studies performed thus far, hepatitis C in children seems to be a milder disease with a more favorable natural course, compared with hepatitis C disease in adults [2–6]. Histological studies confirmed a prevalence of cirrhosis of 1.7% among 229 children with chronic HCV infection [3, 7, 8]. In contrast with these findings, anecdotal cases of HCV-infected children with cirrhosis who require transplantation have been reported [9, 10]. In spite of the indolent course in the majority of cases, a substantial number of children with chronic hepatitis C (CHC) have been treated with IFN [11]. An analysis of published trials of IFN therapy in children with CHC has shown a favorable effect of therapy in terms of sustained response, mainly for patients who are infected with HCV genotypes other than genotype 1 [11]. Studies of IFN plus ribavirin in children have reported promising results with regard to a sustained response rate [12–15], but the real impact of treatment on long-term outcome remain to be established. Moreover, antiviral therapy is expensive, and its efficacy is tempered by several adverse effects and impairments in the health-related quality of life [16]. The aim of our study was to evaluate retrospectively the long-term outcome of HCV infection in a large series of consecutive children with CHC observed at a single health care center, as well as to compare the outcomes among treated and untreated children.
PATIENTS, MATERIALS, AND METHODS

Patients. All children (age, 2–18 years) who had antibodies to HCV (anti-HCV) present for >6 months and who attended the liver unit at our hospital (University of Naples “Federico II,” Naples, Italy) during 1986–2004 were enrolled. Patients who had concomitant systemic diseases or other causes of chronic liver disease, such as chronic hepatitis B, autoimmune hepatitis, Wilson disease, or α-1-antitrypsin deficiency, were excluded from the study. Children observed before 1990 initially received a diagnosis of chronic non-A, non-B hepatitis by conventional exclusion criteria [17]. In these patients, diagnosis of CHC was made after the availability of a screening test for HCV.

For all patients, symptoms and health-related quality-of-life data were evaluated at each evaluation by clinical examination and an appropriate interview. Growth was periodically evaluated using the standard height and weight charting [18].

Furthermore, all patients were evaluated at baseline for clinical history; risk factors for HCV infection; age at the time of infection; clinical signs of liver disease; liver function test results; complete blood cell count; serum HCV RNA level; HCV genotype; α-fetoprotein level; serum immunoglobulin level; presence of non–organ-specific autoantibodies, such as antinuclear antibodies, anti–smooth muscle antibodies, and antiliver/kidney microsomal type 1 (LKM1) antibodies; presence of cryoglobulins; and presence of thyroid hormones. Serum aminotransferase levels were evaluated using standard methods (upper limit of normal, 50 IU/L).

Thereafter, all patients were monitored every 3–6 months with physical examinations, liver function tests, virological tests, and determination of α-fetoprotein levels. At 6–12-month intervals, autoimmunity markers and hormone profiles were determined among treated patients. Ultrasound scanning of the liver, biliary tract, spleen, and portal vein was performed at 12-month intervals.

Liver biopsies were performed after informed consent was obtained from parents or guardians. Histological examination was performed by the same liver pathologist, who was blinded to biochemical and clinical data. Specimens were scored with regard to hepatitis activity (graded 0–18) and fibrotic changes (staged 0–6), in accordance with the methodology of Ishak et al. [19]. Data about the history of IFN treatment (i.e., clinical trials in which patients were included, type of IFN administered, duration of treatment, adverse effects, and reasons for discontinuation of IFN treatment) were also collected.

End-of-treatment response was defined as the absence of HCV RNA in serum samples obtained at the termination of therapy. Relapse was defined as the reappearance of HCV RNA after a virological response. Sustained virological response was defined as the absence of detectable HCV RNA at the end of treatment and 6 months later, until the end of the posttherapy follow-up period. Patients in whom HCV RNA never became undetectable were referred to as “nonresponders” (NR). For untreated children, both aminotransferase and serum HCV RNA levels were monitored throughout the follow-up period.

Procedures. At study entry and at each study visit, a serum sample was obtained from each patient and was stored at −80°C. Biochemical and virological tests were performed on fresh or frozen serum samples.

The presence of anti-HCV was determined using a third-generation ELISA (Ortho Diagnostic Systems). Quantification of HCV RNA level was performed by RT-PCR (COBAS AmpliPrep/HCV Monitor; Roche Molecular System; detection limit, 600 IU/mL of serum). In patients with serum HCV RNA levels less than the assay detection threshold, serum HCV RNA levels were determined using a PCR-based test (Amplicor; Roche Molecular System; detection limit, ~50 IU/mL) [20]. Genotyping was performed by analyzing PCR products with a reverse-hybridization assay (Inno LiPA HCV II; Innogenetics) [21].

Statistical analysis. All data are expressed as medians and ranges. Comparison of categorical variables was performed using the χ² test or Fisher’s exact test, as appropriate. Comparison of continuous data was performed using the Mann-Whitney U test and the Kruskal-Wallis test. A P value of <.05 was considered to be statistically significant.

RESULTS

One hundred twenty-five consecutive, anti-HCV–positive children with CHC (median age at last observation, 14.5 years; range, 7.2–23 years) who did not have concomitant systemic disease were enrolled. All patients were free of symptoms, and none showed an abnormal growth when velocity of ponderal and statural growth were evaluated according to Centers for Disease Control and Prevention criteria [18]. The course of chronic HCV infection was retrospectively evaluated for a median period of 9 years (range, 3.4–20.9 years). On the basis of alanine aminotransferase (ALT) levels during the first year of anti-HCV positivity, children were divided in 2 groups: those with hypertransaminasemia (100 patients, all of whom had detectable HCV RNA) and those with normal ALT values (25 patients, 16 of whom had and 9 of whom did not have viremia). All patients with persistently normal transaminase levels were observed after the availability of a screening test for HCV. Of the 100 patients with hypertransaminasemia, 50 were treated with IFN during the period of observation; these patients were included in clinical trials performed at our department in previous years.

The characteristics of the studied patients at the first observation are summarized in table 1. At baseline, treated patients, untreated patients with hypertransaminasemia, and untreated patients with normal ALT levels were comparable with regard to age, sex, clinical features, duration of HCV infection, and distribution of HCV genotypes; significant differences between
Table 1. Clinical and laboratory characteristics of 125 children with chronic hepatitis C virus (HCV) infection at first observation.

| Characteristic                              | Treated children (n = 50) | Baseline hypertransaminasemia (n = 50) | Normal ALT level at baseline (n = 25) |
|---------------------------------------------|---------------------------|----------------------------------------|----------------------------------------|
| No. of male children                        | 28                        | 18                                     | 11                                     |
| Age, median years (range)                   | 7.4 (2.1–13.7)            | 5.8 (2–16)                             | 8.2 (2–15.2)                           |
| Route of HCV infection a                    |                           |                                        |                                        |
| Transfusion                                 | 22 (44)                   | 17 (34)                                | 5 (20)                                 |
| Vertical transmission b                     | 18 (36)                   | 23 (46)                                | 13 (52)                                |
| Minor surgery                               | 8 (16)                    | 1 (2)                                  | 1 (4)                                  |
| Unknown                                     | 2 (4)                     | 9 (18)                                 | 6 (24)                                 |
| Duration of HCV infection, median years (range)c | 6.4 (1.1–13.7)            | 5.5 (1–15.9)                           | 7.1 (1.2–15.2)                         |
| ALT level, median IU/L (range)d             | 9 (65–279)                | 108 (63–689)                           | <50                                    |
| Presence of HCV RNA in serum a              | 50                        | 50                                     | 16                                     |
| Serum HCV RNA level, median IU/mL (range)   | 264,000 (40,000–1,626,800) | 216,000 (347,00–581,000)               | 149,561 (2790–316,000)                 |
| HCV genotype                                |                           |                                        |                                        |
| 1a                                          | 9 (18)                    | 2 (4)                                  | 1 (4)                                  |
| 1b                                          | 24 (48)                   | 22 (44)                                | 7 (28)                                 |
| 2                                           | 10 (20)                   | 12 (24)                                | 5 (20)                                 |
| 3                                           | 3 (6)                     | 2 (4)                                  | 0                                      |
| Other/mixed                                 | 4 (8)                     | 4 (8)                                  | 2 (8)                                  |
| Unknown                                     | 0                         | 8 (16)                                 | 10 (40)                                |

**NOTE.** Data are no. (%) of children, unless otherwise indicated. ALT, alanine aminotransferase.

a P < .05.

b Vertical transmission was determined to be the route of transmission in the absence of other overt exposures to HCV when the mother had HCV infection with the same genotype.

c Duration of HCV infection is expressed as the time elapsed since the presumed date of infection; for the 17 patients with an unknown route of infection, it is expressed as the time since the first observation of an abnormal ALT level and/or a positive HCV serological test result.

d Normal value, <50 IU/L.

groups were found for route of infection and presence of viremia. All patients remained symptom free throughout the period of observation, with the exception of IFN-related adverse effects among the treated patients. No patient showed signs of hepatic decompensation. All children had normal levels of albumin, international normalization ratio, α-fetoprotein, and thyroid hormones (data not shown).

**Treated patients.** On the basis of trials in which patients had been included, 28 children had received IFN recombinant α-2b (5 MU/m² 3 times per week for 12 months), 9 children had received IFN recombinant α-2a (5 MU/m² 3 times per week, with durations of 6 months in the presence of a genotype other than 1b and of 12 months in presence of genotype 1b), and the remaining 13 children had received IFN α-lymphotoblastoid (3 MU/m² 3 times per week for 12 months). The main characteristics of the 50 treated children, according to the type of IFN therapy received, are shown in table 2. The median duration of the observation period was 8.9 years (range, 4.9–14.4 years). Eight patients (5 infected with HCV genotype 1 and 3 infected with HCV with a genotype other than 1) who did not have a favorable response to IFN received a second cycle of IFN at the median age of 11 years (range, 6.7–15.2 years). Only 1 patient (who was infected with HCV genotype 2a–2b) achieved a sustained virological response. The median duration of follow-up after the second cycle of IFN treatment was 6.1 years (range, 4.4–9.6 years).

A sustained virological response was observed in 11 (64.7%) of 17 children infected with an HCV genotype other than genotype 1 and in 8 (24.2%) of 33 children infected with HCV genotype 1 (P < .05). Among patients treated with IFN α-lymphotoblastoid, sustained response rates did not differ significantly according to genotype. No significant differences were found between patients with a sustained virological response and non-responders for the following parameters: age, sex, route of infection, serum ALT level, serum HCV RNA level, and presence of histological lesions in the liver.

**Untreated patients with baseline hypertransaminasemia.** Fifty untreated patients with basal hypertransaminasemia were observed for a median duration of 9.2 years (range, 3.4–14.9 years). Transaminase levels normalized and HCV RNA cleared in 6 children (12%) (2 with HCV genotype 1 infection) after a median period of 2.4 years (range, 1–5 years) and 3.6 years (range, 2–5 years), respectively. These patients continued to have normal transaminase levels and the absence of viremia.
Table 2. Characteristics of 50 children with chronic hepatitis C virus (HCV) infection who were treated with IFN.

| Characteristic                              | IFN recombinant α-2b | IFN recombinant α-2a | IFN α-lymphoblastoid | All children |
|---------------------------------------------|-----------------------|----------------------|----------------------|--------------|
| Male sex                                    | 28 (15)               | 9 (4)                | 13 (4)               | 50           |
| Age at the start of IFN treatment, median years (range) | 9.4 (3.2–14.5)       | 8.1 (4.7–11.5)       | 7.3 (3.4–14)         | 8 (3.2–14.5) |
| Route of HCV infection                      |                       |                      |                      |              |
| Transfusion                                 | 11 (39.3)             | 4 (44.4)             | 7 (53.8)             | 22 (44)      |
| Vertical transmission                       | 10 (35.7)             | 4 (44.4)             | 4 (30.8)             | 18 (36)      |
| Other                                       | 7 (25)                | 1 (1.2)              | 2 (15.4)             | 10 (20)      |
| Infection with HCV genotype 1               | 22 (78.6)             | 3 (33.3)             | 8 (61.5)             | 33 (66)      |
| Histologic test result, median (range)      |                       |                      |                      |              |
| Hepatitis grade                             | 4.4 (2–7)             | 5.3 (4–7)            | 5.4 (2–8)            | 4.8 (2–8)    |
| Fibrosis stage                              | 1.7 (1–4)             | 1.7 (1–2)            | 1.8 (0–4)            | 1.7 (0–4)    |
| No. of patients who had IFN therapy interrupted because of adverse events | 10                     | 4                     | 5                     | 19           |
| Duration of IFN therapy for patients who had treatment interrupted, median months (range) | 4.9 (2–8)             | 4 (3–5)              | 5.8 (1–10)           | 5 (1–10)     |
| Duration of post-IFN follow-up, median years (range)a | 5.8 (3.7–9.5)         | 4.2 (3.3–5.6)        | 7.9 (4.2–10)         | 6.1 (3.3–10) |
| Response to IFN                             |                       |                      |                      |              |
| End-of-treatment response                   | 6 (21.4)              | 6 (66.6)             | 4 (30.8)             | 16 (32)      |
| SVR                                         | 9 (32.2)              | 3 (33.3)             | 7 (53.8)             | 19 (38)      |
| Nonresponse                                 | 19 (67.8)             | 6 (66.7)             | 6 (46.2)             | 31 (62)      |
| Relapse                                     | 3 (7.2)               | 0                     | 2 (15.4)             | 4 (8)        |
| HCV genotype among children with SVR 1      | 4 (18.2)              | 0                     | 4 (50)               | 8 (24.2)     |
| Other than 1                                 | 5 (38.3)              | 3 (50)                | 3 (60)               | 11 (64.7)    |
| Auto-antibodies before therapy              |                       |                      |                      |              |
| ANA                                         | 2 (7.1)               | 2 (22.2)             | 1 (7.7)              | 5 (10)       |
| SMA                                         | 3 (10.7)              | 0                     | 5 (38.5)             | 8 (16)       |
| LKM1                                        | 3 (10.7)              | 1 (11.1)             | 0                     | 4 (8)        |

NOTE. Data are no. (%) of children, unless otherwise indicated. P values were not significant. ANA, anti-nuclear; LKM1, anti-liver/kidney microsomal type 1 antibodies; SMA, anti–smooth muscle antibodies; SVR, sustained virological response.

a Duration of posttherapy follow-up was calculated as the time elapsed since the suspension of therapy to the last observation.

throughout the subsequent period of observation (median duration, 4.2 years; range, 3.1–7 years). Transaminase levels normalized (without clearance of viremia) in 10 children (20%) after a median period of 2.8 years (range, 1–4 years). In these patients, the ALT level remained normal during the follow-up period (median duration, 4.7 years; range, 3.2–9.9 years). The remaining 34 children (68%) (21 with HCV genotype 1 infection) had persistently abnormal ALT levels and detectable HCV RNA during the entire period of observation (median duration, 5.9 years; range, 4.2–13.7 years).

**Untreated patients with normal ALT levels at baseline.** Twenty-five patients with normal ALT levels at baseline were observed for a median period of 7.9 years (range, 4.3–14.2 years). Among 16 children with baseline viremia, 12 (75%) maintained their status throughout the follow-up period, and 3 (18.8%) had either slightly increased or fluctuating ALT values; only 1 child (6.2%) had clearance of viremia. All 9 children with normal transaminase levels and the absence of viremia maintained their biochemical and virological status during the entire observation period.

**Biochemical and virological status in treated and untreated children at the end of the follow-up period.** All children remained anti-HCV positive during the entire period of observation. At the end of the follow-up period, rates of HCV RNA clearance and ALT normalization were significantly higher in treated children (38%) than in untreated children (12%; P < .05).

**Clinical and biochemical signs of autoimmunity.** None of the children with autoantibodies present fulfilled the criteria for diagnosis of autoimmune hepatitis [22]. A sustained virological response was obtained in 3 of 4 LKM1-positive children treated with IFN; none of them developed overt au-
Table 3. Staging at first biopsy for 58 children with chronic hepatitis C virus (HCV) infection for whom the fibrosis score was available.

| Variable                                      | Fibrosis stagea |
|-----------------------------------------------|-----------------|
|                                               | 0   | 1   | 2   | 4   | P   |
| No. (%) of children                           | 1 (1.7) | 25 (43) | 29 (50) | 3 (5.2) |
| Age at biopsy, median years (range)           | 13.9 | 8.7 (4.6–14.2) | 6.8 (2–13.8) | 2.7 (2.1–13.6) | NS |
| Duration of HCV infection at the time of biopsy, median years (range) | 13 | 8.5 (2.2–14) | 6.8 (2.1–13) | 2.3 (2.2–10) | NS |
| ALT level at the time of biopsy, median IU/L (range) | 54 | 104 (56–320) | 98 (50–350) | 112 (55–200) | NS |

a None of children had staging scores of 3, 5, or 6.

Histological evaluation. A total of 64 patients (median age, 8.2 years [range, 2–14 years]; median duration of HCV infection 6.9 years [range, 2–14 years]) underwent liver biopsy to assess the extent of liver damage and to guide management and treatment. Liver biopsy was performed for 47 of 50 treated children ≤6 months before commencement of treatment and for 17 of 75 untreated children. At the time of liver biopsy, all patients had viremia and hypertransaminasemia, with the exception of a child who had a normal transaminase level. The median hepatitis grade was 4.4 (range, 1–8), and the median fibrosis stage was 1.6 (range, 0–4). No cases of cirrhosis (i.e., fibrosis scores of 5 or 6) were observed. The age of patients at the time of biopsy and the duration of HCV infection did not correlate with fibrosis score (table 3).

Histological analysis also revealed evidence of mild-to-moderate steatosis in 16 children (25%). Only 2 patients with steatosis at biopsy were infected with HCV genotype 3, which is commonly associated with steatosis in adults [25].

Analysis of paired liver biopsy specimens. Biopsy was repeated 5.5 years after the initial histological evaluation (range, 2–11.2 years) for 21 of 50 treated children. Additional liver biopsy was performed to confirm histological improvement in patients with sustained response or to reevaluate disease status in patients with fluctuating serum transaminase levels.

In 6 patients with sustained virological response, the hepatitis grade improved in all patients (from a median value of 5.5 to 2.2), and the fibrosis stage decreased in all children but 1 (83%), in whom fibrosis did not change (score 1). In contrast, of 15 nonresponders, the hepatitis grade improved in 4 children (26.7%); the fibrosis stage improved in 6 patients (40%), did not change in 5 patients (33.3%), and worsened in 4 cases (26.7%) (table 4). In the group of nonresponders who had worsening fibrosis, only 1 HCV genotype 1b–infected obese child was found to have cirrhosis at the second biopsy, which was performed 7 years after the first biopsy and 13.1 years after the acquisition of HCV infection.

DISCUSSION

This 18-year retrospective study of a large number of consecutive children with CHC who were observed at a single health care center confirms that, in the majority of cases, children with CHC are symptom free, experience normal growth, and do not show clinical signs of chronic liver disease. During the entire period of observation, no child had decompensated liver disease or required liver transplantation. Our results are in agreement with those of Casiraghi et al. [4], who described a benign course of HCV infection acquired early in life during the first 35 years after exposure. Our study differs from the study by Casiraghi and colleagues, which included subjects who had been exposed to HCV through blood transfusions involving blood collected from a single HCV-infected donor, and our study enrolled a larger number of patients who had been infected through different routes and with different genotypes.

Although the findings of clinical examinations were unre-
markable, laboratory evaluation revealed hypertransaminemia in 80% of patients, whereas the remaining 20% had normal transaminase levels ab initio. The prevalence of children with normal transaminase levels was similar to that reported for adults [26]. No differences were found between children with normal transaminase levels and those with hypertransaminemia with regard to sex, age, route of infection, and genotype. Recently, it has been hypothesized that a relationship exists between polymorphisms in the promoter region of the osteopontin gene and transaminase levels in adults with CHC [27]; therefore, it is probable that genetic factors may also affect the behavior of transaminase levels in children. Mild liver disease is usually present at biopsy in the majority of adults with persistently normal transaminase levels, whereas few patients have severe histological damage [28, 29]. In our study, liver biopsy findings were not available for this group of patients, but because histological lesions were mild in the children with hypertransaminemia, it seems reasonable to assume that necroinflammation and fibrosis were also mild in children with persistently normal transaminase levels.

It is noteworthy that almost all of the children with normal liver enzyme levels and viremia maintained their status during the follow-up period. Although adults with normal transaminase levels have rates of sustained response to therapy similar to those for adults with hypertransaminemia [26, 30], these days, there is not a clear indication to treat such patients.

In this study, we identified a subgroup of children who, since they were first observed, were anti-HCV positive and had normal transaminase levels and the absence of viremia. It is likely that anti-HCV antibodies in these patients were the sign of a past HCV infection.

As for the group of 50 untreated patients with baseline hypertransaminemia and viremia, the rate of spontaneous viral clearance (12%) was lower than that reported by Vogt et al. [5] (45%) and Locasciulli et al. [6] (26.8%). This discrepancy could be related to the peculiar characteristics of patients included in those studies: the first included children who had posttransfusion HCV infection without clear evidence of chronic hepatitis, and the second evaluated patients who had leukemia that was in remission and an atypical serological profile for HCV infection. Thus far, no predictive factor (including HCV genotype) of spontaneous viral clearance has been identified; it is likely that genetically determined immunological factors could be involved.

In the present study, treated patients had a rate of sustained virological clearance significantly higher than that for untreated children; in particular, this occurred in the presence of genotypes other than genotype 1. These findings confirm the previously reported favorable effects of IFN therapy [11]. In the analysis by Jacobson et al. [11], a sustained response was observed in 36% of treated patients and in 70% of patients infected with genotype other than 1b. Compared with the studies included in Jacobson and colleagues’ analysis, our study had a longer period of observation, both for treated and untreated patients. Despite the longer posttreatment follow-up period, in our patients, the rate of relapse was lower (8% vs. 22%). This discrepancy is probably attributable to the very strict response criteria used in our study, in which frequent determinations of serum HCV RNA level were performed. In addition, our results confirmed that fibrosis may improve after IFN therapy in children, particularly if there is a treatment-induced HCV RNA clearance. In spite of the promising results of IFN therapy for children, at the present time, all children with CHC do not seem to be reasonable candidates for such therapy, because treatment is expensive and is associated to several adverse effects; furthermore, prolonged therapy is required, and a favorable response is achieved only in a subset of patients. Finally, in the vast majority of untreated children, no significant worsening is usually observed.

In contrast with adults with CHC, extrahepatic manifestations were rarely observed in the studied children. Although the presence of autoantibodies—particularly LKM1 antibodies—has been associated with more-severe and -progressive liver disease [31], our LKM1-positive children had low fibrosis grades and a favorable response to IFN therapy [23].

The present study not only confirms that CHC in children is morphologically mild in most cases, but it also shows that fibrosis progression is relatively slow and that cirrhosis is extremely rare. Unlike what has previously been reported [32], no linear correlation between duration of disease and progression of fibrosis was found in the present study. In fact, 2 of the 3 children with moderate fibrosis (score, 4) at the time of the first biopsy had a short duration of disease (2.1 and 2.5 years). On the other hand, the only patient for whom fibrosis was absent had a disease duration of 13.9 years. Therefore, the severity of liver disease does not seem to depend on the duration of HCV infection; instead, a host-virus interplay might be involved.

In conclusion, this study indicates that CHC acquired in childhood is a mild disease with a slow progression of fibrosis. Despite the benign course of HCV infection in the majority of cases, spontaneous clearance of serum HCV RNA is rarely observed. In children with persistent viremia and hypertransaminemia, IFN therapy may be effective in the presence of genotypes other than genotype 1, whereas lower response rates are expected for genotype 1-infected children. Presently, combination therapy using pegylated IFN and ribavirin has dramatically improved the sustained virological response among adults with CHC [33]; preliminary studies have confirmed the efficacy of this therapy for children as well [34]. Therefore, it is probable that, in upcoming years, it will be used for children with CHC. At the present, it seems reasonable to not treat all
children, but to treat only those with more-severe liver disease and/or with positive predictive factors of response.

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