Impact of Hepatitis B and Hepatitis C Virus Infections in a Hematology-Oncology Unit at a Children’s Hospital in Nicaragua, 1997 to 1999

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The risk of acquiring both hepatitis B virus (HBV) and hepatitis C virus (HCV) infections in patients with hematological-oncological disorders has been documented. However, the impact and risk factors for such infections from different geographical areas vary, and the use of both immunological and molecular assays to determine HCV infections has been our approach. Children from a hematology-oncology unit (HOU) in Nicaragua were studied for both HBV and HCV serological markers; studies for the latter used both immunological (anti-HCV) and molecular (HCV RNA) assays. The children from the HOU included patients with leukemia, lymphoma, other neoplasias, and anemia and a smaller group with other hematological diseases. As a control group, children from other units at the same hospital were enrolled, as well as health care workers attending both patient populations. Pertinent clinical and personal data for each child at the HOU were obtained for statistical analysis. Of the 625 children from the HOU enrolled in this study 53.3% were infected with HCV and 29.4% had a prior or present HBV infection. In the child patient control group 3.2% had HBV markers and all were negative for HCV. The group of children with leukemia had the highest infection rate for both HBV and HCV. However, the determination of anti-HCV was found to have an overall low sensitivity in children from HOU, and a retest consisting of a molecular assay to determine HCV RNA was performed to better establish the total number of HCV-infected subjects in this group. The highest independent risk factor for infection was hospitalization. The very high prevalence rates for both HBV and HCV infection in this patient group indicate an urgent need to implement better control of known risk factors and to consider the use of both immunological and molecular assays for HCV diagnostic purposes.

The risk of infection with both hepatitis B virus (HBV) and hepatitis C virus (HCV) is well documented in children with hematological disorders, and prevalence rates as high as 50% in leukemia and lymphoma patients have been reported (4, 21, 22, 26). Many of these children receive multiple transfusions of different blood components, and this could be a potential risk factor for acquiring such infections. Also the children are highly immunosuppressed, and therefore the manifestations of these infections are mostly subclinical and rarely noticed (16, 17).

Over the last decade in the developed world all donated blood products have been screened for both HBV and HCV, and this has led to a major reduction in posttransfusion viral hepatitis (16, 28). However, in developing countries, these screening assays were introduced later and only partially in some areas; in some countries, they were not introduced at all. Therefore, the risk of acquiring both HBV and HCV infections is expected to be higher in such countries. Also, both in the developed world and in countries under development, there have been nosocomial outbreaks in the pediatric populations due to improper implementation of universal precautions such as reuse of disposable materials and incorrect handling of sterile materials (9, 11), to person to person contact, to invasive procedures, and to other unknown risk factors (1, 5, 12). Thus, HBV and HCV infections appeared often as “silent infections” in these patients and were detected only if prevalence studies were performed or if the children underwent testing for HBV and HCV periodically as part of a routine procedure (14). For the diagnosis of HCV infection, the most common methods used are serological, involving indirect detection of antibodies against HCV using enzyme immunoassay (EIA) systems for initial screening (29, 32), followed by a confirmation test with a recombinant immunoblot assay or similar second- or third-generation assay (3, 19). In some immunosuppressed children the anti-HCV assay appears negative due to their disease pattern and/or due to treatment but the child is actually infected with HCV. In these cases it is necessary to retest the children by using a different diagnostic approach, such as a molecular assay which can determine the presence of HCV RNA (6, 15, 25). A few published studies have used a similar approach; Locasciulli et al. showed that by the end of chemotherapy in a cohort of leukemic children 64 were infected with HCV and that, of these, 16 were HCV RNA positive with no detectable levels of anti-HCV, and De Rosa et al. showed that in 60 HCV-infected children with lymphoma, 3 had detectable HCV RNA in the absence of anti-HCV (4, 15).

In this study, we analyzed over 1,000 individuals, 625 of whom were attending a hematology-oncology unit (HOU) at
TABLE 1. Prevalence rates for HBV and HCV infections in all study groups

| Study group          | No. of persons | No. (%) positive for:          |
|----------------------|----------------|--------------------------------|
|                      |                | HbsAg | Anti-HBc | Anti-HCV and/or HCV RNA |
| Children from HOU    | 625            | 61 (9.8%) | 172 (29.4%) | 333 (53.3%) |
| Children from other units | 124         | 0       | 4 (3.2%)  | 0 |
| HCW from HOU         | 23             | 0       | 4 (17.4%) | 1 (4.3%) |
| HCW from other units | 333            | 3 (0.9%) | 25 (7.5%)  | 3 (0.9%) |

the Children’s Hospital in Managua, Nicaragua. They were tested for the presence of HBV and HCV infection by both immunological and molecular assays, since a relatively low sensitivity was found if anti-HCV alone was used to detect HCV infection and we believed that there was a need to establish additional reverse transcription-PCR (RT-PCR) testing for detection of HCV RNA in order to identify all infected children. The results obtained were correlated with other pertinent patient data in order to determine potential risk factors such as hospitalization, blood transfusion, and surgery. Among these, hospitalization was found to represent the highest risk factor for both HBV and HCV infection.

In Nicaragua, at the National Red Cross blood bank, routine screening for HbsAg was introduced in 1987 and screening for anti-HCV was introduced in 1992; commercial reagents were used for anti-HCV, while both commercial and in-house tests were used for HbsAg. The prevalence rates in the blood donor population varied from 0.3 to 0.6% for HCV, and the rate was 0.4% for HBV. Prevalence data for other population groups were not available. As a preventive measure vaccine intervention against HBV was introduced for children undergoing treatment and newly admitted HOU patients. Also, all health care workers (HCW) from this unit and throughout the hospital were offered HBV vaccine.

MATERIALS AND METHODS

Study population. A total of 625 patients attending the HOU at the Children’s Hospital in Managua, Nicaragua, were enrolled in this study. Patients either lived in the immediate area of the hospital or were referred to the HOU from regional hospitals or outpatient clinics. As a control group, 124 children from other units at the same hospital were included. Also, 356 HCW were evaluated, 23 from the HOU and 333 from other areas of the hospital. All children at the HOU were vaccinated with Engerix-B and tested for anti-HBs between 6 months and 1 year after the first dose. The vaccine scheme was four doses of 40 µg given at months 0, 1, and 2 to 6.

All study groups were tested for HbsAg in order to test for a current infection with HBV, and total anti-HBe was used as a marker for detection of both present and prior infection. If the sample was found HbsAg positive, additional anti-HBc, immunoglobulin M, HBeAg, and anti-HBc tests were performed.

For HCV markers, all study groups were tested for the presence of anti-HCV and patients from the HOU that were initially anti-HCV negative were restested by RT-PCR for detection of HCV RNA. Patients positive for either of these two HCV markers were considered infected. A group of 28 infected children were also genotyped for HCV. In some samples it was not possible to perform all of the above assays, due to the small volume of material available.

A questionnaire was used to obtain pertinent data from the HOU patients. Data included period of contact with the hospital (calculated from the first outpatient consultation), sex, age (at time of first consultation), clinical diagnosis, history of blood transfusion (all products were supplied by the local Red Cross blood banks), surgery, biochemical results related to liver disease, and status of chemotherapy. A consent form was signed by the parent or guardian of each participating child. Approximately 50% of the children attending the HOU during 1998 were enrolled in the study.

Methods. Commercial reagent kits from Abbott Laboratories (North Chicago, Ill.) were used to detect HbsAg (Auszyme), total anti-HBe (Corezyme), immunglobulin M, anti-HBc (Corezyme-M), HBeAg, anti-HBe (HBe [recombinant DNA] EIA), and anti-HBs (Abzyme); in-house reagents based on similar immunosay principles were prepared by the Louisiana State University (LSU) International Center for Medical Research and Training (ICMRT) (2). For the screening of anti-HCV second- and third-generation commercial EIA kits (Ortho Diagnostic Systems, Raritan, N.J.) were used; EIA-ICMRT in-house (22) commercial recombinant immunoblot assay (Ortho Diagnostic Systems) and LIA Tek III (Organon Teknika, Boxtel, The Netherlands) kits were used for confirmation of anti-HCV. Any sample being initially reactive for HBV markers by the commercial or the LSU ICMRT assays was restested to correlate the reactivity with that from a second assay. All samples were screened for anti-HCV in parallel with the commercial and in-house reagents.

All anti-HCV-negative patient samples were tested for the presence of HCV RNA by using RT-PCR Amplifor HCV monitor test V20 (Roche Diagnostics) and/or Quanti-Path (CPG, Inc.). If HCV RNA was detected, a second determination was performed in a follow-up sample to confirm the HCV infection of the patient. Also, in 51 anti-HCV-positive patient samples a determination of HCV RNA was done. A LIPA genotype assay (Innogenetics, Inc.) was used to test some samples; testing was performed by courtesy of the National Genetics Institute (Los Angeles, Calif.).

Statistical analyses. Results were analyzed by using SPSS, Inc., standard version 7.5, 1989 to 1996. Risk factors were evaluated by using the Pearson chi-square test, and for the results with statistical significance the odds ratios (OR) were calculated.

RESULTS

The prevalence rates for HBV and HCV markers for all study populations are shown in Table 1. Of the 625 children enrolled from HOU, 53.3% were infected with HCV and 29.4% were anti-HBe positive, revealing a prior or present infection with HBV; of these 9.8% were also HbsAg positive at the time of sample collection, and coinfection was established in 123 patients. Of the coinfections 42% were found in the leukemia patients; leukemic patients represented only 27% of the total HOU study population. The child control group showed a 3.2% prevalence of anti-HBe, and none of these were infected with HCV. Anti-HBe prevalence in the HCV from the HOU was 17.4%, showing a higher prior exposure to HBV in these HCV than in HCV from other units (7.5%).

FIG. 1. Distribution of 558 HOU patients related to 306 HCV and 162 HBV infections and clinical diagnosis. HO, hematological-oncological.
Data on clinical diagnosis were available for 558 children from the HOU, as shown in Fig. 1. Leukemia represented the most common disease (27%), followed by anemia (19.2%) and other neoplasias (16.5%). Figure 1 also shows the relationship between HBV and HCV infections, as correlated with clinical diagnosis. In all groups a higher number of children were infected with HCV than with HBV, and the highest prevalence rates of infection were seen in leukemia patients, where 135 and 68 patients were infected with HCV (P < 0.01) and HBV (P < 0.01), respectively. The increase of prevalence for HCV and HBV related to the time of contact with the Children's Hospital is shown in Fig. 2. Prevalence ranged from 26% at less than 1 month to 72% at 12 months for HCV (P < 0.01), with a similar pattern for HBV (P < 0.01).

Table 2 shows the inability of the anti-HCV assay to diagnose all HCV infections in children from the HOU since, when seronegative samples were retested by RT-PCR for HCV RNA, there was an increased positivity. This implies a high false-negative rate for the immunological test. The group of leukemia patients showed the lowest anti-HCV sensitivity. Of 89 anti-HCV-negative patients, 70.8% had detectable HCV RNA levels, followed by the lymphoma patients with 42.3%. A small group of 36 patients with ≥12 months “off therapy” showed a similar pattern of nondetectable antibodies to HCV in the presence of HCV RNA: 3 of 6, 6 of 13, and 4 of 16 patients with leukemia, lymphoma, and other neoplasms, respectively. Of the 51 anti-HCV patients analyzed for HCV RNA, 41 had detectable levels.

During the last 6 months of the study, an evaluation of the prevalence rates for both HCV and HBV in newly enrolled patients at the HOU was done. Of this group of 43 children, 8 (18.6%) were HCV positive by RT-PCR for HCV RNA, but all had undetectable levels of anti-HCV. None of the children had been infected with HBV.

Of the children from the HOU vaccinated against HBV a group of 94 were tested for anti-HBs between 6 to 12 months after the initial dose, and 62.8% had detectable antibody levels.

No correlation between the alteration of classic hepatitis biochemical markers (alanine aminotransferase, aspartate aminotransferase, and bilirubin) and infection with either HBV and HCV could be established.

The overall outbreak was considered to be nosocomial based on the results of risk factors analyzed. Not all patients had all risk factor information available, as shown in Table 3. The highest independent risk factor for both infections was hospitalization; HBV had an OR of 7.40 (confidence interval [CI], 2.64 to 20.75; P < 0.01), while the OR for HCV infections was 4.85 (CI, 2.68 to 8.79; P < 0.01). Transfusion had an OR of 3.39 (CI, 2.36 to 4.88; P < 0.01) for HCV infection and an OR of 2.40 (CI, 1.60 to 3.61; P < 0.01) for HBV, but both OR were found to be closely related to hospitalization. For patients without transfusion but hospitalized one or more times, the risk of HCV infection had an OR of 2.27 (CI, 1.16 to 4.44; P = 0.01) and the risk of HBV infection had an OR of 4.33 (CI, 1.47 to 12.81; P < 0.01).

Of the total study population 40% had been transfused but had received only a few units of blood, as shown in Table 4. A minor proportion of the children had a history of surgery (32%), which was established to have OR of 1.50 (CI, 1.02 to 2.21; P = 0.04) and 0.70 (CI, 0.48 to 1.00; P = 0.05), with low or no statistical relationship between surgery and risk of infection, for HBV and HCV, respectively.

In the group of 28 patients genotyped for HCV, 89.2% exhibited HCV type 1a, which could indicate a possible common origin of this infection.

### DISCUSSION

The initial outbreak described in this manuscript was classified as silent since no specific symptoms related to viral hepatitis had been observed in the children and since it was only detected when a medical student decided to study the impact of HBV and HCV infection in children attending the HOU at a public hospital in Nicaragua. He studied 60 patients and determined high rates of infection with both HBV and HCV in this group. Based on these preliminary data a more detailed study was designed, and the results are discussed in this paper.

The highest rates of infection for both HBV and HCV were in the leukemia group, probably due to the severe nature of this disease and the concomitant aggressive treatment used for intervention. During the study period HBV infection seemed to be controlled by vaccination, since no new infections occurred during the last 6 months of the study period. The HBV vaccine program was initiated approximately 1 year earlier as part of our intervention efforts. All children newly admitted to the HOU received a complete HBV vaccine schedule, and this seemed to have controlled the infection. However, during this

### TABLE 2. Correlation between the clinical diagnosis and HCV RNA positivity in anti-HCV-negative samples of children from HOU

| Diagnosis                  | Total no. of samples | No. (%) of samples positive for HCV RNA |
|----------------------------|----------------------|----------------------------------------|
| Leukemia                   | 89                   | 63 (70.8)                              |
| Lymphoma                   | 52                   | 22 (42.3)                              |
| Other neoplasias           | 88                   | 28 (31.8)                              |
| Anemia                     | 80                   | 27 (33.8)                              |
| Other hematological diseases| 63                   | 22 (34.9)                              |
| None (patients under evaluation) | 21                | 4 (19.0)                               |

* All samples were anti-HCV negative.
same period 18.6% of the children became infected with HCV. Hospitalization was found to be the highest risk factor for both infections. The high percentage of HCV infection made it impossible to use isolation of infected children from noninfected ones as a preventive intervention. The general precaution to avoid infectious diseases was reviewed in detail as well. Any condition which could be related to risk of infection was corrected, within the economic limits of the country; new sterilization equipment was provided, procedures for total disposal of material were instituted, etc., but none of these measures seemed to reduce the HCV infection rate.

Recently Somarriba et al. (unpublished data) revealed that a low percentage of pediatric HOUs implemented preventive measures related to nosocomial infections throughout Latin America. A total of 13 countries with 17 centers participated in the evaluation, and the implementation of preventive measures varied from 20 to 84% within these countries, with a mean value of 52%; Nicaragua had a 49% value. Among the risk factors not well controlled in this study were the use of multidose vials and the reuse of injection equipment.

The main HCV genotype related to the outbreak was determined to be 1a, which is known to cause high viral loads, fast development of active liver disease, and poor outcome when off treatment (18, 20, 24, 30, 31).

There are conflicting results in the literature on follow-up studies of children infected with HCV having hematological disorders. Some studies show minor liver pathology after 10 to 30 years of follow-up, while others report significant pathological changes in a few years (7, 13, 23, 25, 27). In most of the earlier studies the genotype of HCV was not included, and this may explain such differences. However, one of these studies showed predominant 1a and 1b genotypes and the clinical follow-up revealed severe liver disease in a high percentage of the children (27). In Nicaragua we know that fast-replicating virus 1a causes HCV infection, and therefore infected children need to be monitored closely and the infection should be controlled.

The poor sensitivity of anti-HCV assays to determine HCV infection in children with hematological disease is important to consider when such studies are being performed in the developing world, where molecular methods are often not available. If only an immunological approach had been used in this study, approximately 50% of the HCV infections would have been missed (these were diagnosed only when using RT-PCR for HCV RNA determination). Therefore any kind of intervention applied based on antibody testing provides a poor outcome. A small number of HCV-positive samples were evaluated for HCV viral load and no difference between anti-HCV-positive and -negative samples was observed. Overall these children had a high viral load (>10^6/ml).

Also, it is important to consider that, after more than 12 months without chemotherapy, a similar proportion of HCV-infected children still did not develop HCV antibodies in the presence of detectable HCV RNA, compared to the proportion observed during treatment.

Few data on HCV prevalence are available in Nicaragua. For blood donors this value varies from 0.3 to 0.6%, and approximately 50% of isolates belong to genotype 1 (8). This earlier study result, taken together with a 0.9% prevalence in HCW determined by this study, eliminates the possibility that children were infected by family members or HCW contacts.

This study shows that there is an urgent need to establish the prevalence rate for HCV in at-risk populations in order to be able to control the overall dissemination of HCV to the general population, which at the present time has a low apparent prevalence rate (based on blood donor and HCW results). Efforts to control HVB infections in the HOU children through vaccine intervention are being made, and the initial results appear promising.

Since there is no vaccine for HCV, attention must be directed to other preventive measures. It is necessary to study the prevalence rate in risk groups for a better understanding the mechanisms of viral spread within these groups and possible dissemination into the general population (10).

| Risk factor          | Total populationa | HBV | HCV |
|----------------------|-------------------|-----|-----|
|                     | No. of persons with marker resultb: OR (CI) | P   | No. of persons with marker resultb: OR (CI) | P   |
| Hospitalization      | 539               | 155/4 | 319/61 | 7.41 (2.64–20.74) | <0.01 | 285/16 | 180/49 | 4.85 (2.67–8.78) | <0.01 |
| Transfusion          | 541               | 117/41 | 208/175 | 2.40 (1.59–3.61) | <0.01 | 215/82 | 102/132 | 3.39 (2.36–4.87) | <0.01 |
| Immune supression    | 551               | 77/82 | 193/199 | 0.96 (0.67–1.4) | 0.86 | 168/135 | 97/141 | 1.80 (1.28–2.55) | <0.01 |
| Surgery              | 544               | 61/97 | 114/272 | 1.5 (1.01–2.21) | 0.04 | 85/213 | 86/150 | 0.69 (0.48–1.00) | 0.05  |

a Not all the children had information available.
b HBV markers, HBsAg and anti-HBs; HCV markers, anti-HCV and HCV RNA. Values are numbers of patients with the indicated condition/without the indicated condition.

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TABLE 4. Correlation between the units of blood donations received by the children from HOU and the infection rate for HBV and HCV

| Transfusion (U) | No. of patients | No. of patients (%) positive (any marker) for: |
|-----------------|-----------------|---------------------------------------------|
|                 |                 | HBV                                        | HCV |
| 0               | 216             | 42 (19.4)                                   | 82 (38.0) |
| 1–5             | 204             | 67 (32.8)                                   | 125 (61.2) |
| 6–10            | 56              | 19 (33.9)                                   | 41 (73.2) |
| >10             | 80              | 35 (43.8)                                   | 57 (71.2) |

a Median of 2.0 U with a mean of 2.57 U.
b Prevalence in blood donors of HBsAg, 0.4%; prevalence of anti-HCV, 0.3 to 0.60%.
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