HEPATOTOLOGY

Acute hepatitis C in Israel: A predominantly iatrogenic disease?

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Abstract

Background and Aims: Acute hepatitis C virus infection in the era of universal screening of blood products has not disappeared, and is thought to be transmitted primarily via injecting drug use. A growing body of evidence supports iatrogenic transmission as an important mode of transmission. The aim of this study was to examine transmission routes and clinical characteristics in a group of patients with acute hepatitis C in Israel.

Methods: A retrospective chart review was conducted in three different liver clinics in Israel, of all new hepatitis C patients. Patients identified as possible acute hepatitis C were re-interviewed and all other sources such as blood bank records and pre-employment check-ups reviewed in order to establish the diagnosis of acute hepatitis C infection and to identify the transmission route.

Results: Twenty-nine patients were found to have acute hepatitis C, representing 0.75% of all new referrals for hepatitis C. The most frequent (65%) mode of transmission was iatrogenic involving several, often minimal, procedures and clinical settings. The group in which iatrogenic transmission was suspected was older and the patients more often in monogamous relationship compared with other transmission routes groups. Injecting drug use was the second most common route of infection. Spontaneous seroconversion has occurred in approximately one third of the patients.

Conclusions: Acute hepatitis C in the post universal blood products screening era was found to be predominantly an iatrogenic disease in the investigated localities. This finding should direct attention and resources towards the development and implementation of preventive measures.

Introduction

During the 1980s it became clear that most cases of post transfusion hepatitis were caused by a hepatitis non-A/non-B virus. This virus was cloned in 1989, named hepatitis C virus (HCV), and in 1990–1991 universal screening of blood products for HCV antibodies (Ab) was introduced in this country.

One would intuitively assume therefore that 15 years later acute hepatitis C (AHC) would become a rare event, occurring almost exclusively in injecting drug use (IDU), healthcare workers, following accidental exposure, and perhaps, in high risk nosocomial settings (e.g. dialysis, hematology oncology units).1–3 However, during the last few years we noted two unexpected phenomena. First, it seemed that more cases of AHC were diagnosed than ever before. Ours is not an isolated experience, as there has been an unprecedented surge of interest in the subject.4–7 Second, over half of the patients with AHC we have seen did not have any obvious risk factor. The source of infection could have been classified, at first sight, as ‘unknown’.8

However, after encountering a particularly informative patient, we analyzed the ‘unknown cause’ group more closely, and found to our surprise and dismay that all these patients underwent small, even minimal, procedures that are not generally associated with the transmission of HCV.

As the transmission route is rarely the focus of discussion in most articles on AHC, we present our observations on a group of patients with this condition.

Methods

Settings

This study was conducted in three medical centers in Israel: Sourasky Medical Center, Tel Aviv, an 1100-bed tertiary referral
center in central Israel, catchment area 1,360,000 people; Rambam Medical Center, Haifa, a 900-bed, tertiary referral center in northern Israel, catchment area 1,500,000 people; and Hadassah Medical Center at Mount Scopus, Jerusalem, a 300-bed, university-affiliated community hospital in Eastern Israel, catchment area 300,000 people.

**Study design**

This was a retrospective chart review. Charts of all new hepatitis C patients presenting to the liver units between June 2001 and December 2004, as well as the charts of patients already being followed up in the units for chronic hepatitis C, were reviewed with the aim of identifying every possible episode of past or present AHC.

Every attempt was made to verify that each episode was indeed an episode of past or present AHC, by obtaining hospitalization, outpatient clinics and family physicians’ charts, test results from the central blood bank (regarding past blood donations) and from pre-employment checkups.

In addition, all patients diagnosed as having AHC were re-interviewed and questioned regarding demographic data, signs, symptoms, possible known risk factors and modes of transmission.

All the data and tests were recorded as a part of routine clinical treatment.

**Inclusion criteria**

Adult patients (18 years of age and older) were eligible if a past or present episode of AHC was identified in their charts.

Acute hepatitis C infection was considered to be present, in patients with a positive HCV Ab test, if two or more of the following criteria were met: (i) known or suspected exposure to HCV within four months prior to the onset of acute hepatitis; suspected exposure was defined as: contact with known HCV patient; sharing needles or IV drugs; promiscuous sex; needle stick occupational injury or high risk occupational exposure; high risk patient (e.g. on chronic dialysis); any exposure to intravenous access or invasive procedure; (ii) documented sero-conversion with a negative HCV Ab test within a year prior to the acute episode; (iii) rising titers of HCV Ab indicative of an acute infection; and (iv) transient elevation of serum alanine aminotransferase (ALT) levels to more then 10 times the upper limit of the normal range and/or transient clinical jaundice.3-11

A test for the presence of the RNA of the HCV virus in the serum (HCV-RNA) by PCR was also performed as well as genotyping when feasible.

Toxic hepatitis, hepatitis type A or B, cytomegalovirus infection, acute on chronic auto-immune hepatitis, acute presentation of Wilson’s disease, decompensated chronic liver disease and alcohol abuse were ruled out.

**Route of transmission**

Route of infection was determined based on known risk factors, consideration of temporal relationships and exclusion of other possible routes.

Nosocomial/iatrogenic infection as a route of transmission was determined only after rigorous exclusion of other possible routes including: IDU, tattooing or piercing, sexual contact with a known HCV carrier or multiple sexual contacts (over two per year).

**Laboratory procedures**

Routine blood test (a full chemistry panel, a complete blood count, urinalysis and hepatitis serology) were performed by widely available commercial laboratory methods. Serum HCV RNA was measured by the Amplicore method (Roche Diagnostics, Basel, Switzerland). HCV genotype was determined using the Innolipa kit (Innogenetics, Gent, Belgium).

**Follow-up and treatment**

Follow-up and treatment were conducted according to routine clinical practice in the three liver units, at the discretion of the treating physician.

**Statistical analysis**

SPSS statistical software (SPSS, Chicago, IL, USA) was used for the statistical analysis. Statistical analysis included chi-squared test, independent sample t-tests and ANOVA. A value of \( P < 0.05 \) was considered statistically significant. We compared demographic, clinical and outcome parameters of the iatrogenic transmission group, the IDU group and the remainder of the sample (IDU and all other transmission routes apart from iatrogenic). We compared transmission routes and demographic and clinical parameters of the group of spontaneous converters and the remainder of the sample.

**Results**

**Baseline characteristics**

There were 29 patients (14 female and 15 male) who fulfilled the inclusion criteria. Their ages ranged from 19 to 82 years with a median of 32 years (mean age at diagnosis was 38.2 years). Thirteen patients were from Sephardic ethnicity and 16 from Ashkenazi. Fifteen patients had significant comorbidities, including diabetes mellitus, thrombotic thrombocytopenic purpura, ischemic heart disease, heart valve replacement and epilepsy. Seventeen patients were married or in a long-standing (>1 year) monogamous relationship.

**Fulfillment of inclusion criteria**

All 29 patients who fulfilled the inclusion criteria had a plausible clinical background and/or event that could lead to infection (Table 1).

Twenty-five patients had ALT levels higher then 10 times the upper limit of normal and all 24 patients who were tested for serum HCV-PCR had a positive result. Sixteen patients had a documented HCV antibody sero-conversion and three had rising titers of HCV antibodies. Seven additional patients in the three centers with suspect acute HCV infection were excluded because of insufficient evidence for an acute rather then a chronic infection.

In retrospect, more than 1 year after the acute episode (one patient received blood products in 2001–2002, and although the donors were not reevaluated, the risk of acquiring hepatitis C after the implementation of screening programs is considered extremely low.12,13 There was no difference in outcome between the iatrogenic group and the IDU group, nor was a significant difference identified between the iatrogenic group and the rest of the sample.

Date of infection

Twenty-five patients were identified during the study period (June 2001 to December 2004) while four other patients were identified in retrospect, more than 1 year after the acute episode (one patient in 1992, two in 1997, and one in 1999).

Proportion of AHC referrals of entire HCV referral population

In the study period (June 2001 to December 2004) 3300 new patients with HCV infection were referred to the three participating liver diseases clinics. Thus the 25 patients with acute HCV infection represent 0.75% of all referrals in the study period.

Mode of transmission

Four likely routes of transmission were identified in this group with the iatrogenic route being the most common, responsible for 19 of 29 (65.5%) infections (Table 2). Six patients were, most likely, infected through IDU making this route of transmission the second most common responsible for a little under one fifth of the infections. In three patients sexual intercourse was considered to be the most probable mode of infection, two female patients who had infected spouses who were not available for testing, and one male patient who had multiple sexual partners. Both female patients had other possible routes of transmission: one by manicure performed in an endemic area abroad and one by a single blood test taken in a student healthcare facility abroad. A single patient, a psychiatrist, was infected through a needle stick injury, thus making occupational exposure the least common route of transmission.

The iatrogenic group was generally older than the rest of the patient population (average age 43.47 years and 24.67 years, respectively, \( P < 0.001 \)). A larger proportion of this group was married or in long-standing monogamous relationship when compared with the IDU group and the rest of the sample (73%, 16.6% and 33.3%, respectively, \( P < 0.05 \)). There was no significant difference in sex or ethnicity between the different groups.

HCV-PCR was performed with established viremia in 17 of 19 patients in the iatrogenic group, and in three of six patients in the IDU group. In separate analysis that included only patients who had a positive HCV-PCR, the differences were maintained. Patients in the iatrogenic group were older compared with the rest of the sample (average age 45.05 years and 22.83 years, respectively, \( P < 0.001 \)). A larger proportion of the iatrogenic group was married or in long-standing monogamous relationship when compared with the IDU group and the rest of the sample (76%, 0% and 33.3%, respectively, \( P < 0.05 \)).

Possible infections occurred in seven different hospitals and four different settings, private clinics, university medical centers, small community hospitals and ambulatory facilities. The nosocomially associated infection occurred in various clinical departments, including general surgical and medical wards but did not include high risk settings such as hemodialysis centers or hematology-oncology units. The procedures implicated were often minimal and in some cases included only intravenous treatment (Table 3). Exposure to blood products was found in only three patients. In one of these patients the donors were re-screened and no hepatitis infection was identified. The other two patients received blood products in 2001–2002, and although the donors were not reevaluated, the risk of acquiring hepatitis C after the implementation of screening programs is considered extremely low.12,13 There was no difference in outcome between the iatrogenic group and the IDU group, nor was a significant difference identified between the iatrogenic group and the rest of the sample.

Symptoms and signs

Most patients presented with non-specific symptoms. The most common symptoms were weakness and malaise (19/29), nausea and vomiting (11/29) and right upper quadrant abdominal pain (4/29). Clinical jaundice was diagnosed in 14 (48.2%) patients and

### Table 1

<table>
<thead>
<tr>
<th>Fulfillment of inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
</tr>
<tr>
<td>--------------</td>
</tr>
<tr>
<td>Sero-conversion</td>
</tr>
<tr>
<td>Rising HCV Ab titers</td>
</tr>
<tr>
<td>ALT elevation x10 UNL</td>
</tr>
<tr>
<td>Known or suspect exposure or HCV</td>
</tr>
</tbody>
</table>

Ab, antibodies; HCV, hepatitis C virus; PCR, polymerase chain reaction; UNL, upper normal limit.

### Table 2

<table>
<thead>
<tr>
<th>Mode of transmission</th>
<th>No. patients</th>
<th>Other possible route of infection</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDU</td>
<td>6</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>19</td>
<td>None</td>
<td>See Table 3</td>
</tr>
<tr>
<td>Needle stick injury</td>
<td>1</td>
<td>None</td>
<td>Professional healthcare worker</td>
</tr>
<tr>
<td>Sexual route</td>
<td>3</td>
<td>One patient had her fingernails manicured in an endemic area.</td>
<td>Two female patients with a HCV positive spouse and one male patient with no other risk factor other than multiple sex partners.</td>
</tr>
</tbody>
</table>

IDU, injecting drug use.
in 6 (20.6%) patients the diagnosis was incidental. There was no difference in symptoms between the iatrogenic and other groups. Average duration of symptoms was 24 days, with a range of 5–90 days. Incubation period was defined as the time that elapsed between the suspect culprit infecting event and the onset of symptoms (available in 13 patients) and was on average 57 days with a range of 30–99 days.

**Laboratory values**

Average peak serum ALT levels were 33.8 times the upper limit of normal (range of 7.5–85 times, median 30 and SD 17.8), with no differences in any of the patient groups. In three patients peak serum ALT levels in the acute phase were not available and in only one patient peak serum ALT levels did not exceed 10 times the upper limit of normal. In the 20 patients for whom there were serial measurements available, the average time for normalization of the serum ALT levels was 111 days (range 23–202 days). Average peak total serum bilirubin levels (as times upper normal limit) was 6.9 mg/dL (range 0.9–20.25, median 4 and SD 6.2). Serum bilirubin levels where found to be higher in the iatrogenic group when compared to the IDU group (mean peak levels 7.35 mg/dL and 2.04 mg/dL, respectively, \( P < 0.005 \)).

Twenty-four patients were tested for serum HCV-RNA and all 24 were found to be positive. Genotype was established in 13 patients. All 13 patients were genotype 1, of whom 11 were genotype 1b, and two were 1a.

**Treatment, outcome and follow up**

All but four patients are still followed by the respective liver clinics. In the lag observation period following infection, the
patients (34.5%) cleared the hepatitis virus spontaneously, the majority within the first 12 weeks. Only one of the six incidentally diagnosed patients achieved spontaneous viral clearance.

Patients were then managed at the discretion of their physicians: 13 patients were treated, four declined therapy and two other patients had medical contraindications. Different interferon A and ribavirin treatment protocols were used (one patient did not receive ribavirin due to contraindications) for periods ranging from 3 months to a full year. Eight patients achieved viral clearance following treatment, with a sustained viral response. In two patients the treatment was discontinued because of insufficient response after 6 months and in three patients it was discontinued due to poor compliance. There was no correlation between demographic, laboratory or clinical parameters and outcome.

Discussion

The identification of the HCV in 1989 followed by the implementation of universal screening of blood products in 1991 has reduced transmission of the virus significantly.13 Nevertheless, new infections are still occurring and HCV infection is still a significant cause of liver disease worldwide.14 Despite important advancements, treatment is presently costly, only partly effective and associated with considerable adverse effects.

The key to further reducing disease burden is to understand the current modes of transmission and devise and implement appropriate preventive measures. However, most infections do not have an acute symptomatic phase and thus are only identified years after the infective event. This is true for all but a small proportion of infections, the exact size of which is yet to be defined.15 These infections manifest as an acute symptomatic episode and are identified closer to the actual transmission. Following this ‘tip of the iceberg’ may provide important clues as to how HCV is spread in the post-universal screening of blood products era.

Our first main finding is that the predominant mode of transmission in AHC patients (65.5%) was iatrogenic. Iatrogenic transmission is emerging as an important mode of transmission as demonstrated in several case series in which iatrogenic infection was responsible for 16–53% of cases.4,8,11,13,16–22 Therefore the present series represents the highest percentage of iatrogenic cases so far reported.

We have also shown that the group of patients with iatrogenic transmission is significantly older and with higher percentage of patients who are married or in monogamous relationships. This finding strengthens the conclusion that iatrogenic transmission is indeed the culprit, for it may be presumed that these patients are less prone to high risk behaviors such as IDU, high risk sexual behavior or tattooing. This is an important finding as it may be suggested that high risk behaviors may be under-reported and may bias the results. In addition the average period between the suspected iatrogenic infecting event and appearance of acute hepatitis was 8 weeks, which is in accordance with the estimated incubation period following infection with hepatitis C,15 thus further supporting the association with the iatrogenic events.

It is interesting to note that none of the cases in the present series occurred in clinical settings previously associated with a high risk of iatrogenic transmission such as hemodialysis or hospitalizations in hematology-oncology units,23–26 and exposure to blood products was found in only three patients.

However, we have found a predominant proportion of infections to be associated with relatively minor surgical procedures. In five patients there was no other procedure than the placement of peripheral intravenous access and subsequent intravenous treatment. These patients were hospitalized in surgical as well as medical departments and in seven different hospitals including small community hospitals, private clinics and university tertiary care centers. This, we believe, is an important finding as there is a growing body of evidence implicating patient-to-patient transmission as result of unsafe injection practices and equipment.1,3,8,23,24,27–31

Most of the procedures implicated as possible causes of transmission in this series have been previously described including abdominal surgery, gynecological and dental procedures as well as transmission associated with glucose finger stick testing in diabetic patients.4,8,10,16,20,21,32,33 We have not found previous reports linking HCV transmission with prostate biopsy. We did not find an association with endoscopic procedures in accordance with recent publications.34

The exact role of multidose vials, implicated in the past in iatrogenic transmission,3,28,35 is difficult to determine in this kind of investigation. All operated patients (7/19) received anesthetics, during which multidose vials are often used in Israel. However, some patients were likely exposed to multidose vials in other settings as well. For example they are used in saline flushing of intravenous catheters and heparin flushing of syringes for arterial blood gas measurements.

The second most common mode of transmission was IDU occurring in a little over 20% of the acute hepatitis patients. This may be due to changing illicit drugs administration habits (heroin snorting replacing intravenous injection) or more probably because of lower access to medical treatment making the diagnosis of an often mild symptomatic disease less frequent. This finding is in contrast to Swiss, French and Australian studies reporting an increasing incidence of hepatitis C in IDU despite needle exchange programs that were effective in curbing the spread of HIV.7,35,36 It has been suggested that this is due to the resistant nature of HCV, which may persist in and infect via drug paraphernalia, not strictly via contaminated needles.31

The other two modes of transmissions in our groups were sexual and occupational. Two of the patients with suspected sexual infection had additional possible modes of transmission. The possibility of infection due to a manicure in an endemic area may be as likely as sexual transmission. In agreement with several recent reports, the role of the sexual route of infection appears to be minor.5,37–42

Tattooing and piercing was not associated with AHC infection in this case series, possibly due to the low prevalence of these practices in Israel relative to other countries.41–47 Others have suggested that because of the small inoculum in tattoo-related transmission, it is less likely that a symptomatic acute phase will occur and thus may underestimate this mode of transmission in case series of diagnosed acute infections.48

Acute HCV infection load represented 0.75% of all new cases of HCV infection seen in the participating liver clinics during the study period. An Australian study based on a national notification system reported that newly acquired HCV infection comprised 2.8% of all HCV notifications for the study period (1997–2000).36 An Italian study reported the infection rate among the general population to be 1.4 cases per 10 000 person years,49
This group was not significantly different from other reported case series in the symptoms reported or clinical jaundice. Symptoms reported were generally mild and non-specific, which emphasizes the need for high awareness, especially in primary care, in light of the better treatment results with earlier initiation. Eight patients were completely asymptomatic and in six cases the diagnosis was incidental. Only one out of the asymptomatic patients achieved spontaneous viral clearance similar to previous reports linking asymptomatic acute phase with high chronic carrier state.

Laboratory values were similar to those reported in other case series of AHC patients. Most of the patients had an elevation of the serum ALT level to more than 10 times the upper limit of normal. Genotypes were 1a and 1b, which are the most common genotypes in Israel. When evaluating differences between the transmission groups, we did not find a significant difference between the iatrogenic and the IDU groups in the peak levels of ALT. However, the peak serum bilirubin levels in the iatrogenic group were higher than those found in the IDU group. This might result in patients from this group being more likely to present clinically.

The rate of spontaneous viral clearance in our patients with AHC was 34% (10 patients), the majority within 12 weeks, which is in accordance with previous reports that have shown rates of 15–50%. This supports the present recommended practice of delaying the onset of therapy in these patients for 12 weeks. Demographic, laboratory and clinical variables including mode of transmission did not have any significant effect on the rates of spontaneous viral clearance.

Viral clearance following the delayed treatment was achieved in 61.5% (8/13) of treated patients. This is lower than the 80–90% recently reported. However, it is hard to draw any conclusions from these data as the patients were treated with different regimens and after different lag periods from the acute event.

This study is limited by its retrospective nature, which did not allow thorough epidemiological investigations and may bias the results. Another significant limitation is the non-uniform manner by which the patients were treated, which limited the validity of the outcome results.

In summary, hepatitis C has not disappeared following the implementation of universal screening of blood products. New infections are still occurring, and not exclusively in IDU. Acute symptomatic hepatitis C may provide important insights regarding the spread of HCV. Evidence arising from different sources, including case-control studies, case series and epidemiological investigations of AHC outbreaks, is directing attention towards iatrogenic transmission. Infection control practices in all types of healthcare settings should be reviewed with a special focus on injection practices to prevent nosocomial transmission.

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