Acute Hepatitis in Israeli Travelers

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Background. Acute hepatitis is a well-described cause of morbidity and sporadic mortality in travelers. Data regarding the epidemiology of hepatitis in travelers are lacking. The aim of this study is to describe the epidemiology of acute viral hepatitis among travelers returning from tropical countries, with particular attention to enterically transmitted hepatitis.

Methods. This study is a prospective observational study of ill-returned travelers who presented at two travel medicine clinics in Israel between the years 1997 and 2012. Data of patients with acute hepatitis were summarized. Only travelers were included, immigrants and foreign workers were excluded.

Results. Among 4,970 Israeli travelers who were seen during this period, 49 (1%) were diagnosed with acute hepatitis. Among them, hepatitis E virus (HEV) was the etiology in 19 (39%) cases and hepatitis A virus (HAV) was the etiology in 13 (27%) cases, demonstrating that 65% of all cases were due to enterically transmitted hepatitis. Acquiring acute hepatitis B (two cases) or acute hepatitis C (one case) was uncommon (6.1%). In 27% of the cases, no diagnosis was determined. Fifty-five percent of cases were imported from the Indian subcontinent, with a predominance of HEV infection (84%). A significant male predominance was seen in all groups regardless of etiology. Pre-travel consultation was documented in only 7% of those with vaccine preventable hepatitis (hepatitis A & B) compared to 89% in those with hepatitis E.

Conclusions. Enterically transmitted hepatitis is the main causes of viral hepatitis among travelers. HEV is an emerging disease and has become the most common hepatitis among Israeli travelers. Although an efficacious vaccine has been developed, no licensed HEV vaccine is yet available. Although hepatitis A vaccine is highly efficacious, safe, and easily available, there is a stable number of HAV cases.

Acute hepatitis can be a severe disease among travelers, causing significant morbidity and occasionally also mortality. Among ill returning travelers, the estimated risk for acute and chronic hepatitis is approximately 8% of all travel-related illnesses. Data regarding acute hepatitis in travelers are scanty.

The main causes of acute hepatitis in travelers are viral and are divided into enterically transmitted and nonenterically transmitted. Hepatitis A virus (HAV) and hepatitis E virus (HEV) are enterically transmitted. Hepatitis B virus (HBV) is blood-borne and sexually transmitted. Hepatitis C virus (HCV) is blood-borne.

Gastrointestinal infections are the most frequent group of infections among travelers. They are divided into diarrheal diseases and nondiarrheal diseases that may include enterically transmitted hepatitis. Despite the available HAV vaccine, HAV consists of 16.7% of vaccine preventable diseases, with an incidence of 0.3% per month of travel. Data regarding changes in HAV incidence in travelers throughout the past two decades of available vaccine are lacking. HAV incidence might be declining; however, only limited data among travelers exist.

The other enterically transmitted hepatitis is HEV. Epidemics of hepatitis E are reported throughout the developing world, and in addition there are reported sporadic cases from endemic areas. Its major genotypes in developed countries are HEV1 that is endemic mainly in Asia and HEV2 that is endemic in Mexico and Africa. The main route of transmission of these genotypes is fecally contaminated water. No commercial HEV vaccine is available. It is an emerging disease worldwide, however its incidence among travelers is considered to be low.

In Israel the nationwide HBV universal vaccination program for infants was launched in 1992, and since then all infants receive three doses of recombinant HBV
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Table 1  Acute hepatitis cases by type

<table>
<thead>
<tr>
<th></th>
<th>Enterically transmitted</th>
<th>Nonenterically transmitted</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HAV</td>
<td>HEV</td>
<td>HBV</td>
<td>HCV</td>
<td>Unspecified hepatitis</td>
<td>Total</td>
</tr>
<tr>
<td>No.</td>
<td>13</td>
<td>19</td>
<td>2</td>
<td>1</td>
<td>14</td>
<td>49</td>
</tr>
<tr>
<td>No. males</td>
<td>8 (62%)</td>
<td>14 (74%)</td>
<td>2 (100%)</td>
<td>1 (100%)</td>
<td>10 (71%)</td>
<td>35 (71%)</td>
</tr>
<tr>
<td>Average age (SD)</td>
<td>34 (10.8)</td>
<td>38 (14)</td>
<td>52 (1.4)</td>
<td>51</td>
<td>36 (17.5)</td>
<td>37 (14.2)</td>
</tr>
<tr>
<td>Cases acquired in the Indian subcontinent</td>
<td>7 (54%)</td>
<td>16 (84%)</td>
<td>None</td>
<td>None</td>
<td>4 (29%)</td>
<td>27 (55%)</td>
</tr>
<tr>
<td>Pre-travel consultation</td>
<td>1 (8%)</td>
<td>17 (89%)</td>
<td>0</td>
<td>1</td>
<td>8 (57%)</td>
<td>27 (55%)</td>
</tr>
<tr>
<td>Median travel duration (days)</td>
<td>70 (2–1313)</td>
<td>129 (7–543)</td>
<td>332 (10–654)</td>
<td>348</td>
<td>91 (16–365)</td>
<td>104 (2–1313)</td>
</tr>
<tr>
<td>Mean travel duration (SD)</td>
<td>220 (360)</td>
<td>159 (145)</td>
<td>332 (455)</td>
<td>348</td>
<td>107 (113)</td>
<td>179 (238)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>9 (69%)</td>
<td>11 (57%)</td>
<td>2 (100%)</td>
<td>1 (100%)</td>
<td>9 (64%)</td>
<td>32 (65%)</td>
</tr>
</tbody>
</table>

vaccines at age 0, 1, and 6 months. HAV routine infant vaccination was initiated in 1999, and since then all infants receive two doses of the vaccine at the age of 18 and 24 months. Catch-up immunizations to travelers are given in pre-travel clinics to non-HAV, HBV-vaccinated travelers. As more travelers are immunized against these viruses, we raise a hypothesis that the proportion of these viruses among returning travelers may be decreasing gradually and the percentage of the nonvaccine preventable hepatitis, mainly HEV, may be rising. However, availability of diagnostic tools of HEV in many countries is lacking, and coupled with lack of awareness by many physicians to this particular diagnosis may result in significant underdiagnosis. In Israel, PCR testing for HEV is available since 1997.

The aim of this study is to describe the epidemiology of acute viral hepatitis among travelers returning from tropical countries, with particular attention to the enterically transmitted hepatitis.

Methods

Study design: An observational prospective cohort.

Patient population: Patients who presented with acute hepatitis between 1997 and 2012 to one of the two “posttravel” clinics in Israel—the Sheba Medical Center, Tel-Hashomer, Tel-Aviv or the Shaare Zedek Medical Center, Jerusalem, Israel. Only travelers were included. Immigrants and foreign workers were excluded.

Acute hepatitis was defined as an acute illness with any of the following signs or symptoms—fever, headache, malaise, anorexia, nausea, vomiting, diarrhea, and abdominal pain. Biologic signs include jaundice and/or serum alanine aminotransferase >2.5 times the upper limit.9

Screening for acute HAV was based on IgM anti-HAV enzyme-linked immunosorbent assays. HEV was diagnosed based on positive PCR for HEV-RNA or IgM or IgG serological studies (EIA, Abbott Laboratories, Abbott Park, IL, USA). HBV was diagnosed with anti-HBc IgM and HBsAg. HCV diagnosis was based on positive HCV recombinant immunoblot assay and PCR for HCV-RNA.

Unspecified hepatitis cases were defined as laboratory-confirmed acute hepatitis with a negative viral workup to the above-mentioned viruses and no other obvious etiology by the end of follow-up.

Statistical analysis: Descriptive statistics were used to present demographic data of the study population.

Results

Among 4,970 ill returning Israeli travelers who were seen during the years 1997 to 2012, 49 (1%) were diagnosed with acute hepatitis (Table 1). The enterically transmitted hepatitis is by far the most common group of hepatitis with a total of 32 cases (65%). This group of enterically transmitted hepatitis consisted of 19 cases of HEV (59%) and 13 cases of HAV (41%), equivalent to 39% and 27% of all acute hepatitis cases, respectively (Table 1).

Trends in HAV and HEV incidence throughout the years are shown in Figure 1. There is a stable prevalence of HAV throughout the years. HEV seems to be emerging since 2003.

The nonenterically transmitted cases (blood borne and sexually transmitted) were rare: two acute HBV cases and one acute HCV, compromising together 6.1% of the cohort. The remaining 14 cases (27%) were cases of acute unspecified hepatitis.

All the cohort cases are predominantly in males without significant differences between the groups (Table 1). Median and mean travel duration was long in all hepatitis groups and reached a total of 104 and 179 days, respectively.

Sixty-nine percent of enterically transmitted hepatitis cases were imported from the Indian subcontinent, with predominance in the HEV group (84%). The two HBV cases were acquired in Thailand due to unprotected sex. The HCV case was acquired several weeks after a blood transfusion in Congo. Among the unspecified acute hepatitis group, 29% of the cases were imported from the Indian subcontinent.

Pre-travel consultation was encountered in only 7% of vaccine preventable hepatitis cases (HAV + HBV) while 90% of HEV + HCV cases, which are not vaccine preventable, did visit a pre-travel clinic. Among the
unspecified hepatitis cases pre-travel consultation rate was 57%.

Among all the cohort 32 patients (65%) required hospitalization. In all subgroups more than half of the cases required hospitalization (Table 1). Although as mentioned the morbidity was substantial, there were no cases of mortality.

Discussion

In this cohort, 1% of ill returning Israeli travelers were diagnosed with acute hepatitis. Acute hepatitis is a well-described cause of morbidity and occasionally mortality in travelers. Its main causes in travelers are viral and are divided into enterically transmitted and nonenterically transmitted (blood borne and sexually transmitted).

Travelers to the developing world are at high risk for enterically transmitted hepatitis as it spreads by contaminated food and water. Indeed, during our study period 65% of all acute hepatitis cases were enterically transmitted. Interestingly, in 59% of these cases the etiology was HEV (39% of the total cohort; this may imply that HEV is an emerging disease and is becoming the most common hepatitis among Israeli travelers.

Eighty-four percent of HEV cases were imported from the Indian subcontinent. India is hyperendemic...
for HEV, which is the most common cause of acute sporadic hepatitis in India, and has also been associated with large-scale outbreaks. Most cases are transmitted through contaminated water, owing the very poor sanitation and partial sewage system. The Indian subcontinent is a very popular travel destination among Israeli travelers, mainly India. Throughout a decade and a half, the number of Israeli tourists to India tripled from 14,806 tourists at 1995 to 43,456 at 2010 (World Tourist Organization). The increasing numbers of travelers, along with the endemicity of India to HEV, the awareness to the diagnosis in our travel medical centers and availability of diagnostic tools are probably responsible for this emergence of HEV.

In this report, most HEV cases were imported from the Indian subcontinent. This is consistent with our previous report, more than a decade ago. We then reported five cases which were all acquired in the Indian subcontinent. Our current results show the predominance and emergence of HEV among Israeli travelers. On the basis of our data (with a limitation that the data are not national, thus do not include all cases), throughout the study period 16 HEV cases were acquired in the Indian subcontinent and the number of Israeli travelers to this destination was approximately 500,000 tourists. Therefore, the estimated risk of acquiring HEV in the Indian subcontinent, which is highly endemic, is at least 3.2/100,000 travelers. This may explain the recent Dutch report that found no seroconversion among 1,270 travelers; moreover, most of them did not travel to the Indian subcontinent.

Although two efficacious vaccines were developed, no approved HEV vaccine exists yet for travelers. Efforts to develop an efficacious HEV vaccine for travelers are warranted, with a special emphasis on the need to protect young female travelers who are potentially reproductive. HAV comprised 41% of the enterically transmitted hepatitis in our cohort. Its prevalence throughout the years seems stable, and this is despite a safe and available vaccine. Although the HAV vaccine exists in Israel since 1995, data regarding the prevalence of the disease in travelers since its introduction are scanty. In travelers, Scott et al. compared the prevaccination era (1993–1998) to the postvaccination era (1999–2003) and described a reduction from 24 cases to 12 cases of acute HAV in foreigners in Nepal. No further data are available. Twelve of our 13 HAV cases (92%) did not encounter pre-travel consultation and therefore were at substantial risk for the infection. In 1999 Israel was the first country in the world that implemented a national program for HAV vaccination in infancy, with a dramatic decrease in the endemicity of the disease. Our patients were born in the pre-HAV vaccination era and did not encounter pre-travel consultation and therefore are not vaccinated. Further follow-up is needed to determine whether this program will change the epidemiology among Israeli travelers. Meanwhile, better educational efforts should be implemented to improve the awareness of pre-travel vaccinations.

Acute HBV was rare, occurring in two cases (4%), both did not receive pre-travel consultation and vaccinations. Acute HBV risk in travelers to HBV endemic countries run a much lower incidence than expected by behavioral studies. Behavioral studies in travelers suggest that 33% to 76% of all travelers to endemic areas are at risk for acute HBV infection. Only 30% to 46% are vaccinated against HBV. Despite this discrepancy, HBV may present substantial morbidity to the individual traveler, and can be an important source of imported hepatitis into the origin countries of these travelers. Therefore, HBV vaccination is an essential recommendation for at risk travelers.

HCV manifesting as a clinically acute disease is a rare phenomenon. Most cases are confined to laboratory hepatitis. The chronic phase of the disease is usually found years after the exposure and is hard to trace back to any travel history. In the case described in our cohort, the HCV case was acquired several weeks after a blood transfusion in Congo, given due to severe falciparum malaria with significant anemia.

A total of 14 cases of acute hepatitis remained unspecified. Only four of these cases (29%) were imported from the Indian subcontinent. This is in contrast to the acute HAV group with 16 (84%) cases imported from the Indian subcontinent. This difference is statistically significant (p = 0.003), and allows us to presume that the chances of missed HEV cases in the unspecified group are low. Because acute HAV, HBV, and HCV are easily diagnosed, we believe that the unspecified acute hepatitis cases are a different etiologic group.

In all etiology groups, travel duration was long with a total median travel duration of 104 days. In a previous publication from our clinics the median travel duration of Israeli travelers throughout this study period was between 30 to 45 days. These findings may show that the risk of acquiring acute hepatitis is higher among long-term travelers. However, as our data are limited to Israeli travelers and further data is lacking, more evidence is required to confirm this observation.

The main limitation of this study is the distinct travel patterns of Israeli travelers that may be different from those traveling from other countries such as those in Western Europe or North America. Therefore, further studies are needed before applying our results to other traveler populations.

In conclusion, acute hepatitis possesses a threat to travelers. In this cohort, 1% of ill Israeli travelers were diagnosed with acute hepatitis. Enterically transmitted hepatitis is the main cause of viral hepatitis among these travelers. HEV is an emerging disease and has become the most common hepatitis among Israeli travelers. Although an efficacious vaccine has been developed, licensed HEV vaccine is not yet available. Efforts to develop an efficacious HEV vaccine for travelers are warranted. Despite the available HAV vaccine, there is a steady prevalence of HAV cases. Further follow-up
is needed to determine whether the Israeli national program for HAV vaccination in infancy will affect the epidemiology of hepatitis among travelers.

Declaration of Interest
The authors state they have no conflicts of interest to declare.

References