Hepatitis A outbreak in men who have sex with men (MSM) in Brescia (Northern Italy), July 2016-July 2017

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Summary

Since June 2016, an outbreak of hepatitis A has been reported in Europe. Here we report the HAV outbreak in Brescia (Northern Italy) from July 2016 to July 2017. We actively recorded all HAV cases defined by detection of HAV IgM antibodies in serum. Data on sexual behaviour, travel attitudes, concomitant sexually transmitted diseases (STDs), clinical presentation and laboratory results were collected. Forty-two confirmed cases were recorded: 25 (60%) were MSM and reported sexual contact at risk of STDs. Compared to 2015 and the first half of 2016, when only three hepatitis A cases were recorded, in the 12 months in question the number of cases rose 14-fold. Among 25 MSM, 14 were HIV-infected.

Hepatitis A is usually a self-limiting disease, but it could be more serious in the case of HIV co-infection, immunosuppression and chronic hepatitis. HAV infection has a high outbreak potential in MSM because of more common oro-anal practices compared to HS, a high interconnectedness global network, chemsex practices and a new tendency to travel abroad to attend group sex events. In our experience, most cases occurred in MSM and 56% of them were HIV-infected, suggesting the need to promote active screening, immunization and education in this population.

Keywords: hepatitis A, MSM, HIV infection

Introduction

Hepatitis A is an acute infection caused by hepatitis A virus (HAV). Spread is most commonly from person to person (including sexual contact), but it can be transmitted by faecal-oral route through contaminated food or water, among injection drug users and rarely by infected blood products. HAV infection is usually asymptomatic in children. In adults, after a silent incubation period of 15-50 days, onset is usually gradual with aspecific, flulike symptoms like mild fever, abdominal discomfort, fatigue, anorexia. One to 7 days after jaundice onset, hyperchromic urines and acholic faeces can appear. Normally, HAV infection is self limiting, but rarely it can lead to fulminant hepatitis and liver transplantation. Among several risk factors for poor outcome of hepatitis A the more common are: age >60 years, chronic liver disease, hepatitis B and/or C, HIV/AIDS, immunosuppressive therapy.

The maximum infectivity is during the second half of asymptomatic incubation period until first week of jaundice. To confirm the diagnosis, increased ALT and positive anti-HAV IgM are needed. No specific treatment exists. Prevention with inactivated vaccination, strict control measures, enforced hygiene and contact tracing are therefore the only way to reduce the burden of HAV infection [1].

Men who have sex with men (MSM) have greater risk to be infected and to transmit HAV because
of greater number of sexual partners, longer duration of sexual activity, frequent oral-anal or digital-anal sex [2]. Concomitant sexually transmitted diseases (STDs) or HIV infection are additional risk factors [3].

In the last few years several outbreaks have been reported in MSM. In Europe, the last outbreak involving MSM occurred between 2008 and 2009 [4-6]. An outbreak of HAV infection in MSM also occurred in our Clinic in 2009 [7].

Since June 2016, ECDC (European Centre for Disease Prevention and Control) described an outbreak of HAV infection among MSM [8]. Investigators identified three epidemiological clusters based on genetic sequencing of HAV: VRD_521_2016 with most cases reported in Spain, RIVM-HAV16-090 mainly in United Kingdom and V16-25801 [9-11]. Last ECDC update about notified HAV cases from January 2017 to August 2017, reports more than 7300 cases in 15 European countries. In Italy, from August 2016 to April 2017, 1410 cases were identified, a ten-fold increase compared to 2015 [12]. Here we describe our single centre report of ongoing HAV outbreak.

**PATIENTS AND METHODS**

We actively recorded all HAV cases admitted at University Department of Infectious and Tropical Diseases, University of Brescia and Spedali Civili General Hospital, Brescia (Northern Italy) from 1st July 2016 to 31st July 2017.

Patients were admitted to Hospital in order to guarantee contact isolation and to monitor coagulation profile, transaminases and bilirubin trends. A confirmed case was defined by detection of hepatitis A-specific IgM antibodies in serum and in 83.3% hepatitis A-specific IgG were present (35/42, IgG-negative in 2/42, data not available for 5/24 patients).

Median age of patients was 37 years old (range 17-65) and 37/42 (88%) were men. The main criteria to discharge patients were clinical improvement, decrease of ALT under 1000 U/L and decline in bilirubin trend. The interval between the onset of symptoms and the serological diagnosis, as well as the total of days of hospitalization were recorded.

We investigated about HIV infection and other concomitant STDs like hepatitis B, syphilis, papilloma virus infection and chlamydial or gonococcal proctitis/urethritis. We asked patient about their medical history and we performed specific tests based on reported symptoms at time of admission. Every patient on this study was tested for HIV, HBV, HCV co-infection.

Each patient was asked to declare his sexual orientation and to identify possible risk factors for HAV transmission like recent travel in HAV endemic region, food borne sources or sexual ones. Destinations of recent travels were investigated both in people with foodborne risk and in MSM. We investigated if MSM patients had a recent sexual contact with a partner who received diagnosis of HAV afterwards.

We also retrospectively evaluated all HAV cases since January 2015 in order to confirm the ongoing outbreak and to compare the number of cases recorded in the past.

In conclusion, we assessed the number of HIV patients regularly (at least 1 visit per year) attending our Outpatient Clinic who are at risk for HAV acquisition because of lack of a correct vaccination campaign.

Informed consent has been obtained from persons whose details are described.

**RESULTS**

Between July 2016 and July 2017, forty-two confirmed cases of HAV infection were admitted at University Department of Infectious and Tropical Diseases, University of Brescia and Spedali Civili General Hospital, Brescia (Northern Italy). All cases were confirmed by detection of hepatitis A-specific IgM antibodies in serum and in 83.3% hepatitis A-specific IgG were present (35/42, IgG-negative in 2/42, data not available for 5/24 patients).

Median age of patients was 37 years old (range 17-65) and 37/42 (88%) were men. Twenty-five men (60%) identified themselves as
MSM and all of them reported sexual contacts at risk for STDs. Four men identified themselves as heterosexual (HS), but they don’t report any risk factor, neither sexual or foodborne. The remaining patients were 5 HS women and 5 HS men, whose symptoms started as soon as they returned from a travel in region with high to intermediate HAV endemicity such as India, Egypt, Ethiopia and South Italy.

Among others, 2 HS men usually consumed uncooked fish and 1 HS woman didn’t confirm any clear risk factor.

Compared to HAV cases between January 2015 and first half of 2016, when only 3 hepatitis A were recorded (one woman and two HS men with a clear foodborne acquisition), in the last 12 months, between July 2016 and July 2017, the number of cases raised by 14 times (all cases considered).

Demographic data and patient characteristics are summarized in Table 1. Figure 1 and Figure 2 describe the number of cases month by month.

**MSM cohort**
Considering only MSM patients, 10/25 (40%) reported a recent (<12 months) travel mainly in European destination and the majority of them attended sexual venues during these travels. Destinations were the following: Spain, Greece, France, Germany, Finland, Egypt, and Israel. Moreover, 3/25 (12%) reported a recent sexual intercourse with a partner who afterwards was diagnosed with hepatitis A.

Fifty-six percent (14/25) were HIV-infected and 2 were diagnosed with others STDs (gonococcal and chlamydial proctitis). In MSM population, median time between the onset of symptoms and the serological diagnosis was 9 days (IQR 7-12).

Table 1 - Characteristics of HAV infected patients (n=42).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MSM</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, n (%)</td>
<td>25 (60%)</td>
<td>17 (40%)</td>
</tr>
<tr>
<td>Age, yr, median (range)</td>
<td>38 (24-53)</td>
<td>35 (17-65)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>25 (100)</td>
<td>12 (71)</td>
</tr>
<tr>
<td>Foreign nationality, n (%)</td>
<td>1 (4)b</td>
<td>5 (29)c</td>
</tr>
<tr>
<td>Risk factor declared</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- sexual n (%)</td>
<td>25 (100)</td>
<td>0</td>
</tr>
<tr>
<td>- foodborne n (%)</td>
<td>0</td>
<td>12 (71)d</td>
</tr>
<tr>
<td>Travels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- HAV endemic countries</td>
<td>10 (40)</td>
<td>8 (47)</td>
</tr>
<tr>
<td>- non HAV endemic countries</td>
<td>24 (96)</td>
<td>6 (25)</td>
</tr>
<tr>
<td>HIV serostatus, n (%)</td>
<td>14 (56)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Other STDs, n (%)</td>
<td>2 (12)</td>
<td>0</td>
</tr>
<tr>
<td>ALT peak (U/L), median (IQR)</td>
<td>2907 (2387-3560)</td>
<td>2050 (1587-3091)</td>
</tr>
<tr>
<td>Total bilirubin peak (mg/dl), median (IQR)</td>
<td>8.22 (5.94-10.42)</td>
<td>7.23 (5.69-9.6)</td>
</tr>
<tr>
<td>INR peak, median (IQR)</td>
<td>1.2 (1.1-1.3)</td>
<td>1.3 (1.2-1.45)</td>
</tr>
<tr>
<td>Hospitalization, no. of days (IQR)</td>
<td>9 (7-10)</td>
<td>9 (7.5-10)</td>
</tr>
<tr>
<td>Diagnosis delay, no. of days (IQR)</td>
<td>9 (7-12)</td>
<td>8 (6.5-17.5)</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
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<tr>
<td>- gastrointestinal n (%)</td>
<td>22 (88)</td>
<td>16 (94)</td>
</tr>
<tr>
<td>- acholic faeces n (%)</td>
<td>11 (44)</td>
<td>5 (29)</td>
</tr>
<tr>
<td>- hyperchromic urines n (%)</td>
<td>16 (64)</td>
<td>8 (47)</td>
</tr>
<tr>
<td>- fever n (%)</td>
<td>15 (60)</td>
<td>11 (65)</td>
</tr>
<tr>
<td>- jaundice n (%)</td>
<td>13 (52)</td>
<td>5 (29)</td>
</tr>
</tbody>
</table>

*a* percentage calculated on 42 patients admitted.

*b* patient from Slovenia.

*d* 4 patients from India and 1 from Colombia.

*e* HS don’t report any risk factor.
The median length of hospitalization was 9 days (IQR 7-10). Median value of ALT peak during hospitalization was 2907 U/L (IQR 2387-3560), bilirubin 8.22 mg/dl (IQR 5.94-10.42) and INR 1.2 (IQR 1.1-1.1).

Characteristics of MSM cohort are summarized in Table 1. No difference was observed in peak ALT between HIV-infected and non-HIV-infected patients. Among HIV-infected MSM, two were readmitted to hospital approximately 40 days after discharge because of a novel ALT increase. In both cases, other possible causes of hepatitis were excluded and they were finally discharged with diagnosis of hepatitis A relapse.

In our Outpatient Clinic, among 3736 HIV infected patients on regular follow up, only 2448 (66%) have been tested for HAV serostatus. 1446/2448 (59%) were IgG positive, then about 40% of patients are at risk of HAV infection. In case of HAV IgG positivity, we were not able to distinguish who received vaccination and who faced previous hepatitis A infection.
DISCUSSION

In line with European reports, this study shows a large and long-lasting (≥12 months) outbreak of hepatitis A occurred in Brescia (Northern Italy) between July 2016 and July 2017, involving a high proportion of MSM (60%).

The last epidemiological update of ECDC, published on 1 August 2017, reported that in Italy 85.9% of the 1410 cases reported between August 2016 to April 2017 were men, and 61% were MSM, exactly as described in our cohort. In Europe, this represents an increase by 10 times compared with 2015 (142 cases notified) when MSM accounted only for 8% of the cases [12].

Moreover, the percentage of MSM infected could be underestimated because of reluctance to admit sexual orientation. For example, in our cohort, 4 men identified themselves as HS, but they didn’t report any risk factor, neither sexual or foodborne. Many different reasons could explain the large circulation of HAV seen in the last months among MSM: more common oro-anal practices compared to HS, high interconnectedness global network, chemsex practices and a new tendency to travelling abroad to attend group sex events.

Hepatitis A belong to STDs and the recurrent outbreaks reported in last few years suggest an analogous trend of other sexually transmitted infections as HPV, syphilis, chlamydial and gonococcal infections. But, in contrast to HAV infection, these infections are often under-diagnosed because of more indolent onset. Therefore, ongoing HAV outbreak could be an opportunity to rise surveillance also on other STDs.

Same travel destinations reported by HAV-infected MSM in our study were reported by other authors at the beginning of ongoing outbreak and these data highlight the idea of an interconnectedness MSM European network [9-11].

The beginning of the ongoing outbreak was attributed to EuroPride that took place in Amsterdam on August 2016. Secondary transmission related to this event continued until springtime, as confirmed by sequencing of circulating strains [13]. Moreover, high proportion (56%) of MSM involved in our cohort were HIV-infected. Gallego et al. demonstrated that co-infection prolongs HAV viremia, with a potential increase in the spread of infection [14]. Even if only a little sample size was analysed, authors also observed that HAV infection increased the risk of HIV transmission.

Even if there was no statistically difference in transaminase peak values between HIV co-infected and non-HIV individuals in our cohort, two HIV-infected patients presented hepatitis A recrudescence approximately 40 days after discharge. No similar episodes were observed among non-HIV individuals.

HAV doesn’t seem to cause more severe clinical illness in HIV-infected individuals, but the prolonged durations of a higher HAV viremia may possibly slow transaminases reduction and cause hepatitis recrudescence. Further studies are needed to confirm this hypothesis.

Combination antiretroviral therapy (cART) interruption is necessary to manage severe liver disease in HIV-infected patients, with potential consequences, such as reduced viral suppression when cART is re instituted [15, 16].

In the vast majority of cases, HIV infected patients are regularly followed in outpatient setting and then, an efficacious campaign of vaccination and prevention could be more feasible. By contrast we observed that in our Outpatient Clinic up to 34% of regularly followed HIV infected patients haven’t been tested for HAV serostatus.

Among tested patients, only 60% were IgG positive and, therefore, almost 40% of this population is now at risk to acquire hepatitis A virus. Besides, this data is surely underestimated because of the amount of not tested individuals.

Bisexual attitude of some MSM could explain the increasing number of HAV infected HS woman seen during this outbreak who hasn’t a clear foodborne exposure. Further epidemiologic analysis is needed to explore this hypothesis.

No specific treatment is available for hepatitis A. Even if it is usually a self-limiting disease and clinical improvement is complete in few weeks, it could be more serious in some categories of patients. Vaccination should be mandatory in MSM, particularly in those with chronic liver disease, hepatitis B and/or C, on immunosuppressive therapy and those who inject drugs, because of high risk of severe outcome as a result of hepatitis A.

In last months, Italy, Austria, Denmark, Greece, Malta, Portugal and Spain have faced hepatitis A vaccine shortages with consequent spread of infection between people which could have access to active prevention [17].
Information on vaccine and preventive hygiene measures should be included in health promotion programmes targeting MSM, particularly at sex venues.

MSM living or travelling in areas where there are ongoing HAV outbreaks should be prioritised for vaccination and provision of vaccination at Pride festival venues could also be considered.

Personal hygiene is pivotal to prevent transmission. Washing hands and genital areas before and after sex, using of dental dams for oral-anal sex and latex gloves during fingering can offer protection against HAV infection.

Conflicts of interest
None

REFERENCES