The impact of HIV infection and MSM status on hepatitis A infection: the experience of two tertiary centres in Northern Italy during the 2017 outbreak and in the 2009-2016 period.

Andrea Lombardi[1,3], Roberto Rossotti[4], Maria Cristina Moioli[4], Marco Merli[4], Pietro Valsecchi[3], Valentina Zuccaro[1], Marco Vecchia[1,3], Cecilia Grecchi[1,3], Savino F.A. Patruno[1], Paolo Sacchi[1], Massimiliano Fabbiani[1], Massimo Puoti[4], Raffaele Bruno[1,2]

[1]*Infectious Diseases Unit, IRCCS "San Matteo", Pavia, Italy;* [2]*Department of Medical, Surgical, Diagnostic and Paediatric Science, University of Pavia, Pavia, Italy;* [3]*Department of Internal Medicine and Therapeutics, University of Pavia, Italy;* [4]*ASST Grande Ospedale Metropolitano Niguarda, Infectious Diseases Department, Milano, Italy.*

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Address for correspondence: Raffaele Bruno, Department of Infectious Diseases, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Via Taramelli, 5, 27100 Pavia, Italy. raffaele.bruno@unipv.it

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ABSTRACT

Background Hepatitis A is a self-limiting infection representing the most common cause of viral hepatitis worldwide. Despite being a low incidence region, in the European Union an increasing number of cases have been reported since summer 2016, resulting in a large outbreak in 2017, involving mainly men who have sex with men (MSM). Some reports described a different clinical course of HAV in patients infected by human immunodeficiency virus (HIV) or MSM.

Objectives We consecutively collected all the hospitalized cases of hepatitis A referred to two tertiary centres in Northern Italy in 2017 and retrospectively analysed the electronic records of the 2009-2016 period (pre-2017). We evaluated demographics data, risk factors, comorbidities and laboratory results to see if MSM status or HIV infection influenced the disease.

Results Overall 117 cases were identified in 2017: 107 (91%) were male, 78 reported themselves as MSM (66%) and 17 (14.5%) were infected by HIV. For the pre-2017 period 48 cases were reported: 29 (60%) were male and 3 (6.2%) were infected by HIV. After stratification for HIV infection, MSM status and occurrence period, no differences were found in AST, ALT, GGT, ALP, and bilirubin values, hospitalization length, HIV viral load and CD4+ cells count. HIV positive patients presented a higher number of patients with INR> 1.5 at admission.

Conclusions MSM status and HIV infection did not affect neither the clinical course nor the severity of hepatitis A.

Keywords: hepatitis A; HIV; MSM.

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INTRODUCTION

Hepatitis A is usually a self-limiting disease caused by hepatitis A virus (HAV) infection. HAV is transmitted primarily by the oral-faecal route; additionally, sexual transmission, especially between men who have sex with men (MSM), and parenteral transmission through infected syringes and blood components, have been documented.[1]

Most of the European Union (EU) is considered a region with very low HAV endemicity although some geographical differences exist. As a consequence, susceptibility to the infection is high. In 2014, 13,678 cases of hepatitis A were reported in Europe; most of them were reported in children between the age of 5 and 14 years.[2]

Since June 2016, an increased number of HAV infections has been reported all over Europe. Clusters of the outbreak were initially described in England, Amsterdam (The Netherlands) and Berlin (Germany) and they primarily involved MSM. Three HAV genotype IA strains (VRD_521_2016, RIVM-HAV16-090, and V16-25801) are considered responsible for the outbreak in this group of individuals. Overall, based on the March 2018 update provided by the European Centre for Disease Prevention and Control, since January 2017 21,230 hepatitis A laboratory-confirmed cases were notified by 26 European countries and 4,101 of them were outbreak-confirmed cases.

Some publications suggest different clinical course and disease severity when Hepatitis A occurs in MSM or HIV infected patients [3–5]. The aim of this study is to analyse the demographics, risk factors, comorbidities and laboratory results of hospitalized cases of acute hepatitis A in two tertiary level hospitals in Northern Italy (Fondazione IRCCS Policlinico San Matteo Pavia and Milan Niguarda Hospital) in 2017 and in the 2009-2016 period, to evaluate if HIV infection or MSM status can affect the clinical course of the disease.

PATIENTS AND METHODS

Case ascertainment and clinical/epidemiological investigation

Hepatitis A cases consecutively admitted to the Infectious Diseases Units of IRCCS Policlinico "San Matteo", Pavia, and of ASST Grande Ospedale Metropolitano "Niguarda", Milan, from January 01 to December 31, 2017 were collected (2017 Group). A retrospective analysis of hospital discharge archives for acute hepatitis A was performed based on electronic records from January 01, 2009 to December 31, 2016 (Pre-2017 Group). A case was defined by the presence of symptoms compatible with viral hepatitis, blood tests with an increase in alanine aminotransferase (ALT) and the detection of hepatitis A-specific IgM antibodies. For every patient data about presumptive way of infection, biochemical parameters (ALT; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, γ-glutamyl transpeptidase; bilirubin; INR, international normalized ratio), co-infection with other hepatotropic (hepatitis B virus, HBV; hepatitis C virus, HCV; hepatitis E virus, HEV) and with human immunodeficiency virus (HIV) were recorded. The presumptive way of infection was determined through an interview with the patient. Patient's interview was performed at admission. All the sexual intercourses performed without the use of a condom were considered at risk for HAV transmission. Consumption of undercooked or raw food, in the thirty day before admission, was considered at risk for HAV transmission.

The study protocol, in accordance with the ethical guidelines of the 1975 Declaration of Helsinki, was approved by the Ethical Committee of both hospitals.

Statistical Analyses

Statistical analyses were performed with GraphPad Prism 6 (GraphPad Inc, USA). Continuous variables were reported as median and interquartile range (IQR), categorical variables were reported as absolute and relative frequencies. Groups were compared using the

Kruskal–Wallis H-test, Mann–Whitney U-test and Fisher's exact test as appropriate. Significance was established as a 2- sided P value of <.05.

RESULTS

Description of Cases: 2017 versus pre-2017

We identified 117 cases of hepatitis A in the 2017 period and 48 in the pre-2017 period. Table 1 reports demographics data, risk factors, comorbidities and laboratory results recorded at admission and discharge, divided in 2017 series (including MSM, non-MSM, HIV-infected and non-HIV-infected) and pre-2017 series (including HIV-infected patients and non-HIV-infected patients). The 2017 group showed a significantly higher proportion of male compared to the pre-2017 group; male to female ratio was 11:1 and 2.5:1 in the 2017 and pre-2017 group ($p<0.001$), respectively. The main risk factors were sexual intercourses (68%) in the 2017 group and consumption of contaminated food/water (62.5%) in the pre-2017 group. It is relevant to note that in the 2017 group, among the patients who acquired the infection through sexual intercourse, the majority of the patients identified themselves as MSM (97.5%) and only in 2 cases (2.5%) the presumptive risk factor was a heterosexual intercourse ($p<0.001$). The mean hospitalization length was 7 days in the 2017 group and 11 days in the pre-2017 group ($p>0.05$). None of the patients developed acute liver failure nor died. Comparing the two groups, no differences were found in AST, ALT, GGT, ALP, INR and bilirubin values.

Regarding HIV infected patients, all of them where already aware of their infection and all were receiving combination anti-retroviral therapy (cART). HIV viral load was undetectable in the 2017 group and 605 UI/mL in the pre-2017 group ($p=0.0760$), the mean CD4+ count was 674 cells/mL in the 2017 group and 485 cells/mL in the pre-2017 group ($p=0.2574$). In

the 2017 group HIV prevalence was higher among MSM as compared to non-MSM patients, 19% versus 5%, but without reaching statistical significance (p=0.051).

Other subgroups Analyses

The 2017 Group was stratified according to the MSM status, and demographic, clinical and laboratory data were compared. Overall, no statistically significant differences were found between MSM and non-MSM patients in terms of age and length of hospitalization. As expected, males were significantly more represented in the 2017 MSM group. No differences were found between MSM and non-MSM regarding AST, ALT, bilirubin, ALP, GGT and INR.

All cases were also stratified according to concomitant HIV infection. No difference was found between 2017 HIV-infected, 2017 non-HIV-infected, pre-2017 HIV-infected and pre-2017 non-HIV-infected patients regarding biochemistry parameters apart for hepatitis severity, identified as an admission INR > 1.5. Indeed, the 2017 HIV-infected group presented a higher number of patients with severe hepatitis compared to the 2017 non-HIV-infected (<0.0001).

DISCUSSION

The leading role played by the MSM population in the 2017 hepatitis A outbreak in the European Union was clearly highlighted, with reports from different European cities showing the high prevalence and the early appearance of the infection in this population in the late months of 2016. Our data corroborates these results, with MSM representing most of the infected patients in the 2017 Group (66%) versus the pre-2017 Group (4%). It is difficult to find out how many cases in the non-MSM population were related to a spill over of the virus from the MSM population and how many were due to the endemic HAV circulation.

Unfortunately, in our cohort samples of plasma were not collected for HAV genotyping and therefore it was not possible to evaluate the strains involved. It must be underlined that usually HAV infection is a benign, self-limiting, disease and patients usually do not need to be hospitalized. The fact that HIV infected patients are usually followed at outpatient clinic, with serial biochemistry evaluation, whereas HAV in HIV negative patients is probably acknowledged only in those cases who are symptomatic, could have led to an overestimation of disease severity and relevance in this latter population.

We evaluated if the MSM population presented some peculiar features in terms of disease severity and clinical course: contrarywise to the findings of Chen et al.[4] no differences were found. It might be objected that the general benign course of the disease observed in our cohort could be related to the presence of few patents with underlying liver disease. However, a recent systematic review of the literature has shown a prevalence of HBsAg and HCV-Ab of 0.0%-1.4% and 0.0-4.7%, respectively among European MSM [6]. Our data, showing a HBsAg prevalence of 1.3% and an HCV RNA prevalence of 0% among MSM are comparable with these. Thus, it can be inferred that our results could be applied to the general population: MSM status does not have an impact on acute hepatitis A disease. Obviously, careful monitoring of patients with underlying liver disease, irrespective of their MSM status, must be maintained.

We also assessed the impact of HIV infection on the disease. The only difference observed in biochemical parameters values between HIV infected and HIV non-infected patients, was hepatitis severity at admission between the 2017 non-HIV-infected patients versus the 2017 HIV-infected patients. A higher disease severity can be partially explained in this latter group considering the exposure to hepatotoxic drugs and the concomitant infection by hepatotropic viruses, which share transmission ways with HIV. Nevertheless, hospitalization length and INR at discharge did not differ between the two groups, meaning that disease course was

comparable among the two groups. It must be noted that Ida et al.[5] have previously shown higher HAV viral load, longer HAV viremia, lower elevation in ALT and higher elevation in ALP in a Japanese cohort of HIV-1 infected patients with acute HAV infection. These differences can probably be explained by the different viro-immunological and therapeutic characteristics of the patients involved. In the Japanese study dated 2002, only 60% of the patients were receiving cART, the median HIV viral load was 3300 UI/mL and the mean CD4+ count was 448 cell/mL. Instead, in our cohort all the patients were receiving cART, and achieved a good immunologic and virologic condition. Similar conclusion can be drawn from the more recent work of Lee et al [3], where the mean CD4+ count was 483 cell/mL and viral suppression was achieved only in 68.6% of the patients. It might be argued that the clinical features of acute HAV infection in HIV-positive patients who achieved optimal viro-immunological control are similar to those in HIV-negative individuals. Nevertheless, cART regimes used in 2017, with a lower potential of hepatotoxicity compared to the drugs that were in clinical practice in the early 2000s, could represent a confounding factor in this issue. Additionally, the small number of HIV infected patients included in the study could have affected the statistical power of the analyses.

Our data suggest that HIV infection and HAV acquisition through MSM sexual intercourse have no impact on the acute hepatitis clinical course: thus, HIV infected patients with a well-controlled disease and MSM patients do not require special monitoring during hospitalisation.

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Table 1. Characteristics of patients hospitalized for hepatitis A. Data are subdivided in: 2017 and 2009-2016 (pre-2017) period cases, 2017 MSM and 2017 non-MSM cases, HIV 2017 and non-HIV 2017 cases and HIV pre-2017 and non-HIV pre-2017 cases.

	Total 2017 (n=117)	**Total pre-2017 (n=48)**	**p**	**MSM 2017 (n=78)**	**Non-MSM 2017 (n=39)**	**p**	**HIV 2017 (n=17)**	**Non-HIV 2017 (n=100)**	**p**	**HIV pre-2017 (n=3)**	**Non-HIV pre-2017 (n=45)**	**p**
Age, median (range)	34 (20-67)	33 (12-52)	>0.05	34 (20-67)	32 (21-63)	>0.05	35 (25-55)	34 (20-67)	>0.05	31 (27-36)	33 (12-52)	>0.05
Male gender, n (%)	107 (91)	29 (60)	**< 0.0001**	78 (100)	29 (91)	**< 0.0001**	17 (100)	90 (90)	>0.05	3 (100)	26 (58)	>0.05
Foreign born, n (%)	10 (8.5)	7 (14.5)	>0.05	8 (10.2)	2 (5.1)	>0.05	3 (17.6)	7 (7)	>0.05	0	7 (15.5)	>0.05
Risk factor												
- sexual intercourses, n (%)	80 (68)	2 (4)	**< 0.0001**	78 (100)	2 (5)	-	15 (88)	65 (65)	>0.05	0	2 (4)	>0.05
- foodborne, n (%)	29 (25)	30 (62.5)	**< 0.0001**	0	20 (51)	-	0	30 (30)	**0.0059**	1 (33)	29 (64)	>0.05
- drugs use, n (%)	3 (2)	0	>0.05	0	3 (2)	-	2 (12)	1 (1)	>0.05	0	0	-
- unknown, n (%)	4 (3)	16 (33)	-	0	4 (10)	-	0	4 (4)	-	2 (66)	14 (31)	-
Admission AST (IU/L), median (IQR)	1203 (654-1968)	965 (391-1515)	>0.05	1357 (687-2024)	1104 (480-1927)	>0.05	1108 (358-1769)	1221 (690-2030)	>0.05	1384 (436-1396)	956 (357-1527)	>0.05
Admission ALT (IU/L), median (IQR)	2880 (1633-3814)	2349 (1235-3006)	>0.05	2970 (1637-3871)	2404 (1538-3464)	>0.05	2197 (1357-3359)	2970 (1628-3898)	>0.05	2352 (1624-2812)	2345 (1208-3094)	>0.05
Admission ALP (IU/L), median (IQR)	181 (148-220)	170 (144-222)	>0.05	183 (145-217)	177 (148-22)	>0.05	177 (122-244)	198 (150-227)	>0.05	742 (620-864)	196 (124-356)	>0.05

Admission GGT (IU/L), median (IQR)	206 (118-332)	198 (124-320)	>0.05	192 (109-258)	267 (145-441)	>0.05	194 (106-2470)	281 (133-438	>0.05	339 (198-481)	218 (124-299)	>0.05
Admission Bilirubin (mg/dL), median (IQR)	7.21 (4.63-9.74)	8.26 (5.24-11.96)	>0.05	7.42 (4.87-9.54)	6.66 (3.70-10.20)	>0.05	11.21 (6.16-17.16)	6.69 (4.08-9.45)	>0.05	8.57 (7.21-9.94)	6.09 (3.96-8.35)	>0.05
Admission INR, median (IQR)	1.2 (1.11-1.38)	1.21 (1.09-1-27)	>0.05	1.25 (1.11-1.40)	1.20 (1.10-1.35)	>0.05	1.10 (1.08-1.63)	1.20 (1.08-1.38)	>0.05	-	1.16 (1.10-1.28)	-
Admission INR >1.5 (Severe hepatitis), n (%)	17 (14.5)	6 (12.5)	>0.05	12 (15.3)	5 (12.8)	>0.05	6 (35.2)	11 (11)	**< 0.0001**	0	5 (11)	>0.05
Discharge AST (IU/L), median (IQR)	123 (85-200)	90 (66-141)	>0.05	120 (84-204)	134 (84-195)	>0.05	98 (73-124)	136 (86-213)	>0.05	78 (55-181)	94 (67-141)	>0.05
Discharge ALT (IU/L), median (IQR)	618 (354-972)	326 (240-432)	>0.05	694 (409-1071)	457 (304-754)	>0.05	477 (302-787)	642 (373-1063)	>0.05	356 (282-608)	324 (233-430)	>0.05
Discharge ALP (IU/L), median (IQR)	158 (135-206)	177 (131-306)	>0.05	154 (131-199)	170 (144-222)	>0.05	182 (110-244)	164 (142-206)	>0.05	591 (445-1234)	131 (112-333)	>0.05
Discharge GGT (IU/L), median (IQR)	132 (75-239)	151 (64-277)	>0.05	125 (66-221)	182 (96-324)	>0.05	126 (84-173)	190 (197-274)	>0.05	398 (234-412)	109 (51-170)	>0.05
Discharge Bilirubin (mg/dL), median (IQR)	5.61 (3.41-8.28)	4.84 (2.88-6.88)	>0.05	5.84 (2.77-8.73)	4.64 (3.56-8.20)	>0.05	5.85 (3.22-9.98)	4.62 (3.23-7.00)	>0.05	2.12 (1.46-4.34)	3.93 (2.53-5.32)	>0.05
Discharge INR, median (IQR)	1.06 (1.01-1.13)	1.03 (1-1.11)	>0.05	1.08 (1.02-1.14)	1.04 (0.99-1.09)	>0.05	1.04 (0.96-1.34)	1.04 (0.98-1.07)	>0.05	1.29 (1.18-1.41)	1.01 (0.95-1.06)	>0.05
Other hepatotropic viruses												
- HBsAg, n (%)	2 (1.7)	1 (2)	>0.05	1 (1.3)	1 (2.6)	>0.05	1 (5.6)	1 (1)	>0.05	0	1 (2.2)	>0.05
- HCV-RNA, n (%)	3 (2.6)	1 (2)	>0.05	0	2 (5.3)	>0.05	0	3 (3)	>0.05	0	1 (2.2)	>0.05
- HEV-Ab, n (%)	1 (0.8)	0	>0.05	1 (1.3)	0	>0.05	0	1 (1)	>0.05	0	0	-

HIV-infection - HIV-Ab, n (%)	17 (14.5)	3 (6.2)	0.19	15 (19)	2 (5)	0.051	17	0	-	3	0	-
Hospitalization length (days), n (median)	7	11	>0.05	6	7	>0.05	7	7	>0.05	11	11	>0.05

MSM: men who have sex with men, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, GGT: gamma glutamyltransferase, INR: international normalized ratio, HBsAg: hepatitis B surface antigen, HCV: hepatitis C virus, HEV: hepatitis E virus, HIV: human immunodeficiency virus, IQR: interquartile ratio.

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