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Case report
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FIRST REPORTED CASES OF HEPATITIS A VIRUS AND HUMAN IMMUNODEFICIENCY VIRUS COINFECTION IN VOJVODINA, SERBIA – A CASE REPORT

PRVI PRIJAVLJENI SLUČAJEVI VIRUSA HEPATITIS A I VIRUSA HUMANE IMUNODEFICIJENCIJE U AUTONOMNOJ POKRAJINI VOJVODINI, SRBIJA – PRIKAZ SLUČAJA

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Summary

Introduction. Hepatitis A virus is the most common cause of acute viral hepatitis, and in people over 25 years of age the disease may have different degrees of severity. Even though hepatitis A virus infection was long believed to be transmitted strictly by fecal-oral route, now this virus is classified among sexually transmitted diseases. Homosexual population, especially those positive for human immunodeficiency virus, is at the greatest risk of hepatitis A virus infection. **Case 1.** A twenty-six-year-old male homosexual was admitted with clinical and laboratory findings of acute hepatitis. The patient tested positive for enzyme-linked immunosorbent assay immunoglobulin M antibodies to hepatitis A virus and human immunodeficiency virus antibodies, and later on human immunodeficiency virus infection was confirmed by polymerase chain reaction test. After the discharge, the antiretroviral therapy was initiated. **Case 2.** A twenty-seven-year-old male homosexual was transferred to our clinic from the Regional Hospital, where he was hospitalized due to acute hepatitis A virus infection, after a positive serological test for anti-human immunodeficiency virus antibodies. Human immunodeficiency virus infection was confirmed by polymerase chain reaction test, and upon discharge, antiretroviral therapy was initiated. **Conclusion.** In order to take the most effective preventive measures, it is very important to identify individuals and groups at high risk of coinfection with human immunodeficiency virus and hepatitis A virus. Timely vaccination against hepatitis A virus among people living with human immunodeficiency virus is recommended and therefore it is necessary to design effective strategies for education of groups at risk.

Key words: Hepatitis A virus; HIV; HIV Infections; Risk Factors; Vaccination; Hepatitis A Vaccines; Coinfection

Sažetak

Uvod. Virus hepatitisa A je najčešći uzročnik akutnog virusnog hepatitisa i kod osoba starijih od 25 godina bolest može biti različitog stepena težine. Iako se dugo verovalo da se virusna infekcija hepatitisa A prenosi isključivo fekooralno; sada se ovaj virus klasifikuje među seksualno prenosive bolesti. Jedna od grupa koja je u najvećem riziku od virusa hepatitisa A je homoseksualna populacija, a naročito pojedinci pozitivni na virus humane imunodeficijencije. **Prvi slučaj.** Dvadesetšestogodišnji muškarac, koji pripada homoseksualnoj populaciji, hospitalizovan je pod kliničkom i laboratorijskom slikom akutnog hepatitisa. Testiran je enzimski povezanim imunosorbent testom kojim su potvrđena imunoglobulin M antitela na virus hepatitisa A i na antitela na virus humane imunodeficijencije, a retrovirusna infekcija potvrđena je testom polimeraza lančane reakcije. Nakon otpusta iz bolnice započeta je antiretrovirusna terapija. **Drugi slučaj.** Dvadesetsedmogodišnji muškarac, koji pripada homoseksualnoj populaciji, nakon pozitivnog serološkog testa na IgM antitela na retrovirus prebačen je iz regionalne bolnice u kojoj je bio hospitalizovan zbog akutne virusne infekcije hepatitisa A. Retrovirusna infekcija je takođe potvrđena testom polimeraza lančane reakcije, a po otpustu je ordinirana antiretrovirusna terapija. **Zaključak.** Da bi se preduzele najefikasnije mere prevencije veoma je bitno identifikovati pojedince i grupe koje su u visokom riziku od koinfekcije retrovirusom i virusom hepatitisa A. Pravovremena vakcinacija protiv virusa hepatitisa A među ljudima koji žive sa virusom humane imunodeficijencije je preporučena, stoga je potrebno osmisliti efektivnu strategiju za edukaciju rizičnih grupa.

Ključne reči: hepatitis A virus; virus humane imunodeficijencije; HIV infekcija; faktori rizika; vakcinacija; hepatitis A vakcine; koinfekcija

Introduction

Hepatitis A virus (HAV) is the most common cause of acute viral hepatitis. In children and young adults the infection is often asymptomatic, but in people older than 25 years the disease may have

different degrees of severity [1]. It was long believed that HAV is transmitted strictly by fecal-oral route, but recent studies also classify it as a sexually transmitted disease (STD). The population of men who have sex with men (MSM) is considered to be at an increased risk of hepatitis A infection, since they

Abbreviations

HAV	– hepatitis A virus
STD	– sexually transmitted disease
MSM	– men who have sex with men
HIV	– human immunodeficiency virus
ELISA	– enzyme-linked immunosorbent assay
IgM	– immunoglobulin M
PCR	– polymerase chain reaction
RNA	– ribonucleic acid
HCV	– hepatitis C virus
HBsAg	– hepatitis B surface antigen
ART	– antiretroviral therapy
PLHIV	– people living with human immunodeficiency virus
HBV	– hepatitis B virus

practice oro-anal sex more commonly. A few research papers, such as the research of Mazick et al., report several outbreaks of acute hepatitis caused by HAV in homosexual population [2–4], and others emphasize the fact that in human immunodeficiency virus (HIV) positive patients HAV viremia is prolonged compared to immunocompetent patients, and thus the risk of transmission is higher [5]. The aim of this case presentation is to emphasise the changes in epidemiological characteristics of HAV infection, highlight the need for mandatory testing regarding the sexual transmission of the virus, and stress the importance of educating the public and most importantly the MSM group about positive effects of HAV vaccination.

Material and Methods

Data on the epidemiology of HAV infection in the Autonomous Province of Vojvodina in the period from 2017 to 2021 were obtained from the Institute of Public Health of Vojvodina by the courtesy of Prim. Dr. Svetlana Ilić. In this study, we present two cases of acute hepatitis A in HIV infected patients. Both of these patients were Caucasian males, and belonged to the MSM population. Both patients were hospitalized at the Clinic of Infectious Diseases, Clinical Center of Vojvodina,

during July and August of 2022. As a case definition of acute hepatitis we included signs and symptoms of acute hepatitis infection associated with elevated levels of serum alanine aminotransferase and aspartate aminotransferase above 1,000 IU/L. The HAV infection was confirmed using enzyme-linked immunosorbent assay (ELISA) for the detection of immunoglobulin M (IgM) antibodies to hepatitis A virus. Both patients tested positive to the 4th generation ELISA anti-HIV test confirmed by polymerase chain reaction (PCR) ribonucleic acid (RNA) HIV tests.

Case 1

A twenty-six-year-old male, belonging to the group of MSM, was admitted to the Clinic of Infectious Diseases on the second day of illness. Based on clinical signs and laboratory findings, acute viral hepatitis was suspected. On admission, the patient complained of nausea, vomiting, loss of appetite and general malaise, yellow discoloration of the skin and sclera, as well as dark urine and pale stools which he noticed on the previous day. Initial laboratory tests showed elevated levels of transaminase, hyperbilirubinemia and mild leukopenia, increased lactate dehydrogenase and creatine kinase, as well as prolonged prothrombin time (**Table 1**). Abdominal ultrasound showed a splenomegaly (approximate dimensions 14 cm X 7 cm) and thickening of the gallbladder wall. The patient was admitted to the hospital for further diagnosis and treatment. He tested positive for ELISA IgM anti-HAV antibodies as well as ELISA anti-HIV antibodies. The diagnosis of HIV infection was confirmed using PCR RNA HIV test. The cluster of differentiation 4 lymphocyte (CD4) count at that time was 399 cells/mm³. The patient tested negative for anti-hepatitis C virus (HCV), hepatitis B surface antigen (HBsAg), anti-antibody to hepatitis B core antigen (HBc) total, IgM anti-HBc antibodies.

The further course of the disease was favourable with the expected dynamics of decline in transaminase levels and the patient was discharged after 13

Table 1. Laboratory findings on admission
Tabela 1. Laboratorijski nalazi uzeti na prijemu

	Patient 1/Pacijent 1	Patient 2/Pacijent 2
Leucocytes (10 ⁹ /L)/Leukociti (10 ⁹ /L)	3.74	4.15
Total bilirubin (μmol/L)/Ukupni bilirubin (μmol/L)	104.6	57
Direct bilirubin (μmol/L)/Direktni bilirubin (μmol/L)	91.5	39.3
Aspartate aminotransferase (IU/L)/Aspartat aminotransferaza (IU/L)	2830	225
Alanine aminotransferase (IU/L)/Alanin aminotransferaza (IU/L)	6016	631
Gamma-glutamyl transferase (IU/L)/Gama glutamil transferaza (IU/L)	163	259
Prothrombin time (R)/Protrombinsko vreme (R)	1.36	1.06
Creatine kinase (IU/L)/Kreatin kinaza (IU/L)	1550	-
Lactate dehydrogenase (IU/L)/Laktat dehidrogenaza (IU/L)	1100	166
CD4 count (cells/mm ³)/Broj CD4 ćelija (ćelija/mm ³)	399	691
PCR HIV RNA (copies/ml)/PCR HIV RNK (kopija/ml)	<40	626460

Legenda: PCR – lančana reakcija polimeraze; HIV – virus humane imunodefijencije; RNK – ribonukleinska kiselina

Table 2. Epidemiological data of HAV infection in Autonomous Province of Vojvodina
Tabela 2. Epidemiološki podaci o infekciji virusom hepatitisa A u Autonomnoj pokrajini Vojvodini

Year/Godina	Sex/Pol	Age/Starost									Total/Ukupno
		1-4	7-9	10-14	15-19	20-29	30-39	40-49	50-59	60	
2017	M	0	2	4	3	1	5	3	3	2	23
	F	0	2	0	3	3	5	0	4	1	18
2018	M	0	0	1	1	0	3	3	0	0	8
	F	0	0	0	0	1	1	0	1	0	3
2019	M	0	0	0	0	1	0	1	0	1	3
	F	1	1	0	1	0	1	0	1	0	5
2020	M	0	0	0	0	0	0	0	0	0	0
	F	0	0	0	0	0	0	0	0	0	0
2021	M	0	0	0	1	0	0	0	0	0	1
	F	0	0	0	1	0	0	0	0	0	1
Total/Ukupno	M	0	2	5	5	2	8	7	3	3	35
	F	1	3	0	5	4	7	0	6	1	27

days (**Table 2**). Antiretroviral therapy (ART) (tenofovir/emtricitabine/dolutegravir) was initiated 7 days after the discharge. One month after ART initiation, CD4 level was 622 cells/mm³. Up to now, the patient had no new complaints and tolerated ART well.

Case 2

A twenty-seven-year-old male, belonging to the group of MSM, was transferred to the Clinical Center of Vojvodina, under suspicion of HIV infection. Initially, he was hospitalized in the Regional Hospital with clinical symptoms and laboratory tests pointing to acute hepatitis. He presented with jaundice, darker urine and general malaise. He tested positive for both anti-HAV IgM and anti-HIV antibodies. After he was transferred to our institution, initial elevated levels of bilirubin and aminotransferases were found (**Table 1**). PCR RNA HIV test was positive with viral load of 626460 IU/ml and CD4 count of 691 cells/mm³. The hepatitis B virus (HBV) and HCV infections were excluded by ELISA testing (anti-HCV, HBsAg, anti-HBc total, anti-IgM anti-HBc). The patient was hospitalized in our Clinic of Infectious Diseases for a total of six days and was discharged in good general condition and improved laboratory findings. Seven days after the discharge, the patients started receiving ART (emtricitabine/tenofovir/dolutegravir). The patient feels fine, without complains. Three months after the beginning of the therapy, the viral load was less than 40 IU/ml.

Discussion

The epidemiological situation worldwide concerning hepatitis A virus infection has changed significantly in the last few years. The European Center for Disease Prevention and Control reported several outbreaks of hepatitis A virus infection, largest one being in one of our neighbouring countries - Hungary [6]. Observing the epidemiological data

gathered from 2017 to 2021 in the Province of Vojvodina, there has been an increase of hepatitis A cases in recent years. In the Region of Vojvodina, HAV is more prevalent in males than in females (66% male, 34% female), most common in the age group between 30 – 39 years (**Table 2**). In 2022, 10 patients had HAV, 6 of them were male, the mean age 36.1 years. Two of them who are presented in this paper stated that they had unprotected sex with other men.

Although HAV has long been considered fecal-oral infection, in this era of good hygienic living conditions, sexual route of infection has become one of the main ways of contracting the virus. The MSM population is at risk of HAV infection because sexual practices facilitate fecal-oral transmission. It is a well known fact that the main mode of HIV transmission is unprotected anal sex. Many studies such as the study of Grulich et al., point to increase in MSM HIV incidence in Europe and the world, but none of them claims if the increase is because of the greater number of infected people or it is because more people are tested [7, 8]. Our center manages the needs of around 460 persons living with HIV (PLHIV). About two thirds of PLHIV were diagnosed in the asymptomatic stage of HIV infection, mostly at voluntary counselling testing sites. Regarding hepatitis coinfections, hepatitis B is considered endemic in MSM population and the prevalence of hepatitis B coinfections in PLHIV is about 20 times higher than in general population [9]. It is presumed that 6 – 10% of MSM population have HIV with HBV coinfection. Many studies deal with the reciprocal effect of HIV and HBV or HIV and HCV infection observing the interacting effect of these viruses on patient's organism [10]. In terms of HCV and HIV coinfection, it was found that the odds of contracting HCV were six times higher in PLHIV than in general population [11].

A group of researchers from Slovenia performed sequence-based typing and epidemiological investigation in order to identify circulating strains of HAV [12].

They reported an outbreak of HAV in the recent years which was linked to MSM population. Unsafe sexual behaviors put certain groups, such as MSM, at risk of contracting STDs, and condom use has not proven effective in preventing transmission of certain STDs such as HAV [13].

In this era of pre-exposure prophylaxis (PrEP), we observed a significant increase in STDs, like gonorrhoea and syphilis, so further increase in the incidence of HAV coinfections may be expected. It is often stressed that anal sex is the main route of contracting HIV, but when it comes to HAV, different routes of inoculation are possible. Since the HAV viral particles can be found in saliva, it is reasonable to assume that exchange of saliva through kissing is a way to get infected, without sexual contact [14]. Less is known about the effects of HAV infection on HIV positive patients. Study of Gallego et al. examined the effects of acute hepatitis A infection on HIV viral load in patients who were already on ART and proved that HIV viral load in patients infected with HAV is significantly higher, so transient detectable viremia can be expected in these patients [15]. This study also focused on severity of hepatitis, but observed no difference in clinical presentation in HIV positive compared to HIV negative patients. As previously shown, in our patients the course of HAV infection was uncomplicated and self-limiting.

Today, it is important to detect individuals and groups who are at high risk of contracting HIV and HAV, so frequent screening tests should be performed.

Farangel et al. stressed out the importance of designing good preventive and surveillance measures, health education of groups at risk, as well as the benefits of routine vaccination [12]. Men who have sex with men should be immunized against HAV, especially those who are HIV positive [16]. Two doses of inactivated HAV vaccine are recommended to increase the titre of protective antibodies to a sufficient level, but it was showed that three-dose schedule induces higher sero-conversion rate and higher and longer lasting antibody titers [17]. This vaccine is safe for HIV positive patients, so strategy of preventive vaccination should be included in medical practice of physicians working with patients who belong to high-risk groups. Although there is not much data available on reciprocal effects of ART and HAV vaccine, it was shown that shorter duration of ART leads to lower titre of protective IgG antibodies, so the question of another dose of vaccine leaves much to be answered [18].

Conclusion

As it was previously pointed out, the most important thing is to identify individuals and groups who are at high risk of getting human immunodeficiency virus and hepatitis A virus coinfection, so that most effective preventive measures can be taken. Timely vaccination against hepatitis A virus of people living with human immunodeficiency virus is recommended, and therefore it is necessary to design effective strategies for education of risk groups.

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