# Male-Dominant Hepatitis A Outbreak Observed among Non-HIV-Infected Persons in the Northern Part of Tokyo, Japan

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# Male-Dominant Hepatitis A Outbreak Observed among Non-HIV-Infected Persons in the Northern Part of Tokyo, Japan

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**Abstract:** Recently, we experienced an outbreak of acute hepatitis A virus (HAV) infection between 2018 and 2020. Herein, we describe this male-dominant HAV infection outbreak observed among non-human immunodeficiency virus (HIV)-infected persons in the northern part of Tokyo, Japan. Clinical information was collected from patient interviews and from medical record descriptions. In the present study, 21 patients were retrospectively analyzed. A total of 90.4 and 33.3% of patients were males, and men who have sex with men (MSM), respectively. The total bilirubin levels and platelet counts tended to be lower in the MSM group than in the non-MSM group. C-reactive protein (CRP) levels tended to be higher in acute liver failure (ALF) patients than in non-ALF patients. Prolonged cholestasis was observed in one patient (4.8%). We also found that 18 HAV isolates belonged to HAV subgenotype IA/subgroup 13 (S13), which clustered with the HAV isolate (KX151459) that was derived from an outbreak of HAV infection among MSM in Taiwan in 2015. Our results suggest that the application of antivirals against HAV, as well as HAV vaccines, would be useful for the treatment and prevention of severe HAV infection.

**Keywords:** male-dominant; men who have sex with men; HAV; non-HIV; sexually transmitted diseases



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## 1. Introduction

Hepatitis A virus (HAV), a positive-sense, single-stranded RNA virus, is a major cause of acute hepatitis and acute liver failure worldwide, which occasionally leads to liver transplantation or death [1–4]. Recently, HAV was found to have two virus forms—a membrane-cloaked quasi-enveloped virus (eHAV), and a naked, nonenveloped virion—that exist in the blood circulation and feces, respectively, of patients with acute hepatitis A [5,6].

HAV usually infects humans through the fecal–oral route via contaminated food and water. Because of improved sanitary and socioeconomic conditions, as well as the introduction of the HAV vaccination, the number of patients with acute HAV infection has declined, especially in developed countries [1]. In Japan, as there are no universal vaccination programs against HAV, susceptibility to HAV infection has increased in the general population [7,8].

It is well known that men who have sex with men (MSM) are a high-risk group for HAV infection [9–11]. After 1998, sexual activity was one of the most important transmission

routes of HAV infection in the metropolitan Tokyo area of Japan [12]. Koga et al. analyzed the clinical features of HAV infection in people living with human immunodeficiency virus (HIV) between pandemics in 1999–2000 and 2017–2018 in the metropolitan Tokyo area of Japan [13]. Of interest, all 16 HAV–HIV-coinfected patients (five and 11 in 1999–2000 and 2017–2018, respectively) were MSM [13].

In the present study, we analyzed 21 patients with acute hepatitis A who were admitted to our department of the Nihon University School of Medicine Itabashi Hospital, in the northern part of Tokyo, Japan, between January 2018 and April 2020. Of note, all these patients were HIV-negative; however, we recognized hepatitis A as a male-dominant disease, and identification as an MSM as one of the high-risk factors for HAV infection. These characteristics seem to be recent trends in HAV infections in the Tokyo area of Japan.

## 2. Patients and Methods

### *2.1. Patients*

A total of 21 patients with acute hepatitis A who were admitted to Nihon University School of Medicine Itabashi Hospital, Itabashi-ku, Tokyo, Japan between 1 January 2018 and 30 April 2020 were analyzed in the present study. Acute hepatitis A was diagnosed by positive testing for immunoglobulin M (IgM) antibodies to HAV. All participants were negative for the IgM anti-hepatitis B virus (HBV) core antibody, the anti-hepatitis C virus (HCV) antibody, the IgA anti-hepatitis E virus (HEV) antibody, or for anti-HIV antibody. This retrospective study was approved by the ethics committee of Nihon University School of Medicine Itabashi Hospital (protocol no. RK-180911-12). Participation in the study was posted at the website of our institution. This study conformed to the ethical guidelines of the Declaration of Helsinki.

### *2.2. Clinical and Laboratory Assessments*

Clinical parameters were measured by standard laboratory techniques. When the patients were diagnosed with acute hepatitis A, the attending doctor contacted the staff of Itabashi-ku, Tokyo, and analyzed serum HAV RNA. Because hepatitis A is an infectious disease, by law, a physician must immediately report a diagnosis in Japan to the authorities. Clinical information was collected by patient interviews, and all data were collected from medical record descriptions.

### *2.3. Definition and Classification of Acute Liver Failure*

According to Japanese criteria, patients showing prothrombin time values of 40% or less of the standard value, or international normalized ratios (INRs) of 1.5 or more, due to severe liver damage within 8 weeks of the onset of disease symptoms are diagnosed as having "acute liver failure", where liver function prior to the current onset of liver damage is estimated to have been normal based on blood laboratory data and imaging examinations. "Acute liver failure" (ALF) is categorized into two forms, "ALF without hepatic coma" or "ALF with hepatic coma" [14].

### *2.4. Detection of HAV RNA, Sequence Analysis and Phylogenetic Tree Analysis of HAV Isolates*

Sera were collected by Itabashi City Health Center, and analysis of HAV RNA was performed by the Department of Microbiology, Tokyo Metropolitan Institute of Public Health, Shinjuku, Tokyo, Japan when the patients were diagnosed with acute hepatitis A. Total RNA were extracted from 140 μL serum samples using a QIAamp Viral RNA Mini Kit (Qiagen, Tokyo, Japan) and subjected it to RT-PCR for the amplification of HAV VP1-2A region [15–17]. Complementary DNA (cDNA) was synthesized with primer HAV-JCT-1R-A (YTTRTCATCYTTCATTTCTGTCCA) at 56 °C for 45 s, 50 °C for 40 min and 95 °C for 15 min. Then cDNA was amplified with primers HAV-JCT-1R-A and HAV-JCT-2F (GRAGAACAGGRAAYATTCARATTAG) with 45 cycles of 94 °C for 1 min, 53 °C for 30 s and 72 °C for 2 min, followed by a single cycle of 10 min at 72 °C and 1 min at 20 °C, using QUIAGEN OneStep RT-PCR Kit (Qiagen) in a GeneAtlas Thermal Cycler (Astec,

Tokyo, Japan). Then, first PCR product was amplified further with primer HAV-JCT-2R (CAGTHARMACHCCAGCATCCAT) and HAV-JCT-2F with denaturation of 94 °C for 3 min and 35 cycles of 94 °C for 1 min, 58 °C for 2 min and 72 °C for 2 min, followed by a single cycle of 6 min at 72 °C and 45 s at 20 °C [17].

Direct sequencing of the amplified product was performed with primers previously reported [15–17]. The HAV VP1-2A region was determined and deposited in the DDBJ/EMBL/GenBank databases under accession numbers LC597557 to LC597576. A phylogenetic tree was constructed by the neighbor-joining (N-J) method [17]. To confirm the reliability of the phylogenetic tree, bootstrap resampling tests were performed 1000 times. These analyses were performed using the Molecular Evolutionary Genetic Analysis (MEGA7) software system (http://www.megasoftware.net/).

### *2.5. Statistical Analysis*

Data are expressed as the mean ± standard deviation (SD). Statistical analyses were performed using Student's *t*-test or a chi-squared test. Variables with $p < 0.05$ in the univariate analyses were evaluated using multiple logistic regression analysis. The results were considered statistically significant at $p < 0.05$. Statistical analysis was conducted using DA stats software version PAF01644 (NIFTY Corp., Tokyo, Japan) and the Excel Statistics program for Windows 2010 (SSRI, Tokyo, Japan).

## 3. Results

### *3.1. Patient Characteristics and Comparison of ALF and Non-ALF Patients*

The baseline characteristics of the patients with acute hepatitis A are shown in Table 1. All 21 patients were positive for the IgM anti-HAV antibody, but negative for the HBsAg or anti-HIV antibodies. We performed univariate analyses and compared the clinical characteristics of ALF patients with those of non-ALF patients (Tables 1 and 2). In the present study, there were no cases of coma amongst the ALF patients. The aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH) levels were higher in ALF patients than in non-ALF patients. Of interest, C-reactive protein (CRP) levels tended to be higher in ALF patients than in non-ALF patients. The duration from onset to admission tended to be shorter in ALF patients than in non-ALF patients. Prolonged cholestasis was found in one (4.8%) of the 21 patients in the present study (case no. 20 in Table 2). However, the multivariate analysis did not find factors contributing to ALF, as the study number was too small.

**Table 1.** Clinical characteristics at baseline of patients in the present study.

| Characteristic | Total (*n* = 21) | ALF (*n* = 5) | Non-ALF (*n* = 16) | [1]*P*-Values |
|---|---|---|---|---|
| Male/female (*n*) | 19/2 | 4/1 | 15/1 | 0.9668 |
| Age (years) | 40.7 ± 12.1 | 46.2 ± 5.5 | 39.4 ± 13.2 | 0.2824 |
| BMI (kg/m$^2$) | 21.7 ± 3.0 | 21.0 ± 2.0 | 21.9 ± 3.3 | 0.5773 |
| AST (IU/L) | 3506 ± 3406 | 7215 ± 4228 | 2346 ± 2164 | 0.002510 |
| ALT (IU/L) | 3692 ± 2372 | 5789 ± 2809 | 3036 ± 1864 | 0.01913 |
| γ-GTP (IU/L) | 416 ± 199 | 415 ± 119 | 416 ± 222 | 0.9924 |
| LDH (IU/L) | 2002 ± 2660 | 4838 ± 3841 | 1116 ± 1410 | 0.00329 |
| Albumin (g/dL) | 3.9 ± 0.4 | 3.5 ± 0.6 | 3.9 ± 0.3 | 0.0558 |
| Total bilirubin (mg/dL) | 7.7 ± 5.1 | 6.7 ± 2.2 | 8.0 ± 5.8 | 0.6344 |
| CRP (mg/dL) | 1.6 ± 1.1 | 2.2 ± 1.6 | 1.4 ± 0.9 | 0.1665 |
| Platelet counts (×10$^4$/μL) | 17.9 ± 5.4 | 16.8 ± 6.7 | 18.2 ± 5.2 | 0.6280 |
| Atypical lymphocytes (/μL) | 410 ± 555 | 644 ± 971 | 337 ± 367 | 0.2913 |
| IgM (mg/dL) | 280 ± 115 | 236 ± 124 | 291 ± 114 | 0.3679 |

**Table 1.** *Cont.*

| Characteristic | Total ($n$ = 21) | ALF ($n$ = 5) | Non-ALF ($n$ = 16) | [1]*P*-Values |
|---|---|---|---|---|
| MSM group (yes/no) | 7/14 | 1/4 | 6/10 | 0.8562 |
| Duration from onset to admission (days) | 7.2 ± 4.7 | 4.6 ± 2.1 | 8.1 ± 5.0 | 0.1493 |
| Duration from admission to discharge (days) | 19.1 ± 9.0 | 20 ± 2.4 | 18.9 ± 10.3 | 0.8183 |

[1]*P*-Values (ALF vs. non-ALF); BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; LDH, lactate dehydrogenase; CRP, C-reactive protein; IgM, immunoglobulin M; ALF, acute liver failure; MSM, men who have sex with men.

**Table 2.** Clinical features of the 21 patients with HAV subgenotype IA infection in the present study.

| Case No. | Admission Date (Year/Month) | Age (Years)/Sex | Fever/ALF/MSM | IgM-HAV (S/CO) | Duration of Admission (Days) | History of Syphilis/HBV/Eating of Raw Oysters or Fish | Subgroup/Accession Number of HAV Isolate |
|---|---|---|---|---|---|---|---|
| 1 | 2018/January | 27/male | +/−/− | 1.7 | 22 | −/−/− | S9/LC597558 |
| 2 | 2018/February | 48/male | +/+/− | 6.12 | 22 | −/−/− | S13/LC597557 |
| 3 | 2018/February | 56/male | −/−/− | 7.47 | 15 | −/−/+ | S13/LC597559 |
| 4 | 2018/March | 56/male | +/−/− | 5.41 | 20 | −/−/− | S13/LC597560 |
| 5 | 2018/April | 24/male | +/−/+ | 8.98 | 20 | +/−/− | S13/LC597561 |
| 6 | 2018/May | 37/male | +/−/+ | 6.9 | 21 | −/−/− | S13/LC597562 |
| 7 | 2018/June | 39/male | −/+/+ | 4.61 | 21 | +/+/− | S13/LC597563 |
| 8 | 2018/June | 54/male | +/+/− | 8.5 | 21 | −/−/− | S13/LC597564 |
| 9 | 2018/July | 23/male | −/−/− | 7.42 | 37 | −/−/− | S13/LC597566 |
| 10 | 2018/July | 24/male | −/−/+ | 8.22 | 9 | −/+/− | S13/LC597565 |
| 11 | 2018/September | 44/male | +/+/− | 6.26 | 16 | −/−/+ | S13/LC597567 |
| 12 | 2018/October | 58/male | +/−/+ | 11.3 | 11 | +/−/− | S13/LC597568 |
| 13 | 2018/November | 46/female | +/+/− | 3.43 | 20 | −/−/− | S13/LC597569 |
| 14 | 2018/December | 53/male | +/−/− | 12.7 | 20 | −/−/− | S13/LC597570 |
| 15 | 2018/December | 32/male | −/−/− | 5.25 | 10 | −/−/− | S13/LC597571 |
| 16 | 2019/February | 35/male | +/−/+ | 5.07 | 10 | −/−/− | S13LC597572 |
| 17 | 2019/March | 52/male | +/−/− | 8.77 | 14 | −/−/− | S9/LC597573 |
| 18 | 2019/May | 24/male | +/−/− | 7.57 | 14 | −/−/− | S13/LC597574 |
| 19 | 2019/August | 34/male | −/−/+ | 10.8 | 15 | +/+/− | S13/LC597575 |
| 20 | 2019/October | 38/male | −/−/− | 8.98 | 48 | −/−/+ | S13/LC597576 |
| 21 | 2020/April | 51/female | −/−/− | 11.2 | 16 | −/−/− | N/A |

S/CO, sample value/cutoff value measured by chemiluminescent immunoassay (CLIA); +, positive; −, negative; HAV, hepatitis A virus; ALF, acute liver failure; MSM, men who have sex with men; HBV, hepatitis B virus; S, subgroup; N/A, not available.

### *3.2. Comparison of MSM with Non-MSM Groups' Characteristics*

Patient lists are shown in Table 2. Among the 21 patients, two and three patients had recent histories of eating raw oysters or raw fish, respectively. A total of four and three patients had histories of syphilis and hepatitis B, respectively. Of interest, 19 (90.4%) and seven (33.3%) of the 21 patients were male and MSM, respectively. A total of seven (36.8%) of the 19 male patients were MSM (Tables 1 and 2). Of the two female patients, one spent time in the MSM community.

We compared the baseline characteristics of the MSM group with those of the non-MSM group with acute hepatitis A via univariate analyses. The total bilirubin levels and platelet counts tended to be lower in the MSM group than in the non-MSM group (Table 3).

**Table 3.** Clinical characteristics of men who have sex with men (MSM) and non-MSM groups of patients at the baseline in the present study.

| Characteristic | MSM Group (*n* = 7) | Non-MSM Group (*n* = 14) | [1]*P*-Values |
|---|---|---|---|
| Male/female (*n*) | 7/0 | 12/2 | 0.7926 |
| Age (years) | 35.9 ± 11.5 | 43.1 ± 12.1 | 0.2001 |
| BMI (kg/m$^2$) | 21.4 ± 1.8 | 21.8 ± 3.5 | 0.9314 |
| AST (IU/L) | 3599 ± 3767 | 3458 ± 3360 | 0.8718 |
| ALT (IU/L) | 3569 ± 2716 | 3753 ± 2289 | 0.8718 |
| γ-GTP (IU/L) | 405 ± 212 | 421 ± 201 | 0.8675 |
| LDH (IU/L) | 2319 ± 2791 | 1844 ± 2686 | 0.7101 |
| Albumin (g/dL) | 4.0 ± 0.3 | 3.8 ± 0.5 | 0.3455 |
| Total bilirubin (mg/dL) | 5.6 ± 2.1 | 8.7 ± 5.9 | 0.1980 |
| CRP (mg/dL) | 1.3 ± 1.0 | 1.8 ± 1.2 | 0.3555 |
| Platelet counts (×10$^4$/μL) | 15.5 ± 3.4 | 19.1 ± 6.0 | 0.1599 |
| Atypical lymphocytes (/μL) | 399 ± 328 | 416 ± 651 | 0.9492 |
| IgM (mg/dL) | 281 ± 91 | 280 ± 130 | 0.9857 |
| ALF (yes/no) | 1/6 | 4/10 | 0.8562 |
| Duration from onset to admission (days) | 5.4 ± 3.0 | 7.4 ± 5.2 | 0.3614 |
| Duration from admission to discharge (days) | 15.3 ± 5.4 | 21 ± 10.0 | 0.1783 |

[1]*P*-Values (ALF vs. non-ALF); BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; LDH, lactate dehydrogenase; CRP, C-reactive protein; IgM, immunoglobulin M; ALF, acute liver failure.

### *3.3. Factors of Administration for 20 Days or More in Japanese Patients with Acute Hepatitis A*

We also compared the baseline characteristics of patients with admission for less than 20 days and those with admission for 20 days or more via univariate analyses (Table 4). Patients with admission for 20 days or more tended to have higher AST levels or γ-glutamyl transpeptidase (γ-GTP) levels than those with admission for less than 20 days. However, the multivariate analysis did not find the factors contributing to ALF, as the study sample size seemed to be too small.

**Table 4.** Clinical characteristics between patients with admission for less than 20 days and those with admission for 20 days or more.

| Characteristic | Fewer than 20 Days (*n* = 10) | 20 Days or More (*n* = 11) | [1]*P*-Values |
|---|---|---|---|
| Male/female (*n*) | 9/1 | 10/1 | 0.5007 |
| Age (years) | 41.0 ± 12.9 | 40.5 ± 12.0 | 0.9213 |
| BMI (kg/m$^2$) | 22.2 ± 3.5 | 21.2 ± 2.7 | 0.4700 |
| AST (IU/L) | 2429 ± 3525 | 4484 ± 3131 | 0.1732 |
| ALT (IU/L) | 3090 ± 2491 | 4238 ± 2231 | 0.2790 |
| γ-GTP (IU/L) | 347 ± 118 | 478 ± 240 | 0.1351 |
| LDH (IU/L) | 1334 ± 2649 | 2609 ± 2643 | 0.2838 |
| Albumin (g/dL) | 3.8 ± 0.5 | 3.9 ± 0.5 | 0.6523 |
| Total bilirubin (mg/dL) | 7.7 ± 3.6 | 7.6 ± 6.4 | 0.9657 |
| CRP (mg/dL) | 1.4 ± 1.3 | 1.8 ± 1.0 | 0.4365 |
| Platelet counts (×10$^4$/μL) | 18.0 ± 4.9 | 17.8 ± 6.1 | 0.9352 |
| Atypical lymphocytes (/μL) | 486 ± 371 | 342 ± 693 | 0.5657 |
| IgM (mg/dL) | 279 ± 99.5 | 281 ± 131 | 0.9692 |
| ALF (yes/no) | 2/8 | 3/8 | 0.9692 |
| MSM group (yes/no) | 4/6 | 3/8 | 0.5366 |
| Duration from onset to admission (days) | 7.7 ± 5.7 | 5.8 ± 7.0 | 0.5061 |
| Duration from admission to discharge (days) | 13.0 ± 2.7 | 24.7 ± 9.2 | 0.001042 |

[1]*P*-Values (less than 20 days vs. 20 days or more); BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; LDH, lactate dehydrogenase; CRP, C-reactive protein; IgM, immunoglobulin M; ALF, acute liver failure; MSM, men who have sex with men.

### *3.4. Molecular Analysis of HAV Isolates from Some Patients with Acute Hepatitis A in the Present Study*

We recorded 15 and six patients with acute hepatitis A in 2018 and in the period January 2019 to April 2020, respectively. The HAV VP1-2A region from the 20 isolates derived from 21 of these patients was analyzed in a phylogenetic tree based on the neighbor-joining method (Figure 1). All 20 isolates belonged to the HAV subgenotype IA. Among them, only two isolates were similar to subgroup 9 (S9) [17], and the other 18 isolates clustered (subgroup 13 (S13)) with the HAV isolate (KX151459), which was identified following an outbreak of HAV infection among MSM in Taiwan in 2015 [15] (Figure 1).

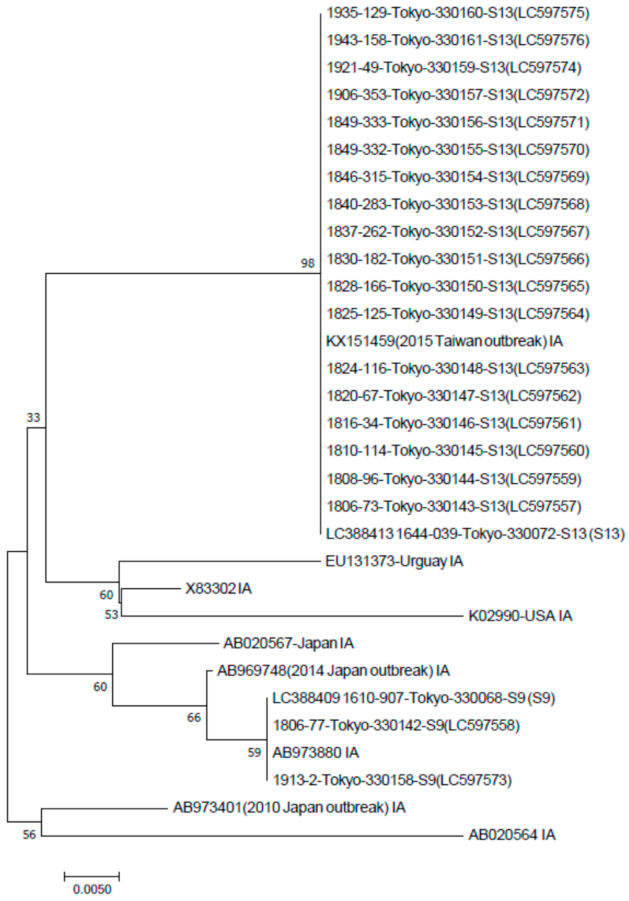


**Figure 1.** Phylogenetic analysis of the hepatitis A virus (HAV) VP1-2A region (168 bp) in the present study, and previously reported sequences of HAV subgenotype IA. Neighbor-joining methods were performed [15,17]. Accession numbers for the DDBJ/EMBL/GenBank databases are indicated. The HAV isolates in the present study ranged from LC597557 to LC597576 (see Table 2).

## 4. Discussion

As sanitation has improved and susceptibility to HAV infection has increased in the general population [7], it seems that outbreaks of hepatitis A can be expected to occur in the near future in Japan [18]. The number of cases of acute hepatitis A was 100–300 annually between 2001 and 2017 in Japan. In 2018, 925 patients with acute hepatitis A were reported [19]. In our institute, we also identified 15 patients with acute hepatitis A and no HIV infection in 2018. We analyzed 21 patients that were identified between January 2018 and April 2020. We also confirmed that the HAV isolates clustered with the HAV isolate (KX151459) derived from the outbreak of HAV infection among MSM in Taiwan in 2015.

We found that AST, ALT, and LDH levels were higher in the five ALF patients than in the 16 non-ALF patients. We also observed that CRP levels tended to be higher in the ALF patients than in the non-ALF patients. Patients with acute hepatitis A often display

fever [20]. The present study also demonstrated that 13 (61.9%) of the 21 patients had a fever (temperature equal to or higher than 38 °C) at admission. In the present study, we found prolonged cholestasis in 4.8% of patients. Jung et al. reported that prolonged cholestasis was found in 4.7% of patients in Korea [21], and could be predicted from preexisting chronic HBV infection, prolonged prothrombin time, and higher total bilirubin levels. Our patient had higher total bilirubin, but no preexisting chronic HBV infection or prolonged prothrombin time (case no. 20 in Table 2).

Our previous study of a hepatitis A outbreak associated with a revolving sushi bar in Chiba, Japan, in 2011 demonstrated that 11 (40.7%) of the 27 patients were male, indicating that the patients were not male-dominant [22]. Further, in an HAV infection study in metropolitan areas in Japan between 1993 and 2003, 39 (65%) of the 60 patients were male [12]. Interestingly, in the present study 19 (90.5%) of the 21 patients were male, indicating that the patients were obviously male-dominant, and seven (36.8%) of these 19 male patients were MSM. Between January and May 2018, 17 male patients infected with HAV were reported in Yokohama, Japan [23]. Of these 17 patients, 14 (82.4%) identified as MSM.

Outbreaks, and patients with severe forms of acute hepatitis A in the MSM category, have been recently reported in Japan [23–25] and other countries [9–11]. Outbreaks of acute hepatitis A, which are described in the present article, are often associated with MSM. HAV vaccination could prevent MSM from experiencing acute HAV infection, and HAV vaccination should be useful in preventing other people from being infected with HAV. It is possible that the administration of antivirals against HAV would be useful for the prevention of severe HAV infection [26–29].

We found similar isolates to the HAV subgroup 9 (S9) [17] in two non-MSM patients (no. 1 and no. 17 in Table 2). Both were non-ALF patients. In 2016 and 2017, respectively, HAV subgroup 9 (S9) was a major HAV subgroup in the Tokyo Prefecture (42.6% (20/47) and 69.0% (31/45)0, although HAV subgroup 13 (S13) was reported in only 10.6% (5/47) and 20.0% (9/45) [16]. Asakura et al. also reported that, in 2018, HAV subgroups 9 (S9) and 13 (S13) were observed in 2.6% (9/344) and 97.3% (334/344) of cases, respectively, in the Tokyo Prefecture [17]. In the present study, it may be possible that HAV subgroup 9 (S9) was not associated with MSM. Of interest, the HAV sequence obtained in one female (no. 13 in Table 2), also intermixes with those isolated from MSM group. These facts indicate that HAV subgroup 13 (S13) may be one of the main HAV variants in this area.

## 5. Conclusions

We described a recent male-dominant hepatitis A outbreak in Japan, which may be associated with MSM to some extent. These facts seem to represent recent trends in HAV infection in the Tokyo area of Japan. Antivirals against HAV, as well as HAV vaccines, may be useful for the prevention of severe HAV infection. Future studies with increased sample sizes could highlight the findings presented in the present study.

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**Institutional Review Board Statement:** The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Nihon University School of Medicine Itabashi Hospital (protocol no. RK-180911-12).

**Informed Consent Statement:** Participation in the study was posted at the website of our institution. Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** All sequences generated by unbiased sequencing were submitted to DDBJ/EMBL/GenBank databases under accession numbers LC597557 to LC597576.

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【背景・目的】

A 型肝炎ウイルス（HAV）は、急性肝炎や急性肝不全を起こし、その感染対策は重要である. HAV は汚染食品や汚染水を摂取することでヒトに感染することが主要な感染経路と考えられてきた. 現在、本邦では公衆衛生環境や社会経済状況改善などにより、汚染食品や汚染水を原因とする A 型肝炎患者数は減少してきた. 2000 年から 2017 年まで、年平均 266 例ほどの A 型肝炎が報告されていた.

本邦では、一般の人々における HAV 抗体保有率が低く、高齢者でも HAV 抗体陽性者が減少し、HAV に対する免疫保持者が減少している. そのため、A 型肝炎の大流行が危惧されてきた. 諸外国では積極的な HAV ワクチン使用により、A 型肝炎発生者数減少が見られるが、本邦では HAV ワクチンのユニバーサルワクチネーションも行われておらず、何らかの A 型肝炎対策が必要である.

また、A 型肝炎は男性間性交渉者(MSM)を中心とした性行為感染症の一つとしても注目されている. MSM が A 型肝炎のハイリスクである正確な理由は不明である. A 型肝炎では夫婦間感染や家族内集積感染例が観察されていることから、MSM 間の性行為を含む濃厚な接触が一因と考えられる. HAV の発症前潜伏期が 2-6 週と比較的長く、この期間は大量の HAV が糞便排泄され、感染源となることも理由の一つとして考えられる. 肝炎症状消失後、約半年間 HAV が糞便中に排出された症例も報告されている(Yotsuyanagi H, et al. Hepatology. 1996 Jul;24(1):10-3.; Ishizaka A, et al. Viruses. 2021 Oct 18;13(10):2101.).

本邦では、2018 年に A 型肝炎の大流行があり、感染経路として男性間性交渉者(MSM)が 50%以上を占め、 男性患者が 9 割に達したことが、2019 年に国立感染症研究所のデータでも示されている. 東京都近隣大学病院から、ヒト免疫不全ウイルス(HIV)感染者を 20-100%含んだ報告がされているが、今回の A 型肝炎流行における HIV 非感染者での病態は不明である.

我々も 2018 年から 2020 年の間に A 型肝炎の大流行を経験した. 本研究では、日本の東京北部にある日本大学医学部附属板橋病院で観察された HIV 非感染者 A 型肝炎症例の特徴について検討した.

【対象・方法】

本研究では、2018 年 1 月 1 日から 2020 年 4 月 30 日まで日本大学医学部附属板橋病院消化器・肝臓内科に入院した A 型肝炎患者 21 名を対象として解析した. 採血データを含む臨床情報は、患者の問診と診療記録から収集、解析した. A 型肝炎は感染症法に基づく四類感染症であり、届出を行う必要がある. 今回は東京都健康安全研究センター 微生物部ウイルス研究科にて業務で解析した HAV 遺伝子を提供していただき、臨床情報とともに解析した. 統計解析は Student's t test または chi-square test で行い、$p<0.05$ で有意差有と判定した. 本研究は日本大学医学部板橋病院の臨床研究倫理審査委員会（プロトコル番号 RK-180911-12）の承認を得た.

【結果】

1) A 型肝炎患者 21 名(平均年齢 40.7±12.1 歳)中 19 名 (90.4%)が男性であり、また 7 名(33.3%)が MSM であった. 21 名全員が IgM HAV 抗体陽性であり、HIV 抗体陰性者であった. 入院時 AST、3506±3406 IU/L; ALT、3692±2372 IU/L; γ-GTP、416±199 IU/L; LDH、2002±2660 IU/L; Albumin、3.9±0.4 g/dL; Total bilirubin、7.7±5.1 mg/dL; CRP、1.6±1.1 mg/dL; 血小板数、17.9±5.4 万/μL であった. 長期胆汁うっ滞は 1 名 (4.8%) で見られた. 13 名(61.9%)で体温 38 度以上の発熱を認めた. 生魚介類摂取は 21 名 3 名(14.3%)のみに見られた. 梅毒および B 型肝炎ウイルス(HBV)既往感染はそれぞれ 3 名(14.3%)および 3 名(14.3%)に認めた. HAV 遺伝子の解析は 21 名中 20 名で施行することが可能であった. HAV Genotype IA subgroup 1 (S1)および S13 がそれぞれ 2 名および 18 名で確認された. HAV Genotype IA S13 は、2015 年に台湾の MSM 間で見られた流行株由来の HAV isolate (KX151459)とクラスターを形成した.
2) 急性肝不全(ALF)患者は 21 名中 5 名(23.8%)で見られた. ALF 症例は平均年齢 46.2±5.5 歳、男性 4 名(80%)であった. ALF 症例では非 ALF 症例と比較し AST、ALT、LDH 値が有意に高値であった(p<0.05). ALF 症例は HAV Genotype IA S13 感染によるものであった. C 反応性タンパク質(CRP) 値は、ALF 症例(2.2±1.6 mg/dL)において、非 ALF 症例(1.4±0.9)よりも高い傾向が見られた(p=0.167).
3) MSM 7 名と非 MSM14 名で臨床像を比較すると各検討項目で有意差は認められなかった.
4) 入院期間が 20 日未満の 10 名と 20 日以上の 11 名で臨床像を比較したが、各検討項目で有意差はみれなかった.

【考察】

2011 年に千葉市内の回転寿司店に関連した A 型肝炎による食中毒では、A 型肝炎患者は 27 名[平均年齢 43.7 歳、男性 11 名 (40.7%)]であった(Tominaga A, et al. Hepatol Res. 2012;42:825-834). 発熱は 92.5%に見られた. ALF は 1 名(3.7%)であった. 全例が HAV Genotype IA 感染によるものと報告されている. この回転寿司店の利用客は家族連れが多く見られ、客層にも男性優位性は見られず、A 型肝炎患者に男性優位性は見られなかった. 感染源としては手桶の汚染水が疑われている(未発表データ). 今回の日本大学医学部附属板橋病院消化器・肝臓内科に入院した A 型肝炎患者 21 名含む本邦での流行は、HAV の分子疫学的検討からも、以前に千葉市内で起きた流行とは感染源が異なると考えらた.

HAV Genotype IA S13 は、2015 年に台湾の MSM 間で見られた流行株由来の HAV isolate (KX151459)とクラスターを形成した. 台湾に始まった MSM 間での流行はヨーロッパおよび米国の MSM 間でも流行した(Watanabe S, et al. Hepatol Res. 2019 May;49(5):521-530.;Tanaka S, et al. Hepatol Res. 2019 Jun;49(6):705-710.). 今回本邦で見られた A 型肝炎の流行も本邦の MSM 間やその周辺など特定の集団内の HAV キャリアから感染し、広まっ

た可能性が考えられ、患者が男性優位であったことと一致する.

今回の検討では ALF が 23.8%と重症化症例が多く見られたことは非常に興味深い. ALF 症例において、CRP 値が高い傾向が見られた. Shin らは急性 A 型肝炎 46 名と急性 B 型肝炎症例 16 名および健康成人 14 名の血清サイトカイン濃度を比較検討している(Yonsei Med J. 2016 May;57(3):652-7.). IL-6、IL-22、granzyme B および soluble Fas ligand (sFasL) が急性 A 型肝炎のみで上昇していた. 我々の ALF 症例でも CRP の増加傾向が見られたのは IL-6 の増加と関連していた可能性がある. 今後の検討課題の一つである.

今回検討した日本大学医学部附属板橋病院の A 型肝炎患者 21 名は全員 HIV 陰性だった. 当科通院中の HIV 患者が少ないことも一因と考えられる.また、HIV 患者では無症候性 HAV 感染率が高いことが知られている(Ida S, et al. Jpn J Infect Dis. 2001 Feb;54(1):31-2.). 2021 年も当科では HIV 陽性 B 型肝炎患者は数名経験している. 2014 年以降当科では HIV 陽性 A 型肝炎患者を経験していないが正確な理由は不明である.

2018 年から 2020 年の流行期に見られた今回の A 型肝炎の症例の病態や臨床像は、男性優位であったことおよび急性肝不全昏睡型は認めなかったが、重症化例が 23.8%と高率で見られたことが、過去の A 型肝炎の病態や臨床像と大きく異なっていた.

東京女子医科大学の小木曽ら(J Gastroenterol Hepatol. 2019 Oct;34(10):1836-1842.)は HIV 陽性症例を含む 2001 年前後の A 型肝炎患者 126 名の臨床像を検討し、2001 年前および後の HAV 感染ルートとして性的接触が 0%および 19%と 2001 年以降で有意に多く($p<0.01$)見られたことを報告している. 今回我々の検討でも少なくとも 33.3%が男性間性的接触によるものであった. 小木曽らは 2001 年以降の症例で ALT および γ-GTP が有意に高値で($p<0.01$)、プロトロンビン時間(%)および血小板数が有意に低値で($p<0.01$)あったことを報告しており、我々の検討で重症化例が多く見られたことを支持しているものと考えられた.

東京大学医科学研究所の古賀らは HIV 陽性者における A 型肝炎の臨床像を 1999-2000 年および 2017-2018 年の 2 つの流行で分けて検討している(Jpn J Infect Dis. 2020 Mar 24;73(2):89-95.). 2017-2018 年の流行群でトランスアミナーゼのピーク値が有意に高値であったことを報告している. HAV の Virulence に少し違いがある可能性と HIV 治療直後の免疫再構築が臨床像に差を与えている可能性を示唆している.

A 型肝炎は HAV ワクチンが開発されており、その予防接種により発症予防可能な疾患である. HAV ワクチンの 1 回接種および 2 回接種ではそれぞれ HAV 抗体陽性率が 10 年後(74%以上)および 15 年後(90%以上)であったことが報告されている(Andani A, et al. Vaccine. 2022 Jan 21;40(2):196-205.). 本邦では HIV 陽性者には A 型肝炎ワクチン(商品名 Aimmugen)の 2 回接種と比較して、3 回接種の効果が高いことが報告されている(Koga M, et al. Hepatol Res. 2022 Mar;52(3):227-234.). HIV 陽性者を含む高リスク患者には、HAV 抗体測定と HAV 抗体陰性者に対する HAV ワクチン接種の推奨が望まれる.

研究の限界(Limitations)について: 日本の人口全国 1 億 2000 万人および日本大学医学部附属板橋病院医療圏人口 200 万人と想定し、2018 年 A 型肝炎届け出数 925 例とす

ると日本大学医学部附属板橋病院医療圏では 15.4 名が A 型肝炎に罹患したと想定される. 21 名中 15 名が 2018 年に当科に入院したこととほぼ一致する. しかし 21 症例の検討であるため、統計解析に限界がみられた.

【結論】

2018 年から 2020 年の流行期に見られた今回の HIV 陰性者に見られた A 型肝炎の症例の病態や臨床像は、男性優位であったことおよび重症化例が高率で見られたことが、過去の A 型肝炎の病態や臨床像と大きく異なっていた. 男性優位の流行は MSM に関連している可能性があり、日本の首都圏における最近の HAV 感染の傾向であると考えられた.