Acute Hepatitis due to Hepatitis A Virus Subgenotype IA as an Imported Infectious Disease from Indonesia

Utsumi, Takako ; Yano, Yoshihiko ; Amin, Mochamad ; Lusida, Maria I ; Soetjipto ; Hotta, Hak ; Hayashi, Yoshitake

(Citation)
The Kobe journal of the medical sciences,60(2):43-47

(Issue Date)
2014

(Resource Type)
departmental bulletin paper

(Version)
Version of Record

(JaLCDOI)
https://doi.org/10.24546/81008725

(URL)
https://hdl.handle.net/20.500.14094/81008725

Kobe J. Med. Sci., Vol. 60, No. 2, pp. E43 –E47, 2014

Acute Hepatitis due to Hepatitis A Virus Subgenotype IA as an Imported Infectious Disease from Indonesia

TAKAKO UTSUMI[1,2*], YOSHIHIKO YANO[2] , MOCHAMAD AMIN[1], MARIA I LUSIDA[1], SOETJIPTO[1], HAK HOTTA[2] and YOSHITAKE HAYASHI[2]

[1]*Indonesia-Japan Collaborative Research Center for Emerging and Re-emerging Infectious Diseases, Institute of Tropical Disease, Airlangga University, Surabaya, Indonesia;*

[2]*Center for Infectious Diseases, Kobe University Graduate School of Medicine, Kobe, Japan*

Received 13 May 2014/ Accepted 30 May 2014

Key words: Acute hepatitis A, Imported infectious disease, HAV subgenotype, Indonesia

ABSTRACT

A 25-year-old Japanese man was admitted with general malaise and fever, which had developed 12 days after coming back to Japan from Indonesia. Blood examination revealed elevated transaminase levels and positivity for the IgM anti-HAV antibody; therefore, he was diagnosed with acute hepatitis A. HAV-RNA was detected in his serum and phylogenetically classified as subgenotype IA. The partial genome in the VP1/P2A region was consistent with the strain recently isolated from Surabaya, which indicated that he had been infected during his stay in Indonesia. Thus, HAV vaccination is recommended before visiting HAV-endemic countries for a long period of time.

INTRODUCTION

Hepatitis A virus (HAV) is a non-enveloped RNA virus with an icosahedral symmetry that belongs to the genus Hepatovirus of the Picornaviridae family (1), and has been classified into 7 genotypes (I to VII) that exhibit distinct geographic distributions (2-4). HAV causes acute hepatitis in humans worldwide, and is transmitted by a fecal-oral route in areas with poor sanitation and weak public-health infrastructures, either from person-to-person contact or through contaminated food or water. The HAV infection is endemic in developing countries including Indonesia, with the majority of individuals in these countries being exposed to HAV during early childhood (5, 6). In contrast, the exposure rate of the adult population in developed countries including Japan to HAV has decreased due to improvements in hygiene. On the other hand, the incidence of the so-called imported hepatitis A, which is carried by a person infected during a visit to HAV endemic regions, has increased (7, 8).

In the present study, we described a 25-year-old Japanese man who developed acute hepatitis due to HAV subgenotype IA (HAV/IA) 12 days after coming back to Japan from Indonesia. The HAV strain that was isolated from the patient, who was presumed to have contracted HAV infection while visiting Indonesia, was consistent with the strain recently isolated from Surabaya. Additionally, it was closest to the Indonesian HAV/IA strain obtained from Genbank, with an identity of 99.1%. These results supported the Indonesian origin of the imported strain.

CLINICAL CASE

A 25-year-old Japanese man from Hyogo prefecture developed a high fever, general malaise, and anorexia from the end of January 2014, and visited a nearby Internal Medicine Clinic 3 days after the onset of these clinical symptoms. A blood examination revealed markedly elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. The patient was transferred to a general hospital in the same area of Hyogo the next day with a clinical diagnosis of acute hepatitis. The patient began living in Surabaya, Indonesia from September 2012 for his work, and had returned to Japan for a short visit 12 days before the onset of clinical symptoms. He had no history of liver disease or hepatitis and had been immunized with the hepatitis B vaccine, but not with the hepatitis A vaccine. Alcohol intake was reported at 330 mL beer on a weekly basis for 5 years. He had not eaten raw fish or shellfish one month before the onset of clinical symptoms, but often bought and

Phone: +62-31-594-0917 Fax: +62-31-594-0917 E-mail: tutsumi@people.kobe-u.ac.jp

consumed food from local food stalls in Surabaya, Indonesia. The patient denied having had sexual activities during his stay in Surabaya.

Table I. Laboratory data on admission

Parameters	Results	Normal range
White blood cell count (/mm^3)	7000	4000-9000
Hemoglobin (g/dL)	17.1	13.5-17.0
Platelet count (x 10^4/mm^3)	13.8	15.0-35.0
Prothrombin time activity (second)	13.0	9.6-12.7
Prothrombin time activity (%)	87	80-125
Albumin (g/dL)	4.4	3.8-5.1
Total bilirubin (mg/dL)	5.2	0.2-1.2
Aspartate aminotransferase (IU/L)	1650	10-30
Alanine aminotransferase (IU/L)	2838	3-30
Alkaline phosphatase (IU/L)	283	165-320
IgM anti-hepatitis A virus antibody (S/CO)	Positive (9.65)	Negative
IgM anti-hepatitis B core antibody	Negative	Negative
Hepatitis B surface antigen	Negative	Negative
Anti-hepatitis C virus antibody	Negative	Negative

On admission, a persistent fever and jaundice were noted. His consciousness was clear, and vital signs were as follows: blood pressure 120/70 mmHg, heart rate 72/min, temperature 38.2℃. Laboratory data on admission are shown in Table I. Serum levels of aspartate aminotransferase (AST; 1,650 IU/L), alanine aminotransferase (ALT; 2,838 IU/L), and total bilirubin (T-Bil; 5.2 mg/dL) were markedly elevated. Tests for the IgM anti-hepatitis B virus core antibody, hepatitis B surface antigen, and hepatitis C virus antibody were all negative. However, the serum IgM anti-hepatitis A virus antibody was positive, and he was consequently diagnosed with acute hepatitis A. HIV test was not performed. The patient was suspected of having imported hepatitis A because he lived in Indonesia, and we genetically analyzed HAV using serum obtained after discharge (24 days and 31 days after the onset of clinical symptoms). HAV RNA was detected by RT-PCR amplifications using HAV-specific primers in VP1/P2A from the samples obtained after his discharge (after 24 days, but not 31 days).[2] The PCR products were then directly sequenced (isolate name KSI25, DDBJ/EMBL/GenBank accession No. AB917146). A phylogenetic tree of the HAV genome constructed using 215 nucleotide sequences in the VP1/P2A region (Fig.1) indicated KSI25 belongs to HAV/IA. KSI25 was 100% identical to a strain recently identified in Surabaya (isolate name SSI19, DDBJ/EMBL/GenBank accession No. AB918714), and 99.1% to previously reported Indonesian strains (AB839696, AB839697, AB839693) from Java Island, in which Surabaya city belongs to (Fig. 1) (5).

The patient was given bed rest during a 4-day hospital stay, recovered rapidly without sequelae, and was subsequently discharged. AST/ALT serum levels gradually decreased and reached normal ranges one month after the onset of clinical symptoms (Fig. 2).

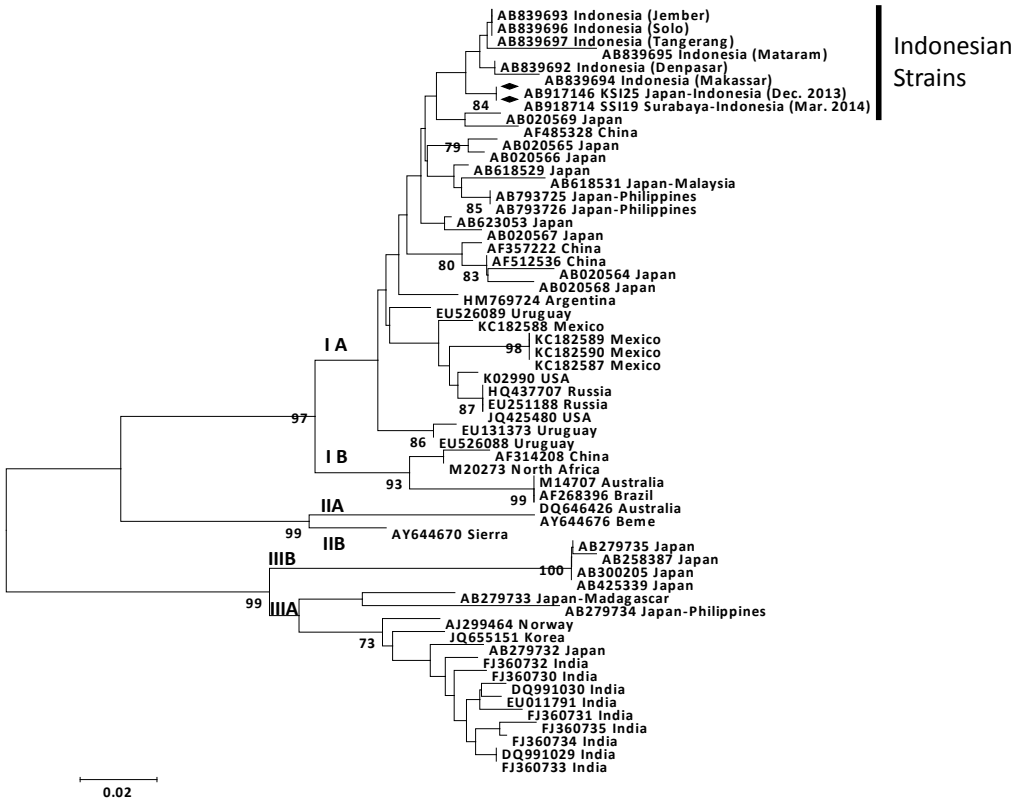

Figure 1. Phylogenetic tree of the VP1/P2A region of the hepatitis A virus (HAV) strain isolated from the Japanese patient and 57 reference strains described herein. Numbers in the tree indicate bootstrap reliabilities. The lengths of the horizontal bars indicate the number of nucleotide substitutions per site. Isolates from the database are indicated by their accession number, and relevant country names have been added to each HAV strain.

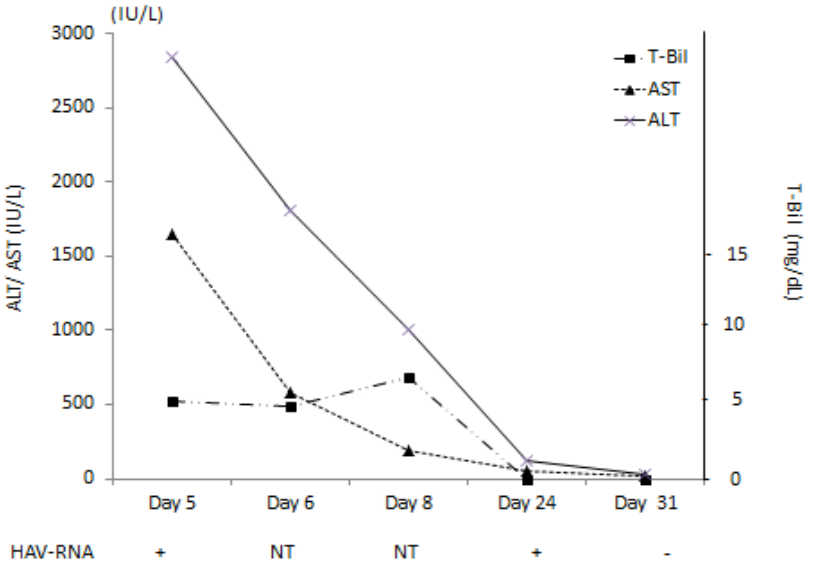

Figure 2. Clinical course of the case. Day shows the period after the onset of clinical symptoms. NT= Not tested.

DISCUSSION

We determined and analyzed the HAV genomic sequence of a HAV/IA isolate that was recovered from a Japanese patient who lived in Surabaya and developed acute hepatitis A 12 days after returning to Japan. The HAV isolate from the patient was consistent with the strain recently isolated from Surabaya, and was closest to the Indonesian HAV/IA strains obtained from Genbank, with an identity of 99.1%. This result supports the Indonesian origin of the imported strain. The period of one month from suspected infection to the onset of clinical symptoms, which represents the average incubation period of HAV infection, was also supportive to this diagnosis. As well as HAV, HEV infection is also endemic in Indonesia (6). HEV outbreak, however, usually occur after flood in the limited areas, and the prevalence is as low as 0.5% in Surabaya (7).

HAV/IA is a common subgenotype worldwide. Furthermore, Indonesia is a well-known endemic region of HAV, and no other HAV subgenotypes has ever reported (5, 8, 11). The incubation phase lasts between 2 and 7 weeks (mean 28-30 days). Thus, we speculated that our patient was infected with HAV/IA in Indonesia in December 2013, just before he left for Japan. Viremia terminates shortly after hepatitis develops, although feces remain infectious for another 1 - 2 weeks (12). However, in this case, HAV RNA was detectable until 24 days after the onset of clinical symptoms and a decrease in serum ALT/AST levels, which suggested that this patient was a source of infection until HAV cleared. A previous study also reported that some cases had HAV viremia after seroconversion to the HAV antibody (13). Hereafter, HAV/IA infection should be considered also as an imported infectious disease. Physicians are recommended to take precautionary measures against the spread of HAV infection when encountering patients with acute hepatitis A.

In 2003, the overall anti-HAV prevalence in Japan was 12%. Fifty percent of individuals over 50 years of age had anti-HAV whereas only 2% of people younger than 50 years of age had immunity (14). Moreover, in recent years, the incidence of hepatitis A in Japan has dramatically decreased, and therefore there might be a decrease in the proportion of persons who have immunity against HAV (15). HAV infection is preventable by vaccination, but vaccine is unavailable for hepatitis E. Regardless of vaccine availability, the improvement of public sanitation and health education for improved hygiene practices is the first line of defense against hepatitis A and E, as well as other enterically-transmitted diseases in developing world including Indonesia. Several countries, including Argentina, China, Israel and United States of America (USA) have introduced the hepatitis A vaccine in routine childhood immunizations. While the two-dose regimen of inactivated hepatitis A vaccine is common in many countries, a single-dose vaccination is used in some countries (http://www.who.int/mediacentre/factsheets/fs328/en/). Some countries also recommended the vaccine for people at increased risk of hepatitis A such as Japan. The current incidence of hepatitis A in Japan might be too low to warrant the introduction of a universal vaccination policy (14). In USA, recommendations now call for routine hepatitis A vaccination for all children beginning at the age of 1 year (12-23 months). In Japan, on the other hand, those more than 16 years old are considered to be vaccinated two-dose with 6 month interval not routinely but on request.

The present patient had not received vaccination for HAV prior to traveling to Indonesia. Therefore, travelers to countries where HAV infection is endemic should receive vaccine before travel, unless they have previously been vaccinated or infected with HAV. For the travelers in a hurry, even single dose can produce 99.3% efficacy for anti-HAV immunization after 4 weeks of vaccination, as previous study in Japan found. Similarly it described that a single dose of hepatitis A vaccine is sufficient to produce rapid immunity within 2 weeks (16).

In conclusion, attention should be paid to HAV/IA infection as an imported infectious disease because HAV IA infection is widespread. The results of the present study indicate that HAV vaccination is recommended prior to visiting HAV endemic countries, especially for long periods of time.

ACKNOWLEDGMENTS

This study was supported by a Grant-in-Aid from the Japan Initiative for Global Research Network on Infectious Diseases (J-GRID) program from the Ministry of Education, Culture, Sports, Science, and Technology (MEXT), Japan. We thank Dr. Masamichi Arao for data distribution.

REFERENCES

1. **Nainan, O.V., Xia, G., Vaughan, G., and Margolis, H.S.** 2006. Diagnosis of hepatitis A virus infection: A molecular approach. Clin Microbiol Rev **19**: 63-79.
2. **Yun, H., Kim, S., Lee, H., Byun, K.S., Kwon, S.Y., Yim, H.J., Lim, Y.S., Jeong, S.H., and Jee, Y.** 2008. Genetic Analysis of HAV Strains Isolated From Patients With Acute Hepatitis in Korea, 2005-2006. J Med Virol **80**: 777-784.
3. **Yoon, Y.K., Yeon, J.E., Kim, J.H., Sim, H.S., Kim, J.Y., Park, D.W., Sohn, J.W., Chun, B.C., and Kim, M.J.** 2011. Comparative analysis of disease severity between genotype IA and IIIA of hepatitis A

virus. J Med Virol **83**:1308-1314.

4. **Robertson, B.H., Jansen, R.W., Khanna, B., Totsuka, A., Nainan, O.V., Siegl, G., Widell, A., Margolis, H.S., Isomura, S., and Ito, K.** 1992. Genetic relatedness of hepatitis A virus strains recovered from different geographical regions. J Gen Virol **73**(Pt6): 1365-1377.
5. **Mulyanto, Wibawa, I.D., Suparyatmo, J.B., Amirudin, R., Ohnishi, H., Takahashi, M., Nishizawa, T., and Okamoto, H.** 2014. The complete genomes of subgenotype IA hepatitis A virus strains from different islands in Indonesia form a phylogenetic cluster. Arch Virol **159:** 935-945.
6. **World Health Organization.** Hepatitis A. 2001. Available at: http://www.who.int/csr/disease/hepatitis/HepatitisE_whocdscsredc2001_12.pdf/ Accesed May 19, 2014.
7. **Wibawa, I.D., Muljono, D.H, Mulyanto, Suryadarma, I.G., Tsuda, F., Takahashi, M., Nishizawa, T., and Okamoto, H.** 2004. Prevalence of antibodies to hepatitis E virus among apparently healthy humans and pigs in Bali, Indonesia: Identification of a pig infected with a genotype 4 hepatitis E virus. J Med Virol **73**: 38-44.
8. **Brown, P., Breguet, G., Amallwood, L., Ney, R., Moerdowo, R.M., and Gerety, R.J.** 1985. Serologic markers of hepatitis A and B in the Population of Bali, Indonesia. Am J Trop Med Hyg **34**: 616-619.
9. **Watanabe, S., Isoda, N., Ohtake, T., Hirosawa, T., Morimoto, N., Aoki, K., Ohnishi, H., Takahashi, M., Sugano, K., and Okamoto, H.** 2014. Full genome analysis of Philippine indigenous subgenotype IA hepatitis A virus strains from Japanese patients with imported acute hepatitis A. Heptol Res **44**: 270-279.
10. **Tominaga, A., Kanda, T., Akiie, T., Komoda, H., Ito, K., Abe, A., Aruga, A., Kaneda, S., Saito, M., Kiyohara, T., Wakita, T., Ishii, K., Yokosuka, O., and Sugiura, N.** 2012. Hepatitis A outbreak associated with a revolving sushi bar in Chiba, Japan: Application of molecular epidemiology. Hepatol Res **42**: 828-834.
11. **Jacobsen, K.H, and Wiersma, A.T.** 2010. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. Vaccine 28: 6653-6657.
12. **World Health Organization.** Hepatitis A. 2000. Available at: http://www.who.int/csr/disease/hepatitis/HepatitisA_whocdscsredc2000_7.pdf/ Accessed March 24, 2014.
13. **Yotsuyanagi, H., Iino, S., Koike, K., Yasuda, K., Hino, K., and Kurokawa, K.** 1993. Duration of viremia in human hepatitis A viral infection as determined by polymerase chain reaction. J Med Virol **40**: 35-38.
14. **Kiyohara, T., Sato, T., Totsuka, A., Miyamura, T., Ito, T., and Yoneyama, T.** 2007. Shifting seroepidemiology of hepatitis A in Japan, 1973-2003. Microbiol Immunol **51**: 185-191.
15. **National Institute of Infectious Diseases.** Infectious Agents Surveillance Report (IASR) 2010. **31**: 286-287. Available at: http://idsc.nih.go.jp/iasr/31/368/dj3681.html/ Accesses May 19, 2014
16. **Nothdurft, H.D,, Zuckerman, J., Stoffel, M., Dieussaert, I., and Van Damme, P.** 2004. Accelerated vaccination schedules provide protection against hepatitis A and B in last-minute travelers. J Travel Med **11**: 260-261.