Dynamic Epidemiology of Acute Viral Hepatitis in Japan

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Key Words

Acute hepatitis · Epidemiology · Hepatitis B virus genotype A · Hepatitis E

Abstract

The epidemiology of acute viral hepatitis (AVH) is dynamic and affected by many factors including hygiene, socioeconomic status and vaccination coverage. A total of 4,302 cases of AVH were sequentially enrolled in this nationwide study between 1980 and 2008. Of the cases of AVH, acute hepatitis A (AHA) accounted for 1,583 (36.8%), acute hepatitis B (AHB) for 1,197 (27.8%), acute hepatitis C (AHC) for 359 (8.3%), and non-A, non-B and non-C (non-ABC) for 1,163 (27.0%). Between 1980 and 1995, the proportions of AHA, AHB, AHC and non-ABC were approximately 40, 25, 10 and 25%; between 1996 and 2003, they were approximately 30, 30, 10 and 30%, and this shifted to approximately 10, 40, 10 and 40% in the last 5 years. The number of AHB caused by genotype A, which is not indigenous to Japan, was 6.0% between 1991 and 1996 but has been markedly increasing since 2000, to reach 52% in 2008. Autochthonous acute hepatitis E (AHE) accounted for 10–15% of non-ABC hepatitis after 2002. The etiology of AVH in Japan has been drastically changing. A marked increase of AHB genotype A and constant occurrence of autochthonous AHE require attention, and necessary measures should be taken.

Introduction

Acute viral hepatitis (AVH) is caused by infection with any hepatitis virus, of which the 3 most commonly identified in Japan are hepatitis A (HAV), hepatitis B (HBV), and hepatitis C (HCV). In addition, after excluding other known non-hepatitis viruses, such as Epstein-Barr virus, herpes simplex virus and other causes of acute hepatic injury including autoimmune hepatitis and alcoholic hepatitis, non-ABC acute hepatitis can be categorized. All of these unrelated viruses can produce an acute illness characterized by nausea, malaise, abdominal pain and jaundice [1]. Epidemiology of acute hepatitis is dynamic and affected by many factors including hygiene, socioeconomic status, prevalence of other diseases such as HIV infection, and coverage of available vaccination [1, 2]. A longitudinal study of surveillance is usually difficult to conduct and rare. In this article, we show the results of our surveillance study which has been conducted for almost 3 decades.

Materials and Methods

A mini-sentinel surveillance involving 28 liver centers of national hospitals located nationwide and which cover almost the whole of Japan has been conducted since 1980. All cases of AVH which were admitted to one of our hospitals have been sequential-

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Fig. 1. Trends of AVH in Japan (1980–2008, n = 4,302).

ly enrolled to the study, and sera taken on admission were stored for further analysis. There were some, but only minor changes in the member hospitals due to personnel transfer and/or elimination and consolidation of hospitals during the observation period.

Clinical Case Definition

Acute hepatitis was defined as acute illness with (1) discrete onset of symptoms (e.g. nausea, anorexia, fever or malaise) and (2) jaundice or elevated serum aminotransferase and/or total bilirubin levels.

The laboratory criteria for confirming each type of AVH were as follows: (1) acute hepatitis A (AHA): positivity for immunoglobulin M (IgM) antibody to hepatitis A virus (anti-HAV); (2) acute hepatitis B (AHB): positivity for IgM antibody to hepatitis B core antigen (anti-HBc) or hepatitis B surface antigen (HBsAg); (3) acute hepatitis C (AHC): positivity for RT-PCR for HCV RNA, and either anti-HCV negativity at the onset of disease or significant increase of anti-HCV in the assay 2 weeks after onset.

Exclusion criteria were as follows: (1) involvement of non-hepatitis viruses, including Epstein-Barr virus, cytomegalovirus, parvovirus and herpes virus; (2) involvement of other etiologies such as autoimmune hepatitis, drug-induced hepatitis, and (3) alcoholic liver diseases. After excluding such types of liver dysfunction, the 4th category of non-ABC hepatitis was made.

Data Collection

In this survey, patients' data and serum samples were collected on an annual basis and stored at the National Nagasaki Medical Center until they were used for analysis. After 2005, all patients' written informed consent for enrollment in this study was obtained.

RT-PCR and Sequencing

Samples that were serologically confirmed for AHB or acute hepatitis E (AHE) were further subjected to DNA or RNA testing by means of PCR and RT-PCR, respectively. Amplification and sequencing of appropriate regions were performed by the methods described elsewhere. Briefly, total RNA or DNA was extract-

ed from the patient's serum sample. Detection of hepatitis virus genome was performed by PCR with primers derived from well-conserved genomic areas. Sequences were compared with those from isolates from various origins. Phylogenetic trees were constructed by neighbor-joining method.

Results

Trends of AVH in Japan

A total of 4,302 cases are the subject of this study. In total, throughout the study period (1980–2008) AHA accounted for 1,583 cases (37%), AHB for 1,197 (28%), AHC for 359 (8%) and non-ABC hepatitis for 1,163 (27%). The period between 1980 and 1995 when AHA was apparently predominant among viral hepatitis can be called the AHA dominant phase. During the following 8 years (1996–2003), however, the proportions of AHA, AHB, AHC and non-ABC hepatitis changed to 31, 28, 8 and 33%, respectively. This phase is characterized by even distribution of AHA, AHB and non-ABC hepatitis. Furthermore, the proportions of AHA, AHB, AHC and non-ABC hepatitis in the last 5 years (2004–2008) were 10, 43, 8 and 39%, respectively. Apparently, these changes in trend of hepatitis were caused by a major decrease of AHA incidence (fig. 1).

Genotype Shifting of AHB

Genotype analyses for AHB cases were done on 498 samples (1991–2008). Figure 2a shows the proportions of genotypes. Respectively, genotypes A, B and C accounted for 23% (115), 8.6% (43) and 67.5% (336) of AHB during

Fig. 2. a Genotype change in AVB (1991–2008, n = 498). **b** Trends of HBV genotypes (1991–2008). Note that HBV genotype A has increased in the course of the observation period. * p < 0.05; *** p < 0.001.

the period, whereas 1 case (0.2%) each of genotypes D, E, G (co-infection with genotype A) and H was found. The trend of genotypes of AHB is shown in figure 2b. HBV genotype A was confirmed in 9 of 150 cases (6.0%) in phase 1 (1991–1996), 19 of 123 (15.4%) in phase 2 (1997–2002) and 87 of 225 (38.7%) in phase 3 (2002–2008). An apparent increment of AHB by HBV genotype A proportion is observed (p < 0.05, 1st vs. 2nd phase; p < 0.0001, 1st vs. 3rd and 2nd vs. 3rd phases). In contrast, HBV genotype B was observed in 9 of 150 cases (6.0%) in phase 1, 9 of 123 (15.4%) in phase 2 and 26 of 225 (11.6%) in phase 3. There was no significant difference among the frequency of AHB by HBV genotype B in the 3 phases. Characteristics of AHB by HBV genotype A include male dominance (94.8% for genotype A, 76.7% for B and 56.0% for C; p < 0.001), higher total bilirubin (10.1 ± 7.9 mg/dl for genotype A, 8.1 ± 7.6 mg/dl for B and 6.9 ± 5.9 mg/dl for C; p < 0.001), lower frequency of severe cases (3.5% for A, 11.0% for B and 8.3% for C; p < 0.05), and higher rate of chronicity (3% for A and 0% for both B and C; p < 0.05).

Domestic or Imported Hepatitis E in Japan

In the 1,163 cases of non-ABC hepatitis, 896 (77.0%) samples were available for anti-hepatitis E (HEV) analysis. Of the 896 cases, 8 were positive for anti-HEV IgM

alone, 78 were positive for anti-HEV IgG alone, and 44 cases tested positive for both anti-HEV IgM and IgG. Based upon studies on specificity tests (data not shown), the 44 cases (4.9%) which were positive for both anti-HEV IgM and IgG were given a final diagnosis of AHE. Among the 44 samples, RT-PCR for HEV was performed for 30 samples which all showed positive. Eleven cases had a history of international travel, whereas 20 did not. Travel history was not confirmed in the remaining 13 patients, who probably acquired HEV infection locally. Phylogenetic analysis revealed that all but 1 (genotype 4) domestic infections were caused by HEV genotype 3, whereas imported infections were caused by either genotype 1, 3 or 4.

Figure 3 shows the trend of non-ABC and hepatitis E that had been buried in non-ABC from 1980–2008 in this study. In Japan, which has been believed to be a non-endemic country for HEV, AHE occurred sporadically as early as the 1980s. Although the number of hepatitis E (1–6 cases per year) and the ratio to non-A, B, C and E hepatitis (0–14.5%) are not very high and insignificant, the occurrence of hepatitis E became constant after 2002. Hepatitis E constituted 11.0% (25/228) of non-ABC hepatitis after 2002. All patients with AHE recovered, and none of the cases showed prothrombin time less than 40%.

Fig. 3. Trends of non-ABC hepatitis (1980~2008, n = 895). Bars indicate numbers of non-ABC hepatitis in each year. Closed bars within, indicate absolute numbers of AHE, and the line plot indicates the ratio of AHE to non-ABC hepatitis.

Discussion

Despite being notifiable infectious diseases, very limited information has been available on the epidemiology of AVH in Japan. Under-reporting of cases has been linked to lack of awareness of the reporting system by medical practitioners and a rather complex process of notification. This study, which is a nationwide longitudinal survey carried out over a long period, provides reliable data on trends of AVH in Japan.

In this study, AHV is classified into 4 categories, namely, AHA, AHB, AHC and non-ABC hepatitis. Other etiologies of AVH, such as Epstein-Barr virus, cytomegalovirus, and herpes simplex virus-associated hepatitis, were excluded to focus on the epidemiology of 'hepatitis virus'. Accordingly, the category non-ABC hepatitis may consist of undiscovered or submerged types of hepatitis, such as AHE which had been paid little attention as a cause of domestic AVH in most industrialized countries, including Japan, until recently.

The overview of trends among all 4,302 cases in chronological fashion reveals that the cause of hepatitis in Japan has been drastically changed during the past 3 decades. This change is largely due to a major decrease of AHA, probably because of improvements in hygienic conditions in this country.

In connection with this decrease of AHA incidence, a marked decrease of anti-hepatitis A prevalence among the healthy population has been observed. More than 99% of individuals who were under 50 years old were sensitive to hepatitis A in 2006 (unpubl. observation). This may paradoxically rouse a debate over the need for vaccination in this low-endemic country. In fact, many out-

breaks have been observed in low-endemic countries [3, 4], which can be linked to imported foods.

There was a remarkable increase in AHB by HBV genotype A from the 1st phase (1991–1996) to the 2nd (1997–2002) and 3rd (2003–2008) phases. This observation is consistent with previous reports [5–11]. Like other investigators, we observed an increase of HBV genotype A which had not been indigenous to Japan, probably because of a marked increase of immigration from countries where HBV genotype A is common. Taking into consideration that all AHB by HBV genotype A patients reported in our study were Japanese and most of them had neither travel histories nor contact with foreign people, it seems to be natural to speculate that original transmission had happened from foreign individuals to Japanese, and secondary spread from Japanese to other native individuals were carried out.

Clinical characteristics of AHB by genotype A is of particular importance. Our data indicate a milder, but prolonged course of AHB genotype A compared to genotype B or genotype C. Although chronicity of HBV genotype A has been a matter of concern, the reported chronicity rate varies [5, 7, 8]. If HBV genotype A is prone to cause chronic infection in immunocompetent adults, the increase of such strains in acute hepatitis may change the picture of chronic infection in this country. Indeed, Matsuura et al. [12] reported that HBV genotype A in chronic hepatitis B between 2005 and 2006 was twice as frequent (3.5 vs. 1.7%; $p = 0.02$) as it was in their previous cohort between 2000 and 2001 [13]. A further study, especially a prospective one, is necessary to confirm the scenario.

HEV is a major cause of acute hepatitis in many developing countries where AHE is an important public health concern. However, cases of sporadic AHE in people with no history of recent travel have been reported in developed regions such as North America, Europe, Japan and Australia [14–21]. The reporting of such infections together with the availability of more comprehensive molecular and serological data has led to the re-evaluation of HEV epidemiology and to the acceptance that autochthonous AHE is a clinical problem in developed countries [14]. Information on AHE in the non-ABC hepatitis population in Japan is limited, although there are many reports of sporadic or epidemic occurrence of AHE [21–28]. The current study also showed the trend of AHE in Japan. AHE constituted 4.9% (44/896) of non-ABC hepatitis. Although the number of AHE cases (1–6 cases per year) and its ratio to non-ABC hepatitis (0–14.5%) are not very high and insignificant, the occurrence of AHE became constant after 2002. Surprisingly, AHE constituted as high as 11.0% (25/228) of non-ABC hepatitis after 2002. The clinical course was generally modest, and none of the patients showed a severe type of hepatitis, probably because most domestic cases were caused by HEV genotype 3 which has been implicated with milder clinical outcome compared with HEV genotype 4 [29–31]. This phenomenon may reflect the fact that our sentinels involve only a few institutes in Hokkaido where HEV genotype 4 is endemic. Nevertheless, the trend of AHE requires particular attention, because mode of transmission is still often unknown, even after taking very careful history of eating particular foods such as raw meat of deer, pigs and boars [29].

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Disclosure Statement

All authors do not have conflicts of interest to declare.

Appendix

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