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Hepatitis E outbreak at a nursing home for aged people in Hokkaido, Japan, between February and March 2016

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ABSTRACT

Background: Infection with hepatitis E virus (HEV) genotypes 3 and 4 are usually asymptomatic but can occasionally result in life-threatening acute hepatitis. To date, only sporadic cases together with a few outbreaks have been documented. Seroprevalence studies with assays for the detection of HEV IgG antibodies, suggest that HEV is more prevalent than previously thought, even in non-endemic regions.
Objectives: The aim of this study was to characterize an outbreak of hepatitis E (HE) in a nursing home for aged people between February and March 2016.
Study design: After the identification of two cases living in the same nursing home, the presence of antibodies against HEV and HEV RNA were examined in serum samples collected from the other residents and staff members to identify any additional cases. An epidemiological investigation was also carried out.
Results: Only 4 patients showed mild symptoms such as anorexia, abdominal pain and fatigue. Among the 125 persons tested, 28 residents and one dietitian were confirmed positive for anti-HEV IgA or IgM antibodies, and/or HEV RNA. Eight samples had only IgG antibodies. Finally, 22 cases were notified with HE on the basis of the presence of IgA antibodies. All HEV isolates obtained were 99.8–100% identical and belonged to genotype 3.
Conclusion: HEV infections seem to be under-reported or underestimated possibly due to cases being generally asymptomatic. Testing for the presence of both anti-HEV antibodies and HEV RNA would be beneficial for both the comprehensive diagnosis of HE infections and the prevention of further infections.

1. Background

Hepatitis E virus (HEV) often causes acute hepatitis, and 4 main genotypes have been isolated from humans [1]. In developing countries, two human-specific HEV genotypes (1 and 2) have been identified and are transmitted generally through contaminated water by the fecal-oral route. It has recently become apparent that autochthonous HEV is also widely distributed in industrialized countries. In these countries, HEV genotypes 3 and 4, which are classified as zoonotic agents, are transmitted to humans through the digestion of contaminated food, particularly undercooked or raw pork. HEV was evidenced as a zoonotic agent by the detection of virus in pigs with a high homology to HEV strains found in humans [2], and was documented in several case reports [3,4].

Commonly observed symptoms of HE include anorexia, abdominal pain, fatigue, myalgia and jaundice [5]. Although most symptomatic patients show a marked rise in liver enzymes, asymptomatic or self-limiting infections are commonly reported [6,7]. The mean incubation period is reported to be approximately 40 days (range: 15–60 days) [5].

Many seroprevalence studies have been undertaken, particularly in Europe, with the results indicating a high variability in the rates of seroprevalence [8]. A recent meta-analysis including a total 73 studies conducted in Europe estimated the seroprevalence to range from 0.6% to 52.5%, with the rates increasing with age, but unrelated to gender. Furthermore, most countries have reported a higher incidence of HEV infection when testing for the presence of infection markers such as specific antibodies and/or HEV RNA, chiefly because of the growing awareness of the disease. Additionally, chronic infection among immunocompromised individuals or those with pre-existing liver diseases have been described [9].

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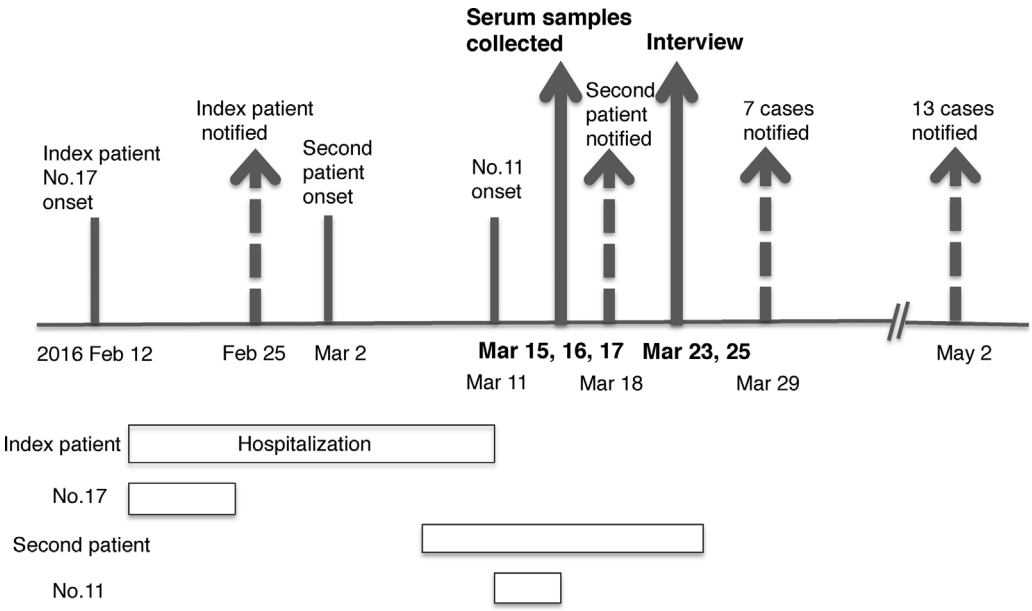

Fig. 1. Time line of events associated with the hepatitis E outbreak at a nursing home for aged people in Hokkaido, Japan, between February and March 2016.

2. Objectives

We experienced an outbreak of HE at the nursing home for aged people in Asahikawa City, Hokkaido, Japan. Herein, we characterize the outbreak in order to obtain a better understanding of this disease.

3. Study design

3.1. Epidemiological investigation and sample collection

Notification of the index case (February 25, 2016) and a second case (March 18), both of whom lived at the same nursing home, was made to the Asahikawa City Center of Public Health (ACPH). Cases defined by the presence of HEV IgA or IgM antibodies, and/or HEV RNA can be reported from case-based surveillance in Japan.

After the notification of HE to the ACPH, we began active surveillance including interviews and questionnaires related to the services provided there, the structure of the home, and the food menus during the possible incubation period. Personal interviews with each resident were difficult due to their advanced age (66–104 years, mean 88 years) and associated mild to moderate cognitive impairment. An environmental investigation including inspection of the kitchen and hygienic conditions was also performed. The home consisted of 2 distinct buildings separated by a connecting passageway. In building A, some residents shared rooms and lavatories, while the residents in building B had private rooms and lavatories. The healthcare workers and nurses worked in designated buildings, and they did not visit each other. Seventy (82%) of the 85 residents were female.

Serum samples, collected from 84 residents and 40 staff members on March 15, 16 and 17, as well as one collected from the second patient on March 9, were tested for the presence of markers of HEV infection.

3.2. Ethical considerations

According to the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections in Japan, HE is defined as mandatorily notifiable infectious disease, and specimens from patients suspected of having HE can be collected and tested for HEV without informed consent from the patients. The Ethics Committee of Hokkaido Institute of Public Health agreed to the publication of this paper.

3.3. HEV serological determination

In accordance with the manufacturer's instructions, HEV IgA antibodies were tested using an enzyme-linked immunosorbent assay (ELISA) [10] (IMMUNIS® IgA anti-HEV EIA, Institute of Immunology Co., Ltd., Tokyo, Japan) for serum samples from 85 residents and 40 staff members. Among the 125 potentially exposed residents and staff, serum samples from 84 or 85 residents, 2 dietitians and 2 staff members who consumed the same meals as residents were additionally tested for the presence of HEV IgM and IgG by ELISA (IgG/IgM anti-HEV EIA, Institute of Immunology Co., Ltd., Tokyo, Japan).

3.4. Reverse transcription PCR and phylogenetic analysis

IgA antibody-positive or possibly positive (over 40% of the cut-off value, 29 samples) serum samples were further examined for the presence of HEV RNA. RNA was extracted from 200 µL of serum using a QIAamp mini elute virus spin kit (QIAgen. Hilden, Germany) following the manufacturer's instructions. Reverse transcription PCR was performed according to the previously described protocol with sets of primers targeting a highly conserved sequence within HEV open reading frame (ORF) 1 and ORF2 [11,12]. Nucleotide sequencing was performed, and nucleotide alignments and a phylogenetic tree were constructed using MEGA version 5.1 by the neighbor-joining method with 1000 bootstrap replicates.

4. Results

4.1. Epidemiological investigation

A time line of the events associated with this outbreak is shown in Fig. 1. On February 25, 2016, the ACPH was notified of a male resident (the index patient, shown as No. 4 in Table 1) with HE. He had an abdominal aortic aneurysm, and complained of abdominal pain on February 12. Another patient (No. 29) with anorexia and fatigue, who went to a doctor with a suspected cerebral infarction on March 2, was diagnosed initially with drug-induced liver injury, and subsequently confirmed as having an HEV infection on March 18. Both cases showed moderately elevated aspartate aminotransaminase (AST) and alanine aminotransaminase (ALT) levels, and both were positive for HEV IgA antibodies as shown in Table 1. They had been living in the same building (building A). As the above reports were close together, they