Identification of Indigenous Hepatitis E Virus from a Japanese Patient Who Contracted Sporadic Acute Hepatitis in 1982

To the Editor—We read with great interest the article by Takahashi et al. [1], who recovered 7 hepatitis E virus (HEV) isolates of genotype I, III, and IV from Japanese patients with sporadic acute hepatitis who were treated during 1996–2001 and showed the wide genetic diversity of HEV in Japan. On the basis of the existence of pairs of highly homologous isolates, Takahashi and colleagues speculated that multiple HEV strains have already made inroads and are spreading in Japan.

HEV is a major cause of outbreaks and sporadic cases of viral hepatitis in tropical and subtropical countries [2]. There is growing consensus that sporadic hepatitis E disease occurs in individuals in industrialized countries who have no epidemiologic evidence of exposure to HEV strains from countries where the disease is endemic and that HEV is a zoonotic virus, as suggested by the close genetic relationship between swine and human viruses [2–4]. HEV variants of genotypes III and IV have been isolated from sporadic cases of acute hepatitis in the United States, Europe, China, Taiwan, and Japan [2–6]; however, when such variants emerged in these industrialized countries remains unknown.

The findings of Takahashi et al. [1] led us to analyze stored serum samples from a 38-year-old man who came to our hospital in January 1982 for treatment of jaundice and general fatigue. The serum samples were obtained on hospital admission, and the patient was given a clinical diagnosis of sporadic acute hepatitis of non-A, non-B etiology at that time. The serum samples were tested for IgM and IgG antibodies to HEV (anti-HEV) by in-house EIA, using purified recombinant open-reading frame 2 (ORF2) protein, which had been expressed in silkworm pupae, as the antigen probe. The serum samples were also tested for HEV RNA by reverse-transcription polymerase chain reaction, using a method described elsewhere [7] and primers targeting the ORF2 region. The amplified product was sequenced directly on both strands. A phylogenetic tree was constructed by the neighbor-joining method [8], on the basis of a partial nucleotide sequence of the ORF2 region (301 nt).

The patient’s stored serum sample tested positive for anti-HEV IgM and HEV RNA. He had never traveled outside Japan and had no contact with travelers to areas in which HEV was endemic, and there had been no cases of hepatitis in his family. On admission, the patient’s liver enzyme and bilirubin levels were considerably elevated (alanine aminotransferase, 778 IU/L; aspartate aminotransferase, 615 IU/L; and total bilirubin, 4.5 mg/dL), but they decreased rapidly and normalized on day 21 after admission. Retrospective serologic tests ruled out acute infection with hepatitis A, B, or C viruses, cytomegalovirus, or Epstein-Barr virus. A serum sample that had been obtained when the patient visited our hospital with herpes zoster in July

Figure 1. Phylogenetic tree constructed by the neighbor-joining method and based on the partial nucleotide sequence (301 nt) of the open reading frame 2 region of 50 human and swine hepatitis E virus (HEV) isolates. The nucleotide sequences of 49 known human and swine HEV isolates were retrieved from GenBank/DDBJ/EMBL databases on 22 July 2002. The partial nucleotide sequence of HE-JO-1982 obtained in the present study is deposited under accession no. AB088418 and is boxed for visual clarity. All human and swine HEV strains of Japanese origin are indicated by boldface type. Bootstrap values >70% are indicated for the major nodes as a percentage of the data obtained from 1000 resamplings [9].
1999, 17.5 years after the onset of hepatitis, was reproducibly positive for anti-HEV IgG, with an optical density of 0.274 (cutoff value, 0.152). The optical density value decreased to 0.015 after absorption with the same recombinant ORF2 protein that was used as the antigen probe, but it remained at 0.258 after absorption with a mock protein obtained from the pupae of silkworms infected with nonrecombinant baculovirus.

The HEV isolate (HE-JO-1982) from the infected patient was close to known genotype III isolates, with 87.6%–94.4% identity in a 412-nt sequence, and was most closely related to the JRA1 isolate of genotype III, which is considered to be indigenous to Japan [5, 7]. The phylogenetic tree constructed on the basis of a 301-nt ORF2 sequence confirmed that the HE-JO-1982 isolate belonged to genotype III, and the isolate segregated into a group consisting of 3 HEV strains that were isolated from a Japanese patient with sporadic acute hepatitis and who had no known history of travel to areas in which HEV is endemic (JRA1) [5] and from farm pigs in Japan (swJ3570 and swJ681) [7] (figure 1).

Our results indicate that a presumably indigenous HEV isolate was circulating in Japan even in the early 1980s. The finding that a domestic HEV strain has been present for ~2 decades in Japan needs to be taken into consideration in future epidemiologic studies on clinical and subclinical HEV infection and for the proper diagnosis of hepatitis E disease in industrialized countries where HEV infection was believed to be nonendemic.

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Reply

To the Editor—In a previous study [1], we suggested that the presence of hepatitis E virus (HEV) infection in Japan is no longer solely due to imported cases from countries in which HEV is endemic; however, we left unanswered the question of how long ago the ancestors of the presently domestic HEV strains made inroads into Japan. In their letter, Aikawa et al. [2] provide an answer, although not the final one, from at least 20 years ago. Aikawa and colleagues performed nucleotide sequencing on an HEV isolate (HE-JO-1982) from the stored serum sample of a Japanese patient who had contracted non-A, non-B hepatitis in 1982. Among all known sequences, HE-JO-1982 was most ho-

Figure 1. Genetic segregation and geographic distribution of hepatitis E virus genotype III isolates found in Japan. The phylogenetic tree was adapted, with permission, from Aikawa et al. [2].