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Commentary

Hepatitis E In Transplant Recipients: Why Is This Not A Problem In Japan?

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Chronic hepatitis E virus (HEV) infection in immunosuppressed patients is increasingly recognized as a relevant clinical problem in European countries. However, it is unclear whether chronic hepatitis E is also a potential problem in eastern Asia. The study by Ilnagaki et al. published in this issue of *EBioMedicine* is therefore of major interest (Inagaki et al., 2015). The authors performed a large multi-center study examining the frequency and clinical relevance of chronic hepatitis E in Japanese liver transplant recipients. About 75% of all liver transplant centers participated in this study, comprising HEV-RNA testing of 1651 liver transplant recipients. Of note and very importantly, only two chronic HEV infections were detected, which is a surprisingly low rate of HEV infected patients (0.12%). The finding is remarkable considering that the median time from transplantation was 81 months (range 0–297 months) representing a long time of potential exposure post-transplantation.

The findings in Japan are quite different from European experiences where many studies describe frequencies of chronic hepatitis E of more than 1% in liver transplant cohorts (Fig. 1) (Behrendt et al., 2014). In contrast, no case of chronic hepatitis E was found in India in a study on 205 renal transplant recipients (Naik et al., 2013). This has led to the hypothesis that HEV genotype 1, which is common in India, may not cause chronic infection. However, most reported cases of chronic

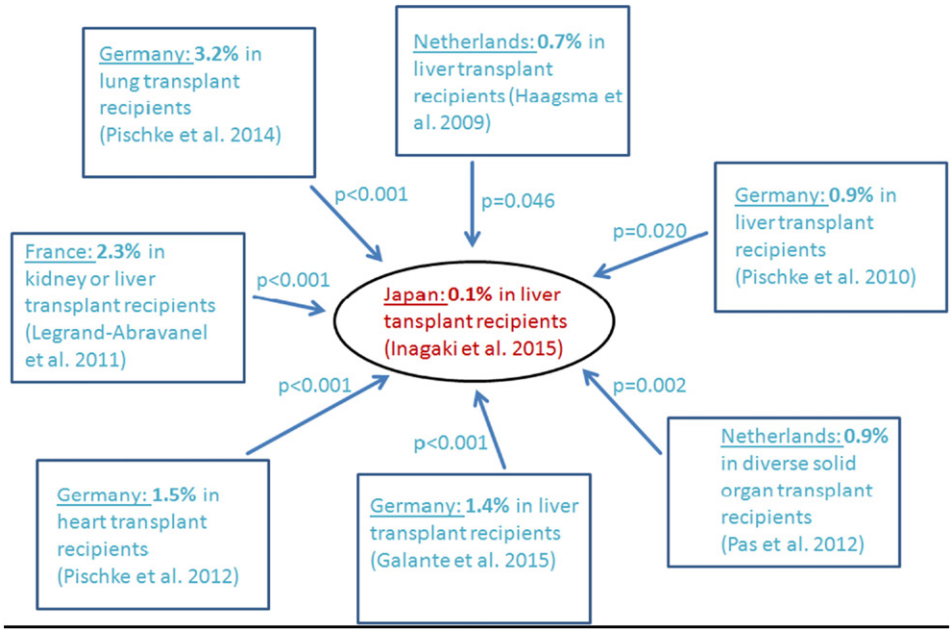

Fig. 1. Chronic hepatitis E in Japanese liver transplant recipients is less common than in Europe (Behrendt et al., 2014).

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hepatitis E are associated with HEV genotype 3 infections, and more rarely HEV genotype 4. In Japan, HEV genotypes 3 and 4 are endemic (Okano et al., 2014). The HEV subtype 3e is most frequently found in Japan (Okano et al., 2014), as in Central Europe. HEV genotypes or subtypes are therefore unlikely to explain the apparent differences in chronic HEV frequencies — even though it is still possible that distinct HEV strains circulating in Japan may be less likely to cause chronicity.

What then could explain the very low frequency of chronic hepatitis E in Japan (Fig. 1)? First, it is possible that distinct genetic factors in the Japanese population confer some level of resistance to chronic HEV infection. For other infections such as hepatitis C, differences in interferon-lambda 3 genotypes between Asians and Caucasians indeed explain, to some extent, distinct outcomes in these populations (Thursz et al., 2011). Second, there are obvious differences in food consumption habits between Japan and Europe. Regarding HEV infection, food products containing raw or undercooked pork meat are particular popular in some European countries and thus exposure to HEV may be more likely. Third, blood products may be less likely to carry HEV in Japan than in Europe (Hewitt et al., 2014). Of note, HEV-IgG antibodies have been shown to be lower in Japan (6%) than in Korean Chinese (51%), indigenous Chinese (48%), South Koreans (34%) or Koreans living in Japan (14%) (Taniguchi et al., 2009).

In summary, Inagaki et al. demonstrated for the first time that chronic hepatitis E also occurs in Japan, albeit at a far lower frequency than in European transplant cohorts. The explanation for this difference still needs to be defined.

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