Veterinary Microbiology 237 (2019) 108379

Contents lists available at ScienceDirect

Veterinary Microbiology

journal homepage: www.elsevier.com/locate/vetmic

Letter to the Editor

A comment on "Current status of hepatitis E virus infection at a rhesus monkey farm in China"

To the Editor

With great interest, I read the article published by Yang and colleagues (Yang et al., 2019). The authors reported the presence of anti-hepatitis E virus (HEV) IgG in 70.8% of rhesus macaques present in a Chinese farm. HEV RNA could be detected in the serum of 1/88 macaques and in the stool of 10/88 macaques.

HEV is subdivided into 8 genotypes (gt) (1-8); among them, HEV gt3, 4, and 7 are zoonotic. HEV gt4 includes several subtypes (4a-4i), and these subtypes are common in Asia, where pig, wild boar, and wild deer are the main reservoirs (Sayed et al., 2015). A study of HEV infection (gt1-4) was conducted on non-human primates (cynomolgus, rhesus monkeys, and chimpanzees) (Purcell et al., 2013). Although rhesus macaques (Macaca mulatta) inoculated with HEV gt(1-3) developed signs of acute hepatitis (Choi et al., 2018; Purcell et al., 2013), the clinical course of HEV gt4 infection in rhesus macaques was variable. Ji et al. reported that rhesus macaques inoculated with swine HEV gt4 (subtype 4b) developed acute hepatitis (Ji et al., 2008). Similarly, *Huang et al.* reported that rhesus macaques inoculated with human HEV gt4 demonstrated acute hepatitis, elevated alanine transaminase (ALT), and development of anti-HEV IgM and anti-HEV IgG in all infected animals (Huang et al., 2008). In the same study, 2/4 rhesus macaques inoculated with swine HEV gt4 demonstrated acute hepatitis and development of anti-HEV IgM in 3/4 infected macaques and anti-HEV IgG in all infected animals (Huang et al., 2008). In parallel, active HEV infection was established in rhesus monkeys inoculated with cow milk containing HEV gt4 (subtype 4 h) (Huang et al., 2016a). *Arankalle* et al. reported that ALT was not elevated in rhesus macaques infected with Indian swine HEV genotype IV, while increasing titer of anti-HEV IgG and virus shedding were observed in the infected animals (Arankalle et al., 2006). On the other hand, it was reported that persistent HEV infection was established in rhesus macaques challenged with swine HEV gt4 (KM01 strain), HEV RNA was consistently detected in the serum and stool of infected macaques up to 272–650 days post-inoculation. Slight elevation of liver transaminases and a very weak and transient humoral immune response were recorded in chronically infected macaques (Huang et al., 2016b)

In this study, the authors reported the circulation of HEV gt4 infection in natural, non-inoculated, rhesus monkeys present in the farm. Detection of anti-HEV IgG and HEV RNA in the rhesus monkeys indicated previous/ongoing infection. Phylogenetic analysis of the isolated strains revealed that they belong to HEV gt 4 subtypes 4b and 4 h. Importantly, no significant clinical signs were observed in these animals, and the status of anti-HEV IgM was not reported (Yang et al., 2019). Surprisingly, previous studies reported that acute hepatitis was developed in rhesus macaques inoculated with these strains (Huang et al., 2016a; Ji et al., 2008).

The discrepancy in the course of HEV gt4 infection in rhesus macaques could be attributed to several factors. First, the difference in exposure dose between nature exposure and experimental infection could affect the course of infection, as the inoculum doses determine the outcome of HEV infection in the animal model (Purcell et al., 2013; Sayed et al., 2017b). The HEV viral load was not reported in macaque feces in this study (Yang et al., 2019), and hence, the degree of infection in these animals was unknown. Second, the variation in the adaptive immune response among rhesus monkeys can affect the course of HEV infection, as it plays a role in the development of acute hepatitis. In human liver chimeric mice, liver transaminases were not elevated, as there is lack of adaptive immunity in these mice (Sayed et al., 2017a, b). Finally, HEV gt/isolate affects the course of HEV infection, pathogenesis, and/or susceptible animals affected. It was reported that BALB/c mice could be infected with swine HEV gt4 (Huang et al., 2009; Yu et al., 2018), while other studies reported that murine hepatocytes are resistant to HEV infection (Sayed and Meuleman, 2017; Schlosser et al., 2018). Similarly, active HEV infection (HEV gt4 subtype 4 h) was recently reported in Chinese cows (Huang et al., 2016a); however, to date, cows are not reported as a source of HEV infection in Europe (Baechlein and Becher, 2017; Vercouter et al., 2018). Extrahepatic manifestations were reported in the kidney and brain of rhesus macaques infected with HEV gt4 (Huang et al., 2016b; Zhou et al., 2017), while these manifestations were not reported in human liver chimeric mice infected with HEV gt1 or gt3 (Sayed and Meuleman, 2017).

In conclusion, the course of HEV infection, pathogenesis, and susceptibility of animals to infection due to HEV genotype 4 are not completely known.

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DOI of original article: https://doi.org/10.1016/j.vetmic.2019.01.021

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Received 11 April 2019

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