EBioMedicine 36 (2018) 3–4

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

EBioMedicine
Published by THE LANCET

Commentary

Extrahepatic manifestations and HEV, the genotype matters

Thomas Horvatits, Sven Pischke *

Department of Medicine, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany

Extrahepatic manifestations and viral hepatitis: a topic attracting the attention of hepatologists for more than 30 years. Hepatitis B and C virus infections have been associated with various extrahepatic diseases and in some of these phenomena a causal relationship has been proven.

Within the last two decades there was growing interest and awareness for hepatitis E virus (HEV) infections worldwide [1,2]. HEV genotype (GT) 3, the predominant GT in Europe and the USA, presents as zoonosis, mainly transmitted by infectious swine meat [3]. In contrast GT 1 and 2 are mainly transmitted by contaminated drinking water in tropical developing countries. A special situation is the setting of GT 4. This is a tropical virus, but in contrast to GT 1 and 2 it is mainly transmitted by consumption of swine meat, as GT 3 [1,2].

In the last five years several assumed extrahepatic manifestations have been observed in the context of HEV infections [4]. In particular, pancreatitis has been associated with HEV GT 1 infections, while neurological diseases as neuralgic amyotrophy or Guillain-Barré syndrome have been observed in patients with GT 3 infections. One of the most impressive studies regarding this topic was the paper by Dalton et al. [5]. They studied the prevalence of acute HEV infections in a large cohort of neurological patients presenting with various non-traumatic acute neurological diseases. They reported evidence of current HEV infection in 11/464 patients (2.4%): HEV viremia was shown in seven patients and anti HEV IgM positivity only in four patients. Notably, none of these patients had jaundice or other clinically signs of acute hepatitis. The majority of these cases included Neuralgic amyotrophy and cerebral ischemia/infarction but also patients with seizures, encephalitis and acute facial and vestibular neuropathy. This observation affirmed an association of HEV and neurological diseases in general and especially Neuralgic amyotrophy.

In *EBioMedicine*, Wang et al. studied a similar approach from China, an area endemic for GT 4 [5]. They enrolled 1117 patients with neurological illness and 1475 healthy controls and tested them for HEV and anti-HEV. In contrast to the previous study from Europe, the rate of anti-HEV IgM antibodies did not differ significantly between groups, as authors found 6 positive cases in the neurological illness cohort (0.54%) and 10 positive cases in the healthy controls (0.68%). All detected individuals were HEV RNA positive. Patients with acute HEV infection included cases of viral encephalitis, posterior circulation ischemia, peripheral neuropathy as well as one case of Guillain-Barré syndrome. Notably, rate of anti-HEV IgG antibodies did not show a significant difference between groups (neurological cases 39.51% vs. controls 35.63%; p = n.s.). Therefore, Wang et al. concluded that HEV genotype 4 seems not to contribute directly to acute neurological illness in China.

The study of Wang et al. raises several questions as their findings were unexpected and in absolute contrast to previous European and Japanese studies [6–9]. However, we have to be very careful in comparing such data. Whereas Wang et al. included a control group in their study, Dalton and van Eijk et al. reported cohort studies without controls [6,8,9]. Beside this, one could discuss that sample sizes and degree of heterogeneity of neurological entities of different etiologies vary a lot between these studies. Fukae et al. recently reported that 5% of Guillain-Barré patients in Japan were associated with acute HEV infection – in line with European findings by van den Berg [7,9]. However, what is true for Guillain-Barré syndrome does not need to be true in neuralgic amyotrophy. The main factor is the geographical distribution of HEV, as it can be assumed that the European studies reported solely HEV GT 3 associated cases, and the study by Wang et al. reported HEV GT 4 associated infections [5].

Irrespective from geographical factors, HEV GT 3 and GT 4 resemble each other regarding the majority of viral, epidemiological and clinical factors [2]. This is not really surprising if we look at the evolution of HEV: It has been supposed that lineages of the progenitors of HEV (which existed 536–1344 years ago) split into 2 main groups: the anthropotropic GT 1/2 and the enzootic forms, GT 3/4 [10]. Here again, GT 3/4 behave similarly as an analysis of population dynamics of HEV proposed an expansion of both, GT 3 and GT 4, during the 20th century, followed by a clear decline in the 1990s. However, there are differences, e.g. GT 4 exhibits country specific variants, as in Chinese and Japanese claims different population dynamics have been observed [10].

The association of HEV and neurological disorders seems to be a further differentiation of GT 3 and GT 4 also depending on the neurological entity. Future studies are needed to further elucidate similarities and differences of these 2 GTs.

Disclosure

The authors declare that they have no conflict of interest regarding this manuscript.

No financial support was received.

DOI of original article: https://doi.org/10.1016/j.ebiom.2018.08.053.

* Corresponding author at: Department of Medicine, University Medical Centre Hamburg-Eppendorf, Matrinistr. 52, 20246 Hamburg, Germany.

E-mail address: s.pischke@uke.de (S. Pischke).

https://doi.org/10.1016/j.ebiom.2018.09.004

References

[1] Wedemeyer H, Pischke S, Manns MP. Pathogenesis and treatment of hepatitis e virus infection. Gastroenterology 2012;142:1388–97 [e1381].

[2] Hoofnagle JH, Nelson KE, Purcell RH. Hepatitis E. N Engl J Med 2012;367:1237–44.

[3] Horvatits T, Ozga AK, Westhoelter D, et al. Hepatitis E seroprevalence in the Americas: A systematic review and meta-analysis. Liver Int Apr 2018 16. https://doi.org/10.1111/liv.13859 [Epub ahead of print].

[4] Pischke S, Hartl J, Pas SD, et al. Hepatitis E virus: Infection beyond the liver? J Hepatol May 2017;66(5):1082–95. https://doi.org/10.1016/j.jhep.2016.11.016 [Epub 2016 Nov 29].

[5] Wang Y, Wang S, Wu J, et al. Hepatitis E Virus Infection in Acute Non-Traumatic Neuropathy: A Large Prospective Case-Control Study in China. EBioMedicine 2018. https://doi.org/10.1016/j.ebiom.2018.08.053.

[6] Dalton HR, van Eijk JJJ, Cintas P, et al. Hepatitis E virus infection and acute non-traumatic neurological injury: A prospective multicentre study. J Hepatol 2017;67:925–32.

[7] Fukae J, Tsugawa J, Ouma S, et al. Guillain-Barre and Miller Fisher syndromes in patients with anti-hepatitis E virus antibody: a hospital-based survey in Japan. Neurol Sci 2016;37:1849–51.

[8] van Eijk JJ, Madden RG, van der Eijk AA, et al. Neuralgic amyotrophy and hepatitis E virus infection. Neurology 2014;82:498–503.

[9] van den Berg B, van der Eijk AA, Pas SD, et al. Guillain-Barre syndrome associated with preceding hepatitis E virus infection. Neurology 2014;82:491–7.

[10] Purdy MA, Khudyakov YE. Evolutionary history and population dynamics of hepatitis E virus. PLoS One 2010;5:e14376.