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A Case of Genotype 3a Hepatitis E Virus Infection Manifesting Neurological Symptoms after Travelling to Indonesia

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Abstract: This report describes an infection of hepatitis E genotype 3a in an individual returning from a vacation to Indonesia. The patient had signs of hepatitis as well as neurological symptoms. This case illustrates that a zoonotic type 3 HEV infection should also be considered as a travel health risk.

Key words: Hepatitis E virus, genotype 3, Indonesia, neurology, returning, vacation

INTRODUCTION

Hepatitis E Virus (HEV) is a leading cause of acute viral hepatitis in many developing countries (WHO., 2015). The epidemiology and clinical presentation of HEV infection vary greatly by geographic location, based primarily on differences in circulating HEV genotypes; (Tei *et al*., 2004; Li *et al*., 2005 Dalton *et al*., 2008). Autochthonous HEV infection is an increasing problem in the Netherlands (Hogema *et al*., 2014) where HEV genotypes 3 and 4 are primarily transmitted zoonotically, especially, after consumption of undercooked meat from infected swine (Arankalle and Chobe, 1999; Van der Poel *et al*., 2001; Der Honing, *et al*., 2011). In the Netherlands, HEV infection is usually mild but ranges in severity from subclinical to fulminant hepatitis. Patients with pre existing liver disease, immune compromised patients and pregnant women are at greater risk for severe disease (Khuroo *et al*., 2009). Contrary to hepatitis a chronic HEV infections have been described but they do not seem to occur in otherwise healthy individuals (Krain *et al*., 2014). HEV genotypes 1 and 2 are found exclusively in humans whilst 3 and 4 are found in both human and animal populations. The four mammalian genotypes have a distinct distribution both geographically and within human and animal populations (Fig. 1). Support for zoonosis in genotype 3 or 4 HEV comes from the close RNA sequence homology shared between human and swine HEV circulating within the same regions (Arankalle *et al*., 2007).

We report the case of HEV transmission of the unexpected genotype 3a in a patient returning from Indonesia, where genotypes 1 and 4 are endemic.

MATERIALS AND METHODS

Case presentation: In May 2014, a 70 years old male presented to the hospital with jaundice and complaints of retrosternal and shoulder pain. His past medical history comprised coronary artery disease for which he used once daily isosorbide mononitrate 100 mg, acetylsalicylic acid 80 mg and omeprazole 20 mg. He had used these medications for a long time without any indication of drug-related hepatotoxicity. There were no risk factors for blood borne viruses nor for an underlying liver disease.

He recently visited Java Indonesia. Prior to this, patient had a pre-travel health consultation. He was parenterally vaccinated for hepatitis A, typhoid fever and diphtheria, tetanus and poliomyelitis. He also received a prescription for azithromycin in case of traveller's diarrhoea but did not use it.

He spent nearly 4 weeks of travelling and staying in hotels in Java. His diet was unrestricted and he had no history of eating undercooked pork meat or liver. Neither he nor his contacts suffered from diarrhoea in Indonesia or after their return to the Netherlands.

About 4 weeks after his return he complained about nausea, dizziness and transpiration and shoulder pain with a burning sensation in both arms.

Upon physical examination patient was jaundiced but he had normal vital signs and no fever. Besides a mild tenderness in the right hypochondriac region, no thoracic or abdominal abnormalities were found. The EKG showed no changes compared to previous EKG's.

Neurological consultation revealed a peripheral neuropathy in both arms characterized by a painful paresis without aesthetic impairment. There were no

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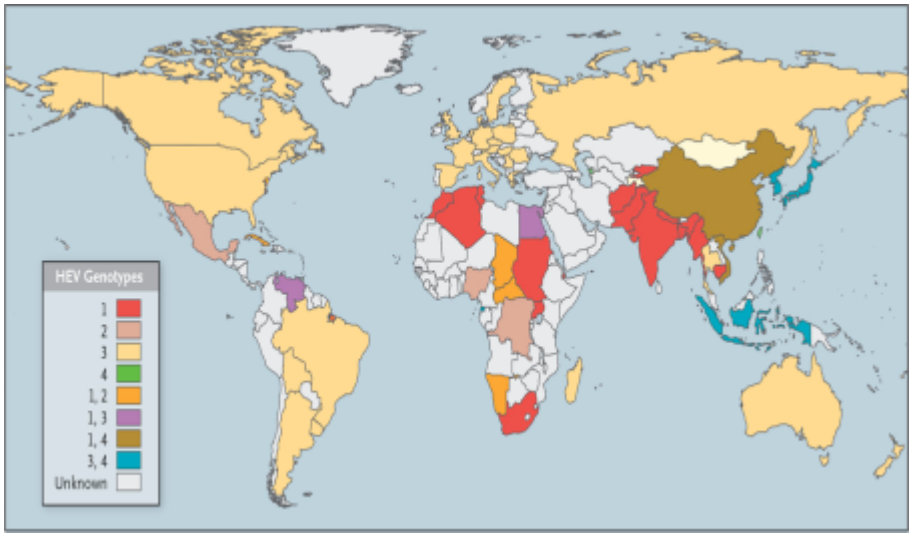

Fig. 1: Geographic distribution of HEV genotypes in locally acquired HEV infection. Figure adopted from: Teshale E, Ward JW. N Engl J. Med 2015;372:899-901. Data are from the division of Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, USA

Table 1: Liver laboratory tests, HEV titres and viral load on admission and during follow-up in our case (week 0, 1 and 10)

Variables	Normal values	Week 0	Week 1	Week 10
CRP (mg/L)	<10	18	40	9
Leukocytes (10^9/L)	4-10	5.0	4.1	5.2
Trombocytes (10^9/L)	150-400	118	139	196
Total bilirubin (umol/L)	<17	50	147	15
Direct bilirubin (umol/L)	<5	37	132	12
Alkaline phosphatase (U/L)	<125	301	436	180
Gamma GT (U/L)	<50	808	946	65
ASAT (U/L)	<40	2205	2727	78
ALAT (U/L)	<45	1648	3335	77
LD (U/L)	<250		875	297
Hepatitis E (IgG) [Threshold 1.00]		5.56		12.05
Hepatitis E (IgM) [Threshold 1.00]		9.37		5.53
HEV-RNA viral load $1.9*10^1$<$1.5*10^1$ (IU/mL)		$8.89*10^6$		

pyramidal signs. Electromyography showed long thoracic and brachialis denervation signs but without amyotrophy of the supraspinatus and infraspinatus fossae or arm musculature.

Laboratory investigations confirmed cholestatic and parenchymatous liver test abnormalities (Table 1) without compromised liver synthesis and no cardiac enzyme rise. Doppler ultrasound revealed a normal shaped liver with signs of steatosis, normal vessels and a non-dilated biliary tree without splenomegaly.

A full screen for acute and chronic liver disease was performed on admission. HBsAg, anti-HCV, HAV IgM, CMV IgM and EBV IgM serological results were all negative. Several infectious diseases responsible for neurologic symptoms (HIV, syphilis, cytomegalovirus, Epstein-Barr virus, mycoplasma, HSV, VZV, leishmaniasis, arboviruses) were excluded by nucleic acid and serological assays respectively. In contrast, an acute HEV infection was diagnosed through the detection of anti-HEV immunoglobulin IgM (Index 9.37, threshold value 1) and anti-HEV IgG positivity [ELISA test DIAPRO, RIVM, Bilthoven]. The 10 weeks after initial diagnosis, HEV IgM titre had fallen to 5.53 (Fig. 1). Subsequently, HEV-RNA was detected by RT-PCR with a viral load of 8.89×10^6 IU/mL (Fig. 1).

Liver transaminases returned to normal within 10 weeks. HEV-RNA was cleared in serum 16 weeks after the first blood sample, however, clinical neuropathy lasted for 24 weeks until full recovery.

RESULTS AND DISCUSSION

Genotype analysis: PCR amplification and sequence analysis was carried out across a 280 base pair region of ORF-2, using generic HEV primers and comparing the generated sequence against human and swine genotypes 1-4 viruses retrieved from GenBank. The analysis indicated that the virus isolated from this patient belonged to genotype 3a, a genotype which has been isolated from swines in Indonesia (Widasari *et al*., 2013).

Until now, intercontinental travel related HEV infection is sparsely documented in the Netherlands. We describe a case of HEV genotype 3a infection of which the

time course and clinical presentation is compatible with an acquisition in Indonesia. The genotype 3 strains that have been isolated on Java Indonesia are predominantly of genotype 3a (Widasari *et al*., 2013). Although, genotype 3a has been found in the Netherlands, the predominant 'Dutch' genotypes are 3c and f (Berto *et al*., 2012; Koot *et al*., 2015). Despite the ubiquity of HEV genotype 3 in the swine population in over 22 countries worldwide (Fig. 1) (Berto *et al*., 2012), clinically apparent human infections with this genotype have been reported almost entirely in developed countries. Given the relative high prevalence of both HEV 3 and HEV 4 genotypes in the Indonesian swine population (Wibawa *et al*., 2004), it is surprising to note that cross-species infection of genotype 3 has not been described more frequently as a travel-related health risk.

One can postulate that in Indonesia, due to a high prevalence of circulating HEV genotype 4 antibodies, an actual symptomatic infection with the genotype 3 virus may not commonly occur. Specific HEV IgG antibodies against viral capsid protein might confer protection against reinfection, however, the protective titre and the duration of its persistence are uncertain as well as it is still unknown if protective antibodies are cross-reactive between genotypes (Teshale and Ward, 2015).

Like other viral hepatitides (Van Aalsburg *et al*., 2011), extra-hepatic manifestations can occur in HEV infection and in particular, neurological disorders have been described, like in our patient (Woolson *et al*., 2014). Such infections may elicit an immune response that cross-reacts with axolemmal or Schwanncell-antigens and thereby damages peripheral nerves (Cheung *et al*., 2015). Frequently, HEV-RNA is detected in the CSF of patients with chronic HEV infection and neurologic signs and symptoms, suggesting that local viral replication is occurring in the central nervous system which may cause direct neuronal damage (Cheung *et al*., 2015). In a recent case series from England and France (Deroux *et al*., 2014), the prevalence of neurological complications associated with HEV infections was estimated as 5.5%. Of 19 acute HEV cases documented, 8 patients suffered from Guillain-Barre syndrome and 3 had associated brachial neuritis like in our patient. Also, polyradiculopathy (n = 3), peripheral neuropathy (n = 3), transverse myelitis and encephalitis with ataxia (both n = 1) were reported. Interestingly, all of the reported neuropathic HEV cases were genotype 3, as in our case. HEV genotype 3 might be a human neurotropic species directly affecting the nervous system but in swine the neurological sequels of genotype 3 have not been well documented. HEV RNA has been detected in the brain of 2 out of 4 wild boars which were intravenously inoculated with HEV (Schlosser *et al*., 2015). However, the researcher did not note any neurological signs before sacrificing the animals in their study.

HEV incidence now seems to rise in the Netherlands. According to a Bayesian model, HEV seroprevalence in the Netherlands was estimated as high as 2% in the general population) but 6 and 11% in non-swine veterinarians and swine veterinarians, respectively (Bouwknegt *et al*., 2008). However when the presence of silent HEV infection among dutch blood donors was studied, the HEV seroprevalence was much higher. Of the 5,239 donations, 1,401 (27%) tested repeat-positive for HEV IgG of which 49 (3.5%) also tested positive for anti HEV IgM in an age group between 30 and 60 years and it potentially applies to larger parts of Europe also (Zhu *et al*., 2010; Slot *et al*., 2013). The attack rates seem the highest among young to middle-aged adults suggesting that infections usually occur later in life and/or that infection during early life may not confer lifetime protection.

CONCLUSION

We recommend that healthcare workers taking care of ill returned travelers consider the possibility of HEV acquisition. We also recommend that clinicians should consider HEV infection in patients with combined neurologic and liver abnormalities. Continued vigilance for HEV is needed as it may support the public health response to the apparent increasing HEV burden in the Netherlands not only as an locally emerging infection but also as a travel-related disease.

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