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Hot Topic

# Autochthonous hepatitis E: a common and fatal but neglected emerging disease in France

During the summer of 2016, a feature article entitled 'Europe's new hepatitis problem' was published in *Science* and focused on the emergence, risk factors and clinical concern about autochthonous hepatitis E in European countries, particularly in France [1]. However, in France itself, hepatitis E is deeply neglected.

Hepatitis E virus (HEV), discovered in 1983, is the leading cause of acute hepatitis in developing countries, mostly in Asia and sub-Saharan Africa, and is responsible for an estimated 20 million infections, 3 million symptomatic cases and 70 000 deaths per year [2]. In these geographical areas, the HEV involved are mostly of genotypes 1 and 2 and transmitted through the faecal–oral route [2]. In France, as in other developed countries in Western Europe and worldwide, HEV infections were considered until 2006 as acquired only while travelling abroad. However, this paradigm changed during the last decade as it was revealed that the majority of these infections were autochthonous, involved viruses of genotype 3, mostly, or 4, and were linked to a porcine viral reservoir and often related to consumption of uncooked pig liver sausages [1,3–5]. Some HEV transmissions might occur through drinking water or eating shellfish. HEV RNA can be detected for 5 weeks in faeces, and for a longer duration in immunocompromised people [5,6]. Concomitantly, it was shown that acute autochthonous HEV infection could lead to liver transplantation and death [7–9]. It can also evolve towards chronic hepatitis, in severely immunocompromised people, particularly solid organ transplant recipients, and can cause cirrhosis as soon as 2 years post-infection in such patients [5]. Moreover, HEV is also increasingly described as a causative agent of neurological disorders that occur in ≈6%–8% of infections and include most commonly Guillain–Barré syndrome, Parsonage–Turner syndrome and encephalitis/myelitis [5]. Ribavirin was shown to be efficient to clear HEV infection in most chronically infected patients, although some experience virological rebound [5]. In addition, efficient recombinant vaccines were developed, one being used in China, which might open the door to control, especially as only one serotype has been recognized for HEV and the available HEV genotype 1-based vaccine showed cross-protective efficacy against different genotypes [5].

Unfortunately, in the absence of a mandatory report for hepatitis E in France, there is currently no robust estimation of the HEV incidence, and there is no accounting of the number of individuals with chronic hepatitis or subsequent cirrhosis, liver transplantations or deaths due to HEV. A total of 1851 HEV infections were reported by the French reference centre in 2013, 99.8% being autochthonous and 555 being confirmed by PCR (http://www.cnrvha-vhe.org/wp-content/uploads/2012/03/2014-Rap-Act-VHE-VHA.pdf). However, this number probably only reflects a small proportion of cases. In southern France, the incidence of HEV diagnoses was found to range between 0.7 and 2.7/100 person-years among kidney transplant recipients [10]. We have described that HEV was, in Marseille public hospitals, southeastern France, the first cause in 2008 of autochthonous acute hepatitis among adults, accounting for 51% of the 34 cases. In addition, from 2006 to 2010, HEV was the first infectious cause with hepatitis B of liver transplantation, being involved in two of the ten cases, and two other HEV-infected individuals died while on the waiting list [7]. Overall, between 2006 and 2015, we have reported five fatal HEV infections [7,9]. It is also worthy to note that HEV infection is reported to be asymptomatic in 63%–88% of immunocompetent or immunosuppressed people [4,10] and may lead silently to chronic liver diseases in immunocompromised hosts. At the country scale, IgG and IgM prevalence among blood donors was determined to be 22% and 1%, respectively, and for southern France, prevalence exceeded 50% for IgG and reached 3.2%–4.6% for IgM [11]. Hence, seroprevalence varied greatly according to the geographical area. In this study, the same serological assays were used for all blood samples, which is relevant because the performance of serological tests can vary considerably [5]. Moreover, HEV RNA was detected in France in one out of 2300 (0.4‰) blood donations, and this rate was of 0.7‰–0.9‰ in southern France [11]. Human infections with HEV of genotype 3 are widespread in Western Europe, with differences in incidence and immunoglobulin prevalence according to the country [5,11]. In England, it was estimated, based on a similar HEV prevalence for blood donations (1/2848) as found in France and a similar population size, for a duration of viraemia of 8 weeks, that ≈80 000–100 000 acute HEV infections may occur yearly across the country [6]. Data are also lacking in France on the incidence and clinical outcome of transfusion-transmitted HEV infections, which would be useful to consider the relevance of systematic HEV RNA testing of blood products [11,12]; currently, only a fraction of the solvent/detergent-treated plasma is tested. At least 13 transfusion-transmitted hepatitis E infections occurred between 2012 and 2014 in France, with various types of blood products (http://ansm.sante.fr/var/ansm_site/storage/original/application/4ee5a6f35365ab8b2ab1ad5eaccb5bd6.pdf). Registered cases most commonly involved immunocompromised patients, and five individuals with chronic hepatitis E required ribavirin therapy [12].

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Based on these data, it is puzzling that HEV infection has remained neglected in France. In public health, other targets whose clinical impact has been very limited in metropolitan France were favoured (http://invs.santepubliquefrance.fr/). Among these infectious agents are Chikungunya virus with 509 cases between 2006 and 2016 including only 13 autochthonous and none fatal; SARS-coronavirus with four cases in 2003 including one fatal; Middle East respiratory syndrome-coronavirus with two cases between 2012 and 2016 including one fatal (in 2013); and avian influenza virus with no case since 2004. With respect to the observed clinical burden of HEV infection in metropolitan France, greater efforts are warranted for its surveillance and prevention. This should include improving the epidemiological surveillance of HEV-related morbidity and mortality, as well as enhancing the awareness of clinicians and people about the sources and routes of HEV transmission, particularly in the case of individuals who are immunocompromised or have underlying liver diseases and are therefore at higher risk of severe outcomes.

## Transparency Declaration

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