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Hepatitis E virus infections in Europe

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ABSTRACT

Hepatitis E virus (HEV) is the most common cause of acute viral hepatitis worldwide. The systematic use of improved tools for diagnosing and genotyping has completely changed our understanding of the epidemiology and clinical consequences of HEV infection. Most cases of HEV in Europe arise from infected animals such as pigs, wild boar, deer and rabbits. Zoonotic HEV genotypes (HEV genotypes 3–8) are mainly food-borne or transmitted by direct contact, but recent data suggest that infection can also be water-borne or even iatrogenic throught contamined blood products.

HEV-3 is the most prevalent genotype in Europe but the geographic distributions of the 3 major clades and subgenotypes (HEV-3abjkchi, HEV-3efg, and HEV-3ra) differ. Most HEV-3 infections are asymptomatic but they can result in severe acute hepatitis in patients with chronic liver disease, chronic hepatitis in immunocompromised patients, and to extra-hepatic manifestations.

Despite more frequent reports of symptomatic hepatitis E cases across Europe, systems for monitoring HEV infections vary greatly. Severe HEV-associated illnesses, hospitalizations and deaths are probably underestimated. The seroprevalence and incidence of locally acquired hepatitis E varies between and within European countries and over time. The precise origin of these variations is uncertain but may be linked to environmental factors or the degree to which HEV contaminates the human food chain. Collaborative initiatives such as the establishment of the One Health platform for HEV sequences (HEVnet database) will be very useful for a better understanding of the epidemiology of HEV in Europe and the development of effective prevention strategies.

1. Introduction

Hepatitis E (HEV) is the causative agent of hepatitis E in humans. Over the past two decades progress in understanding HEV infections has been hampered by a lack of powerful virological diagnostic tools. Now, recently-introduced robust serological and molecular assays have revealed that the virus is as endemic in many industrialized countries as it is in ressource-limited Asian and African countries. Studies published as early as 2004 revealed that most HEV infections occuring in Europe are not acquired by people traveling in epidemic-prone areas, but are linked to the presence of animal reservoirs of HEV (mainly: pigs) [1–4]. We now know that HEV is widespread in Europe; is transmitted zoonotically; that chronic HEV infections occur in immunocompromised patients; and that extra-hepatic manifestions of HEV include renal and neurological symptoms.

2. The virus

2.1. The viral particle

HEV is a small RNA virus with an icosahedral capsid. The two forms of infectious particles are: unenveloped particle and quasi-enveloped particle [5]. Unenveloped virions, first identified by Balayan [6], are found in the feces and are 27–34 nm in diameter, with a density of 1.22 g/cm3. The virions that circulate in the blood (quasi-enveloped) are cloaked in host cell membranes. They are 50–110 nm across and their density is 1.08 g/cm3 [7–9]. The HEV lipid membrane could play an important role in cell entry, tissue tropism and infectivity. An *in vitro*

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study showed that the naked virus is more infective than the quasi-enveloped virus but that anti-HEV antibodies neutralize only the naked virus [7].

2.2. The virus genome and proteins

The HEV genome is a single-strand positive-sense RNA approximately 7.2 kb long. It has a short 5′ noncoding region that is capped with 7-methyl-guanosine, three open-reading frames (ORFs: ORF1, ORF2, and ORF3), and a short 3′ noncoding region that ends in a poly-(A) tail.

ORF1 encodes a nonstructural protein about 1700 amino acids long that is involved in HEV RNA replication. This protein contains several functional domains: a methyltransferase/guanyltransferase, a cysteine protease, a macrodomain (X domain), an RNA helicase that has 5′-nucleoside triphosphatase activity, and an RNA-dependent RNA polymerase [10]. A variable region encoding a proline-rich hinge, the polyproline region, is an intrinsically disordered region in which segments of human genes have been identified [11–16]. Certain specific HEV strains contain an additional ORF within ORF1, named ORF4 [17]. ORF4 is expressed after endoplasmic reticulum stress and interacts with eukaryotic elongation factor 1 isoform-1 to stimulate virus polymerase activity.

ORF2 encodes the 660-residue virus capsid protein, which has three glycosylation sites (Asn 132, Asn 310, and Asn 562) and an N-terminal signal peptide that drives its translocation to the endoplasmic reticulum [18]. The capsid protein has been divided into three domains: shell (S), middle (M), and protruding (P). The P domain is the major target for neutralizing antibodies and contains a putative receptor-binding domain [19,20]. Capsid monomers self-assemble to form first dimers, and then the decamers that encapsulate the virus RNA. The capsid consists of 180 copies arranged as an icosahedron with T = 3 symmetry [21]. Immunological and structural studies of the capsid protein have contributed to the development of an anti-hepatitis E vaccine [22].

ORF3 encodes a small protein (113/114 residues) that is essential for virus egress. ORF3 protein is only associated with enveloped HEV particles. The protein must be phosphorylated on Ser80 before it can interact with the unglycosylated form of the capsid protein [23]. The ORF3 protein is palmitoylated at cystein residues and contains a conserved proline-serine-alanine-proline motif that enables it to interact with the endosomal sorting complex required for transport, including the tumor susceptibility gene 101 (Tsg 101) [24–30].

2.3. Taxonomy

Hepatitis E virus (HEV) belongs to the *Hepeviridae* family [31], which has two genera (*Orthohepevirus* and *Piscihepevirus*) and five species. *Orthohepevirus A* includes strains that infect humans and several other mammals: pigs and wild boar, deer, rabbits and mongooses. *Orthohepevirus B* infects chickens, *Orthohepevirus C* infects rats and ferrets, *Orthohepevirus D* infects bats, and *Piscihepevirus A* infects cutthroat trout. A human pathogenic strain belonging to *Orthohepevirus C* was identified recently [32]. *Orthohepevirus A* consists of at least eight distinct HEV genotypes but only one serotype. Genotypes 1 and 2 infect humans exclusively and are responsible for outbreaks of hepatitis in developing countries [33]. Genotypes 3 and 4 have animal reservoirs and infect humans in developed countries. HEV genotypes 5 and 6 have been detected in wild boar in Japan, but not in humans as yet [34]. Lastly, genotypes 7 and 8 have been detected in dromedary and Bactrian camels and could infect humans [35–37].

2.4. HEV life cycle

Improved cell culture systems have led to better knowledge of the HEV life cycle [38] but there are still gaps to be filled. For example, we know little about a high affinity receptor or whether the ORF1 protein undergoes proteolytic processing. It was recently demonstrated that there are several forms of ORF2 protein. The unglycosylated form is a component of infectious particles while the glycosylated form is secreted in the bile and blood [39,40]. The secreted form of ORF2 protein is the target of anti-HEV antibodies and the acute phase serum HEV antigen concentration in immunocompromised patients is a predictor of chronic infections [41]. The great genetic heterogeneity of HEV quasispecies, involving several genomic regions, is also associated with chronicity in these patients [12,42,43].

3. Epidemiology

3.1. Transmission

The four major HEV genotypes (1, 2, 3 and 4) infecting humans are mainly transmitted by the fecal-oral route. HEV-1 and HEV-2 are found only in humans and are predominant in low-income Asian and African countries. Drinking contaminated water is the main route of transmission. Outbreaks are often linked to the fecal contamination of drinking water. Outbreaks have also occured in refugee camps with limited facilities for water hygiene and sanitation. The transmission of HEV from infected women to their newborn is well documented. HEV-3 and HEV-4, which have large animal reservoirs (mainly pigs), are predominant in high-income countries. HEV-3 circulates in most countries while HEV-4 is mainly found in Asia. While HEV-3 and HEV-4 genotypes can be transmitted by direct contact with infected animals, the main route of transmission is the consumption of HEV-infected animal products, especially undercooked meat. These include infected pork liver, pork products containing liver, and other pig meat consumed raw or undercooked [44–46]. Infected game meat is another source of human infection. Strains of rabbit HEV have been detected in humans [47,48]. HEV shed by infected animals can contaminate water sources and lead to the accumulation of HEV in fruit, vegetables, and shellfish. HEV-3 RNA has been detected on red fruit, strawberries, salad greens and in spices [49], as well as in oysters and mussels [50]. Studies in many European countries have shown that HEV can be transmitted by the transfusion of blood products [51]. Several developed countries have adopted measures to improve blood safety based on the epidemiology of HEV [52].

3.2. Surveillance

The number of symptomatic cases reported by the French National Reference Center has increased over the years, from about 20 cases/year before 2004 to more than 2200 cases/year in 2017. Over 98% of these infections are autochthonous and the predominant genotype is genotype 3 (HEV-3, 97.5%; HEV-4, 1.3%; HEV-1, 1.2%). The few cases due to HEV-4 are autochthonous while those caused by HEV-1 are linked to travel in Asia. The increasing numbers of symptomatic cases reported in France is linked to more frequent testing as a result of greater clinical awarness and the optimisation of test algorithms. More and more patients with symptoms consistent with acute hepatitis are tested for hepatitis E. Similar trends have been reported elsewhere in Europe despite the heterogeneity of surveillance systems for hepatitis E based on national notification, sentinel network, reference laboratories or blood service [53]. The total number of reported symptomatic cases in Europe increased ten-fold between 2005 and 2015, but the percentage of cases hospitalised decreased from 80% in 2005 to around 50% in 2015 [54]. The number of reported cases varies greatly from one country to another, reflecting differences in clinical awareness and diagnostic testing algorithms.

3.3. Molecular epidemiology

The distribution of HEV-3 subtypes circulating in France involves phylogenetic analyses of a 348-nt fragments within the ORF2 gene [55].

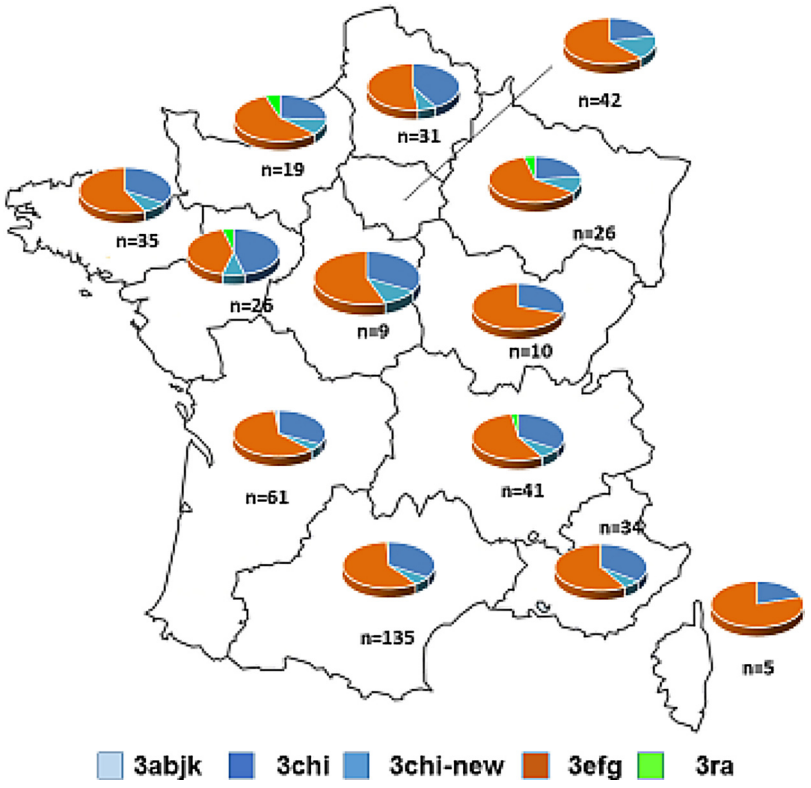

Fig. 1. Distribution of HEV-3 subtypes by region in France (2017).

Table 1
Change in HEV-3 subtypes distribution in France before and after 2012 based on 2447 strains.

Clade	Subtypes	2005-2011 (n = 158)	2012-2017 (n = 2289)	*p*
HEV-3.1	3aj	1.3%	0.5%	*ns*
	3b	0.0%	0.1%	*ns*
	3k	0.0%	0.0%	*ns*
	3ci	8.2%	25.5%	*< 0.001*
	3chi-new	0.0%	4.8%	*< 0.01*
	3 h	9.5%	4.1%	*< 0.01*
HEV-3.2	3e	3.8%	2.0%	*ns*
	3f	75.9%	62.0%	*< 0.01*
HEV-3.3	3ra	0.6%	0.6%	*ns*
Unassigned		0.6%	0.3%	*ns*

ns, not significant.

They indicate that HEV-3f (59%), belonging to HEV-3 clade 2, and HEV-3c (22%), belonging to HEV-3 clade 1, are predominant. HEV-ra strains cluster in the third clade of HEV-3 and represent less than 1% of all HEV strains [47,48]. Because 12% of strains were not assigned to a specific subtype using the panel of reference sequence recommended by Smith et al [56], we used 250 full-length HEV-3 sequences and an automated partition of phylogenies to determine clusters [57]. The subtypes were clearly separated, except for subtypes a/*j* and c/i, and we were able to determine the HEV-3 subtype of > 99% of the 2447 strains analysed. This analysis also identified a possible new subtype (3 chi-new) in clade 1 [55]. The distribution of HEV-3 subtypes by region in France is quite uniform, with clade 2 subtypes being more abundant than clade 1 subtypes (Fig. 1). There was a fascinating change in subtype distribution from before to after 2012: the proportion of subtypes 3c and 3 chi-new increased while that of subtypes 3f and 3 h decreased (Table 1). There have been similar changes in subtype distribution in other European countries with switches from clade 2 to clade 1 in the Netherlands [58], England and Wales [59,60], and Scotland [61]. The subtype 3 chi-new has been detected in Spain (since 2011), France (since 2012), Belgium, the Netherlands and the UK [58,59,62–64]. HEV-3 clade 1 is predominant in the Netherlands, Germany and UK, while HEV-3 clade 2 is predominant in Spain and France (Fig. 2). These distributions probably reflect the distributions of HEV-3 subtypes in the pig reservoirs of each country, as demonstrated in France [65], but it could also be influenced by imports of pigs and/or pig meat.

3.4. HEV markers

HEV markers can be indirect and detected with anti-HEV IgM and IgG, or direct, such as HEV RNA in the blood and feces or HEV antigen in blood. Most IgM tests are available in a microplate format but rapid tests and automates have been developed recently. Despite some discrepancies, there is relatively good agreement between these assays. IgG tests are available in a microplate format and an automate. Nevertheless the analytical sensitivity may be very different from one assay to another: from 0.25 to 2.5 WHO units/ml. A meta-analysis showed that the IgG seroprevalence in the general population in Europe is strongly influenced by the seroassay used (17% with the Wantaï test and 2% with the Abbott test) [66]. In this analysis, 52% of the heterogeneity was explained by three parameters: the seroassay used, the geographical location and the study cohort. The estimated seroprevalence of IgG in more than 10,000 French blood donors was 22.4% [67]. However, it varied widely, with higher rates in the South and North-East areas. Even in the hyperendemic South-West of France, the seroprevalence varied from place-to-place: from over 80% to below 20%. The IgM seroprevalence, which is an indicator of recent infection, was 1%, but it too varied; the highest rates were in Ariege (4.6%) and Corsica (3.8%). The factors that were associated with IgG seroprevalence in multivariate analysis were age, geographic location, and consumption of liver sausage or figatella, game meat and giblets. Consuming bottled water was a protective factor, indicating that the environment may well play a role in the epidemiology of HEV in France. Hot spots of HEV seroprevalence have also been found in other

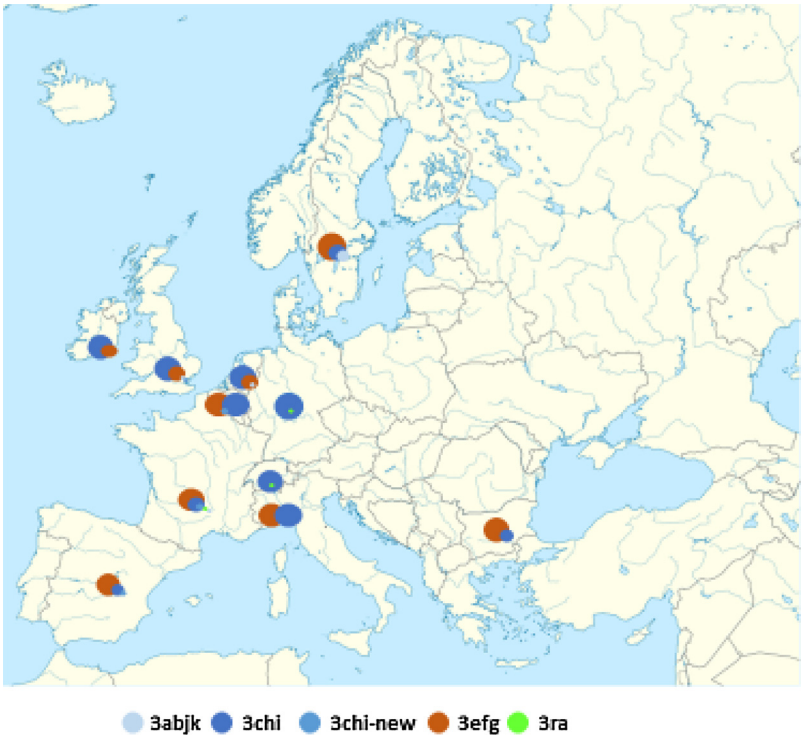

Fig. 2. Distribution of HEV-3 subtypes in Europe according to littérature data.

Table 2
Prevalence of anti-HEV IgG and HEV RNA in European countries with high endemicity.

Country	Anti-HEV IgG (%) Wantaï test	HEV RNA(+)	Reference
Germany	29.5	1:1,200	Volmer et al., 2012 [99]
Netherlands	27.0	1:2,671	Slot et al., 2013 [100]
		1:600	Zaaijer et al., 2014 [101]
France	22.4	1:2,218	Mansuy et al., 2016 [67]
		1:744	Gallian et al., 2014 [102]
			Gallian et al., 2017 [103]
Switzerland	20.4		Niederhauser et al., 2018 [69]

Table 3
Prevalence of anti-HEV IgG and HEV RNA in European countries with intermediate/low endemicity.

Country	Anti-HEV IgG (%) Wantaï test	HEV RNA(+)	Reference
Spain	19.9	1:3,333	Sauleda et al., 2015 [104]
Austria	13.5	1:8,416	Fischer et al., 2015 [105]
UK	12.0	1:2,848	Hewitt et al., 2014 [51]
		1:7,000	Ijaz et al., 2012 [106]
			Beale et al., 2011 [107]
Italy	8.7	< 1:10,000	Spada et al., 2018 [68]
Ireland	5.3	1:5,000	O'Riordan et al., 2016 [108]
Scotland	4.7	1:14,520	Cleland et al., 2013 [109]
		1:2,481	Thom et al, 2018 [61]
Denmark		1:2,330	Harritshoj et al, 2016 [110]
Sweden		1:7986	Baylis et al, 2012 [111]

European countries, including Italy [68] and Switzerland [69]. Commercial tests for HEV RNA (detection and/or quantification) have limits of detection ranging from 7 to > 180 UI/ml, based on the WHO reference standard. Current data on blood donors in European countries where HEV is endemic (IgG seroprevalence > 20% ; Wantaï test) indicate that the viremia prevalence varied from 1 :600 to around 1 :2500 (Table 2). Variations within a single country are linked to different rates of infection over the time, to different screening strategies (individual testing or pooling) and to the size of the pool tested. Similarly, the prevalence of viremia ranges from 1:14,500 to 1:2300 in countries where endemic infection rates are intermediate/low (IgG seroprevalence < 20%) (Table 3). The high rate of viremia reported recently in Scotland could be linked to a high rate of infection [61].

4. Clinical consequences

4.1. Acute and chronic hepatitis E

While many HEV infections are clinically asymptomatic, symptomatic infections are underdiagnosed. European studies have shown that the elderly and patients with chronic liver disease are most likely to suffer from severe acute hepatitis E but not pregnant women [70–72]. The numbers of HEV-associated hospitalizations in France have been estimated at 546/year, resulting in and 20 deaths per year [73]. Several cases of pregnant women suffering from acute hepatitis E have been reported in Europe but none with fulminant hepatic failure or obstetric complications [74–76], unlike HEV-1 infections in developing countries. We have developed a model of HEV infection based on the *ex vivo* culture of decidual and placental tissues and used it to obtain a clearer picture of the mechanisms underlying these infections [77,78]. We found that HEV-3 replicated more slowly than HEV-1 in both decidual and placental explants, indicating that the pathogenicity of HEV is genotype-specific during pregnancy [79].

The first described cases of chronic HEV infections in adults were solid organ transplant recipients [80,81], patients with a hematological disease [82–85], and patients with HIV and a low CD4 cell count [86–88]. Children with chronic HEV infections have also been found to be solid organ transplant recipients or suffer from a hematological disease [89,90]. The infection becomes chronic in approximately 60% of both solid organ transplant recipients and stem cell transplant recipients [91,92]. Patients with chronic hepatitis rapidly develop liver fibrosis and cirrhosis occurs in less than 3–5 years. The first step in

treating these patients is to reduce their immunosuppression and, if this fails, to treat them with ribavirin [93–95].

4.2. Extra-hepatic manifestations

Both immunocompetent and immunocompromised patients can develop glomerulonephritis (96–98). Case reports and case series indicate that 5.5% of HEV-infected patients also have neurological manifestations such as Parsonage Turner syndrome, Guillain-Barré syndrome and encephalitis [96]. A prospective multicenter European study of patients with non-traumatic neurological injuries found that 2.4% of them showed evidence of an HEV infection [97]. However, a recent French prospective study on 200 cases of acute hepatitis E and 200 controls found that 16.5% of infected patients showed neurological manifestations [98]. The most frequent manifestations were neuropathic pain, painless sensory disorders, Parsonage-Turner syndrome, Guillain-Barre syndrome, encephalitis and meningitis. Neurological manifestations were more frequent in immunocompetent patients than in immunocompromised patients, suggesting the involvement of an immunological mechanism [98].

5. Conclusions

Zoonotic HEV is endemic in Europe and HEV3 is the most prevalent genotype. Increased clinical awareness and better testing algorithms have led to increased reports of symptomatic hepatitis E cases in all countries. Standardization of diagnostic testing algorithms, reporting systems, case definitions and populations under surveillance should help to determine the burden of HEV infection in Europe in terms of hospitalization and mortality. The seroprevalence and incidence of HEV infection varies between and within countries and over time. The precise origin of these variations is uncertain but may be linked to the degree to which HEV contaminates the human food chain and/or the environment. Collaborative initiatives such as the establishment of the One Health platform for HEV sequences (HEVnet database) will contribute considerably to our understanding of the epidemiology of HEV in Europe and the development of effective prevention strategies.

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Competing interests

None declared.

Ethical approval

Not required.
The signature of all authors are on the declaration form.

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