SEOUL VIRUS INFECTION IN HUMAN, France, 2014-2016

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Introduction

Seoul hantavirus (SEOV), the etiological agent of a mild to moderate hemorrhagic fever with a renal syndrome, is associated worldwide to the Brown Rat (*Rattus norvegicus*), a commensal species of humans and as such occurs almost in human settlements (Clement J et al, Emerg Infect Dis 1997). However, except for Russia, South Korea and China for which a few tens to a few thousands human cases are annually reported (but for which there is also a potential confounding with Hantaan virus, another circulating and serologically cross-reactive hantavirus), most countries since they have started hantavirus surveillance in the 90's have reported very few sporadic cases, mostly serologically confirmed (Clement J et al. Emerg Infect Dis 1997, Kariwa H et al. Microbiol Infect Dis 2007, Knust B et al. Emerg Infect Dis 2013, Jameson LJ et al. Euro Surveill 2013). Three human cases were recently described in the United Kingdom and France (Jameson LJ et al. 2013, Macé G et al., Euro Surveill 2014). Continuous surveillance in France identified 4 new cases within a 24 months period, three of them being virologically confirmed and reported here.

Cases Report

Case 1: A 27 years-old man presented in February 2014 at hospital on day 2 after symptom onset (D2). The clinical and biological picture corresponded to a severe haemorrhagic fever with renal syndrome and liver disorders. Presence of IgM and IgG against Hantavirus were detected on a D3 serum using commercial ELISA assays, performed in a private clinical laboratory. Presence of IgM was confirmed at the French National Reference Center (NRC) for Hantavirus using reference ELISA and IF test with native antigens (Macé G et al. Euro Surveill 2013). Molecular virus detection was performed according to the procedure reported elsewhere (Mace G et al. Eurosurveill 2013). Partial SEOV S sequence was recovered from the serum sample, as stated by a Blast search. Exposition was suspected to occur during a building restoration work in Dijon (Côte d'Or) or in Vézelay (Yonne).

Case 2: A 22 years-old man from Erize-Saint-Dizier (Meuse) presented in September 2014 at hospital on D4. The clinical and biological picture was with a fever associated to thrombocytopenia and liver disorders. Presence of IgM and IgG against Hantavirus were detected on a D4 serum using commercial ELISA assays, performed in a public hospital clinical laboratory. Results were also confirmed at the NRC. Molecular virus detection was performed and partial SEOV S sequence was recovered from the serum sample, as stated by the Blast search. Interestingly, his pet rat (*Rattus norvegicus*), bought about one month before the onset of the disease, was the suspected unique source of hantavirus. The animal was then euthanized by the veterinarian of the patient with his consent. The same partial SEOV S sequence was obtained from the liver of the animal.

Case 3: A 32 years-old man from Turckheim (Haut-Rhin), presented in January 2016 at hospital on D4. The clinical picture was consistent with a severe haemorrhagic fever with renal syndrome and liver disorders. Presence of IgM and IgG against Hantavirus were detected on a D6 serum using commercial assays, performed in a private clinical laboratory. These results were also confirmed at the NRC. Molecular virus detection was performed according to Klempa B et al. method (Emerg Infect Dis 2006) and partial SEOV L sequence was recovered from a D4 serum sample, as stated by the Blast search. The patient raised brown rats as food source for his snakes and was routinely capturing and killing wild brown rats visiting his henhouse. The breeding unit was the highly probable source of the human infection: organs of 10 rats sampled from this unit tested positive by the same nested RT-PCR method and the partial L sequence obtained was identical to the one of the strain detected in the human case (only one wild rat caught around the henhouse was sampled and tested negative).

Furthermore, complete S coding domain sequences were obtained from the samples of cases 2 and 3, from pet or farmed brown rats suspected to be the source of infection of these two cases, and from two brown wild rats suspected to be the source of infection of another SEOV serologically confirmed human case detected in 2014 (Bour A et al. Rev Med Interne 2016). Using MEGA version 5.1 (Tamura K et al. Mol Biol Evol 2011) phylogenetic analysis based on S CDS and on the generalized time reversible model with a Gamma distribution (+G) with five rate categories (according to the best fit substitution model proposed) confirmed that all the strains belongs to SEOV species (Figure 1).

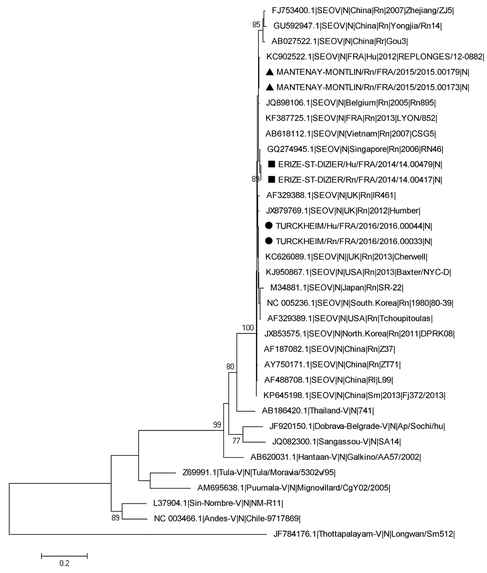

Figure 1: Phylogenetic tree based on the entire S (small) nucleotide coding sequence from the 3 patients with Seoul virus infection, France 2014-2016, and representative strains of SEOV virus and other hantavirus species. ■ indicates the sequences of the strains detected in Case 2 and in his pet brown rat; ● indicates the sequences of the strains detected in case 3 and in one of his farmed brown rat; ▲ indicates the sequences of the strains detected in wild brow rats (this study) associated with the SEOV serologically confirmed case reported in Bour A et al., Rev Med Interne 2016. Bootstrap percentages ≥ 70% (from 500 resamplings) are indicated at each node. The scale bar indicates nucleotide substitution per site.

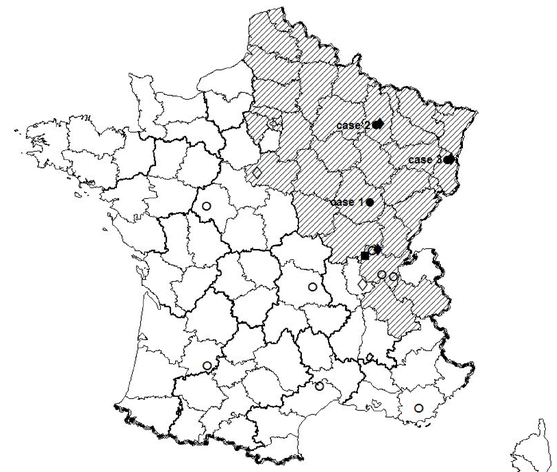

Figure 2: Geographic distribution of Seoul virus infection among human and rats, France 2016. The hachured area represents the Puumala virus endemic area; ○ indicates Seoul virus (SEOV) serologically confirmed human cases reported in Ragnaud JM et al., Gastroenterol Clin Biol 1986 and Le Guenno B, Méd Mal Infect 1997, Bour A et al., Rev Med Interne 2016; ■ and ● indicate SEOV virologically confirmed human cases reported in Macé G et al., 2013 and in this study (Case 1, 2 and 3) respectively; ◊ and ♦ indicate SEOV infection virologically confirmed in brown rats reported elsewhere (Heyman P et al. Eur J Clin Microbiol Infect Dis 2004 & Dupinay T et al., Virol J 2014), and in this study respectively.

Conclusion

Four hantaviruses (Puumala (PUUV), SEOV, Tula and Nova viruses), have been reported in continental France, the first three being associated with human cases and PUUV being the most prevalent in humans. The detection of SEOV in 3 additional cases (this report) and the report of a SEOV associated case (Bour A et al., Rev Med Interne 2016) within a 2 years period indicate that SEOV infection in human are uncommon but not rare in France. They accounted for 1.3% (n= 234) of the hantavirus infection cases serologically or virologically confirmed during theses 2 years period, mostly being attributed to PUUV.

However, SEOV cases are probably under-detected in France. Hantavirus diagnostic is few requested outside the PUUV area (17% of the request in 2014 for example) and 11 of the 15 clinical laboratories performing this diagnostic used the Reagena POC Puumala IgM rapid test. When the admission sera of the 3 SEOV cases were tested using the Reagena ReaScan Puumala IgM test, all three gave negative result (data not shown), suggesting that SEOV cases are missed by the laboratories using these PUUV rapid tests. That is probably the case in other European countries where these test are used. The use of a pan-hantavirus serological assay should be preferred.

It has recently been showed that PUUV was molecularly detected in the majority of PUUV infected patient during the acute phase of the disease (Lagerqvist N et al., J Clin Mircobiol 2016). Although there is no such data with SEOV, in order to avoid misdiagnosis, it seems reasonable to promote also the use of molecular diagnostic in order to detect hantavirus infection more accurately.

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