Clinical Microbiology and Infection xxx (2017) 1–7

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Review

# Update and new insights in encephalitis

A. Mailles [1, 2, *], J.-P. Stahl [2, 3], K.C. Bloch [4]

[1] Santé publique France, Saint-Maurice, France
[2] ESCMID Study Group on infections of the Brain
[3] Joseph Fourier University, University Hospital, Grenoble, France
[4] Vanderbilt University Medical Center, Nashville, TN, USA

ARTICLE INFO

*Article history:*
Received 2 February 2017
Received in revised form
30 April 2017
Accepted 1 May 2017
Available online xxx

Editor: C. Pulcini

*Keywords:*
Autoimmunity
Bornavirus
Chikungunya
Ebola
Encephalitis
Guidelines
Lassa
*Naegleria fowleri*
Next-generation sequencing
Zika

ABSTRACT

Infectious encephalitis is a rare but severe medical condition resulting from direct invasion of the brain by viruses, bacteria, fungi or parasites, or indirect post-infectious immune or inflammatory disorders when the infectious agent does not cross the blood–brain barrier. Infectious encephalitis cases represent an interesting and accurate sentinel to follow up on trends in infectious diseases or to detect emerging infections. Using Pubmed and Embase, we searched the most relevant publications over the last years. We present here an update on the important findings and new data recently published about infectious encephalitis. **A. Mailles, Clin Microbiol Infect 2017;▪:1**



## New and emerging viruses

### *Variegated squirrel bornavirus 1*

Bornavirus are neurotropic viruses that infect birds, horses, rodents and, more rarely, humans. In Germany, three individuals, aged 62–72 years, who knew each other, presented with encephalitis of unknown cause but highly similar presentation in the same hospital from 2011 to 2013 [1]. They presented with sub-acute onset, decreased consciousness then coma, and died in hospital after 2–4 months. All three experienced late ocular paresis, myoclonus and bilateral crural veinous thrombosis, and two of them experienced pulmonary embolism. Necropsy demonstrated brain necrosis, microglial activation and perivascular lymphocyte infiltration.

The investigation revealed that all three were exotic squirrel breeders of *Sciurus variegatoides* (Fig. 1). This species originates from South America and *S. variegatoides* are only rarely kept as pets in Europe. The three patients had exchanged some squirrels.

A new Bornavirus, close to those usually infecting horses, was identified thanks to metagenomic analysis from brain samples of the three patients and named Variegated Squirrel Bornavirus 1 (VSBV1). The virus was also identified in various organs of a squirrel belonging to one of the three patients by metagenomic analysis.

Finally, RT-PCR and serological diagnosis were developed and some other squirrels were found to be positive (serology and RT-PCR) in zoos and private collections in Germany and the Netherlands [2].

This episode illustrates the risk of emerging diseases acquired from pet animals captured in the wild. Although bats are frequently cited as a potential reservoir for emerging pathogens, rodents should be considered too because they represent 40% of all mammals and account for 1700 species.

It is not known if Variegated Squirrel Bornavirus 1 can be responsible for milder clinical presentations in humans. However, the virus was discovered because the cluster of encephalitis attracted attention, emphasizing the value of this syndrome as a sentinel of emerging infectious agents.

* Corresponding author. A. Mailles, Santé publique France, 12 rue du Val d'Osne, 94415 Saint-Maurice cedex, France.
*E-mail address:* alexandra.mailles@santepubliquefrance.fr (A. Mailles).

http://dx.doi.org/10.1016/j.cmi.2017.05.002
1198-743X/

**Fig. 1.** *Sciurus variegatoides* in its natural environment in Costa Rica (courtesy of Dr Didier Boussarie).

A number of questions still remain unanswered about other possible reservoirs and the routes of transmission of the virus to humans. Of note is that no other human cases were reported despite the spread of these findings among the exotic pet breeding community.

*Lassa fever virus*

Lassa fever virus (LFV) is a highly transmissible Arenavirus and a biosafety-level-4 pathogen. LFV infection is endemic in West Africa with seasonal peaks and frequent outbreaks. LFV infection is most frequently asymptomatic but can result in a severe disease, including haemorrhagic fever, in 20% of patients. Survivors experience hearing deficit in 25%–30% of cases. Rare encephalitis cases caused by LFV infection have been reported [3].

In Sweden, during spring 2016, a woman in her 70s was hospitalized with encephalitis of unknown origin after returning from a 6-week stay in Liberia, where she had been exposed to rodents [4]. Magnetic resonance imaging demonstrated hypersignals but the cerebrospinal fluid (CSF) characteristics were normal. She received supportive standard healthcare. On day 26 of hospitalization, genome amplification on serum was positive for LFV and she was transferred to a reference hospital. She progressively recovered but was discharged with hearing loss. In all, 118 healthcare workers (HCW) and family members were considered possible at-risk contacts and were followed up for a 3-week period. Five of them presented with symptoms suggesting LFV infection but all tested negative.

Encephalitis and encephalopathy are not common clinical presentations of Lassa fever. A number of other infectious agents possibly responsible for encephalitis are far more frequent both in Africa, including more usual causes like herpes simplex virus or malaria. These frequent causes of encephalitis need to be considered as first-line diagnosis also in returning travellers. However this case emphasizes the need for careful interview of patients returning from tropical areas with encephalitis.

It is also important to note from this report that no secondary case was recorded although ‘only’ standard protection measures were used by HCW.

*Ebola virus and the brain*

From 2014 to 2016, the largest ever reported outbreak of Ebola virus diseases (EVD) occurred in West Africa. An unprecedented number of HCW were deployed in the affected countries, resulting in better management and more accurate description of the disease. Neurological syndromes during the course of EVD had been described during previous outbreaks, but with only limited investigation [5].

During the 2014–16 outbreak, reports suggested that various neurological syndromes may be associated with EVD, namely encephalitis, encephalopathy or isolated seizures [6,7]. However, despite an increased number of HCW in the field and more sophisticated medical equipment, the neurotropism of Ebola virus (EV) was still difficult to assess, as some examinations such as electroencephalogram were not available in all treatment centres, or were difficult to perform in highly contagious patients (for example lumbar puncture or imaging). Moreover, at some point during the outbreak, the high number of patients in the treatment centres would have made it difficult if not impossible to perform a complete investigation.

The neurological cases described during the last outbreak had some interesting details, and raised new questions (Table 1). The majority of cases had neurological onset during the second week of illness. In some cases [8], encephalopathy with metabolic disorders was the major hypothesis, whereas it was ruled out in a severe encephalitis case with white matter lesions [10]. In other cases, imaging [11] and high viral load in CSF [9,13] suggested a direct invasion of brain parenchyma. When both CSF and serum/plasma were tested, the results could be divergent, suggesting the existence of different pathophysiological mechanisms (Table 1). Finally, some authors suggested that experimental therapy could have driven neurological side effects in some patients [12].

Besides these acute cases, preliminary data from survivor patients suggest a high prevalence of persisting cognitive and neurological symptoms and complaints in both short and long term:

- In Liberia, 82 patients included in the ‘Prevail III’ cohort still presented cognitive or neurological signs 6 months after the onset of EVD, with increased mRankin scores [14]. Main complaints were memory loss, headaches, weakness, myalgias and depressed mood. Tremors and sensory disorders were present in a third of cases and abnormal ocular movements in two-thirds, frontal release in one of six patients.
- In Guinea, among 105 survivors examined 4–9 months after acute EVD, 32% had mood disorders, 27% memory deficits, and 10% dizziness [15].
- In Sierra Leone, 38 patients were followed up after discharge: 1 year later, 74% complained of headache, 55% of sleep disorders and 29% of anxiety (Howlett, 26th ECCMID, Abstract OLB21).

The pathophysiology of these ‘sequelae’ remains undetermined and more studies are needed to clarify these important preliminary findings, especially to distinguish between primary neurocognitive disorders and post-traumatic stress syndrome. However, their convergence is in favour of a systematic long-term follow up of Ebola survivors, including neurocognitive assessment by trained HCW, using tools that can be administered independently of the language of the patients and their ability to read.

Another unexpected finding was the ability of the virus to persist in ‘protected’ body sites such as the eye or the brain. In early 2015, a 38-year-old HCW returning from Sierra Leone was successfully treated for EVD in the UK [16]. During her initial hospitalization, specific treatment included brincidofovir, convalescent plasma and ZAMb (Public Health Agency of Canada, MB, Canada). She was discharged with full recovery, but she was re-admitted 9 months later with severe meningo-encephalitis. Remarkably, RT-PCR on admission showed lower CT values in CSF than plasma, suggesting viral multiplication in CSF. Infectious virus could be cultured from CSF samples but not from blood samples. It was therefore considered that the virus was multiplying in the central

Please cite this article in press as: Mailles A, et al., Update and new insights in encephalitis, Clinical Microbiology and Infection (2017), http://dx.doi.org/10.1016/j.cmi.2017.05.002