What is new about epidemiology of acute infectious encephalitis?

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Purpose of review
This review aims to describe new features on the epidemiology of encephalitis world-wide. As this neurological presentation is most frequently related to transmitted viruses, surveillance of encephalitis is of major importance to detect their emergence or re-emergence.

Recent findings
Rabies causes one of the most severe types of encephalitis as it is lethal in all cases, and it is endemic in some countries. It was thought that the virus had been eradicated in Western Europe, but it re-emerged in Greece and Italy. Physicians should be aware of this diagnosis in the case of severe encephalitis. Some viruses (Powassan, Nipah, and Hendra) are becoming endemic in some new parts of the world (USA and Australia). Because of their severity, they are healthcare concerns in those countries and for travelers (e.g. in Asia). Finally, a concept is emerging: herpes simplex virus is suspected to be a trigger for autoimmune encephalitis. This is of major importance for the future management of patients (corticosteroids early in the course of the disease?), and the epidemiology of sequelae.

Summary
Encephalitis is a good marker for the detection of emerging infections. New findings about the relationship between herpes simplex virus encephalitis and autoimmune encephalitis open a new concept for a better management of patients.

Keywords
autoimmune encephalitis, encephalitis, henipaviruses, herpes simplex virus, rabies

INTRODUCTION
The basic epidemiology of encephalitis is now better known, as some large-scale studies have assessed the frequency of various pathogens in high healthcare level countries [1–4].

Neurological infections are considered as a good marker for detection of new pathogens or for the conditions for spreading. More knowledge about encephalitis causes in Asia and Africa still needs to be determined.

RABIES
Rabies is responsible for an estimated 50,000 deaths every year (Africa, Southeast Asia, and Asia) according to the WHO, and has re-emerged in formerly rabies-free European countries (Greece and Italy, see below). Preventing the transmission of the virus as well as providing postexposure treatment remains a challenge with regard to the limited availability of both vaccines and immunoglobulin and to the fatal outcome of the disease. Keeping an updated knowledge on its epidemiology can be challenging but is essential for clinicians.

The distribution of rabies viruses is related to animal travel and trade, as demonstrated by a study of 24 new viral strains obtained from Nepal, collected from 2003 to 2011 [5]. The authors analyzed these strains using neighbor-joining and maximum-likelihood phylogenetic methods with representative viruses from all over the world, including new related strains from neighboring or more distant countries (Afghanistan, Greenland, Iran, Russia, and USA). Nepal has a limited land surface within the Indian subcontinent, but surprisingly

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the authors demonstrated a wide genetic diversity of rabies virus, with the coexistence of three different phylogenetic groups: an Indian subcontinent clade and two different Arctic-like subclades within the Arctic-related clade. It suggests at least two independent episodes of rabies introduction from neighboring countries.

Most human cases worldwide are because of dog bites. However, some recent cases showed an increasing risk of rabies transmission by cats. In Pennsylvania, USA, over the last 10 years, between 1.5 and 2.5% of cats submitted to Pennsylvania’s state laboratories for testing of rabies were positive [6]. The recent identification of an imported rabid cat in France, responsible for risk of exposure in several persons, confirmed that we should be aware of transmission from this animal [7].

Italy and Greece recently experienced re-emergence of rabies in fox and in some pets. In 2008, fox rabies was re-introduced in the Udine province, after a 13-year absence from Italy, and resulted in the contamination of various domestic animals and postexposure [8*]. The outbreak was detected after some people were attacked by foxes. Italian veterinary services organized the vaccination of foxes in this area and estimated in 2010 that 68% of the targeted fox population had been vaccinated. The situation now seems to be under control, but this episode demonstrates the need for continuous awareness and surveillance in rabies-free countries, and the need for collaboration between human and animal health authorities.

In Greece, the last human case was diagnosed in 1970, and the last animal case in 1987. In 2012/2013, rabies has re-emerged in wild and domestic animals in northern Greece [9], probably coming from Macedonia where rabies remains uncontrolled in wildlife. The first rabid animal was a wild red fox, and the second one a shepherd dog. By March 2013, rabies had been diagnosed in 14 red foxes, two shepherd dogs, and one cat; 104 subsequent human exposures required postexposure prophylaxis according to the WHO criteria. At this time, no human case has been reported.

Even islands, usually considered as having a lower risk of introduction of rabies, are concerned. Bali in Indonesia was rabies-free until 2008 when an epidemic in domestic dogs began, resulting in the deaths of over 100 people. This island became at high risk for inhabitants and travelers (it is one of the major Asian travel areas), so a program for the control of the epidemic is crucial. Using data from Bali, the authors [10**] estimated the basic reproductive number, \( R(0) \), of rabies in dogs to be 1.2, almost identical to that obtained in 10-fold less dense dog populations and confirming that rabies might not be effectively controlled by reducing dog density. They then developed a model to compare options for mass dog vaccination. They demonstrate that a comprehensive high coverage campaign in 2012 would likely result in elimination, saving 550 human lives and US $15 million in prophylaxis costs over the next 10 years.

Besides terrestrial rabies, bat lyssaviruses are distributed worldwide, for instance in Texas [11]: the number of rabid bats during the first 5 years of a study period (2001–2010) remained static until a more than two-fold increase in 2006; during the subsequent 4 years, the annual number of rabid bats remained at this higher level, including a peak in 2008. In South America, rabies viruses spread gradually and involve different vampire bat subpopulations with different transmission cycles [12]. New lyssaviruses are identified regularly, with potential pathogenicity for humans, as demonstrated by the recent implantation of Bokeloh bat lyssavirus in Europe [13].

**ENDEMIC InFECTIONS CAUSING ENCEPHALITIS**

Petersen et al. [14] reviewed the West Nile virus (WNV) infection in the United States. WNV is now endemic, with 16 196 human neuroinvasive disease cases and 1549 deaths reported since 1999. Neuroinvasive infection (meningitis, encephalitis, and acute flaccid paralysis) develops in less than 1%, but the case-fatality ratio averages 10%. WNV encephalitis has a highly variable clinical course but often is associated with considerable long-term cognitive and physical morbidity.

Influenza outbreak in the United Kingdom was investigated in order to assess the incidence of neurological presentations [15**]. A 2-year surveillance study was undertaken through British adult and pediatric neurological surveillance units from February 2011. Twenty-five cases were identified:
21 (84%) children and 4 (16%) adults. Six (29%) children had pre-existing neurological disorders. Influenza A was identified (PCR) in 21 (81%) (20 (95%) H1N1) and influenza B in four (15%). Twelve children had encephalopathy, eight had encephalitis, and one had meningoencephalitis. Two adults had encephalopathy with movement disorder, one had encephalitis, and one had Guillain–Barré syndrome. Seven (six children) had specific acute encephalopathy syndromes: four acute necrotizing encephalopathy, one acute infantile encephalopathy predominantly affecting the frontal lobes, one hemorrhagic shock and encephalopathy, and one acute hemorrhagic leukoencephalopathy. Twenty (80%) required intensive care; 17 (68%) experienced poor outcome; and four (16%) died. Neurological involvement in cases of flu is important, and it emphasizes the value of vaccination in the case of preexisting neurological condition.

Powassan virus (POWV) is a rare neuroinvasive arbovirus, first described in 1958. It has been isolated from *Ixodes* ticks (hosts are woodchucks, red squirrels, chipmunks, groundhogs, and white-footed mice). Symptoms of infection vary from mild myalgia to acute flaccid paralysis and neurologic involvement. In the United States, it has been reported in northeastern and north-central states, and incidence is increasing. Cases were recently reported in New York State [16*]. In 2011, the Centers for Disease Control and Prevention confirmed 16 cases of POWV infection, a substantial increase compared to previous years. New York State alone reported 12 POWV neuroinvasive cases during 2001–2010. This increase is most likely underestimated because underdiagnosis is probably common, and there are concerns that POWV might become endemic in North America with comparable patterns as those of tick-borne virus in Europe [17].

**ENCEPHALITIS IN SPECIFIC GEOGRAPHIC AREAS**

Henipaviruses (*Paramyxoviridae* family) first emerged in the mid-1990s and are re-emerging in Australia and Asia almost every year. More than 12 Nipah virus (NiV) and 48 Hendra virus (HeV) outbreaks have been reported in this area [18]. HeV is associated with carriage and diseases in horses, and NiV is related to pigs and bats. Transmission from human to human is rare. Both viruses are responsible for encephalitis, with high reported case fatality rates: 75% for NiV encephalitis, 57% for HeV encephalitis, although some mild or asymptomatic cases probably exist and only severe presentations are reported. NiV is also responsible for severe pneumonia. There are no vaccines or therapeutic remedies available.

The emergence of NiV infection into the pig population and subsequently into the human population is believed to be due to changes in ecological conditions [19]. In Malaysia, an outbreak occurred in pigs and humans from September 1998 to April 1999. It resulted in infection of 265 patients and death occurred in 105 persons. About 1.1 million pigs were culled to control the outbreak. There were series of human NiV incidences in Bangladesh from 2001 till 2013 almost every year, with mortality exceeding 70%. The traditional transmission from pigs acting as an intermediate host was observed during Malaysian and Singapore outbreaks. It has changed in Indian and Bangladesh outbreaks, with a transmission directly from bats to humans, followed by human to human. In Bangladesh, it was probably related to drinking of raw date palm sap contaminated with fruit bat urine or saliva. Therefore, the virus is now known to exist in various fruit bats of *Pteropus* as well as bats of other genera in a wider belt from Asia to Africa. This finding is important for eradication measures and for counselling travelers.

In India, through a new surveillance system, the authors [20] investigated frequency and etiologies of encephalitis. Their findings illustrate the difficulty to obtain reliable results: they were expecting more than 150 Japanese encephalitis cases per year, as a result of previous studies based on clinical findings and serological tests, but they diagnosed only three PCR documented cases. The question is how to monitor such a disseminated infection in such a huge country.

The Chinese authors [21] recently investigated so-called unknown encephalitis (not dengue, nor Japanese encephalitis) and aimed to demonstrate importance of other viruses in this category. The study period was 2002–2012 and included 1165 cases. They analyzed 1180 samples: 13.9% cerebrospinal fluid and 31.1% stool samples were positive for enteroviruses. This rate fluctuated from 4.8 to 35.2% in different years. Echovirus 30 was found to be the periodically predominating serotype in the periods of 2002–2004 and 2010–2012. By contrast, no Echovirus 30 was detected from 2005 to 2007, and coxsackievirus B3 and B5 was the predominating serotype for 2008 and 2009, respectively. In 2010, coxsackievirus B4 was found to cause an epidemic for the first time here.

Other Chinese authors [22*] aimed to identify key climatic factors that are associated with the transmission of Japanese encephalitis virus in areas located near the Three Gorges Dam, between 1997 and 2008. The eastern region, which is closest to the dam, suffered the highest incidence of Japanese
encephalitis, whereas the western region experienced the lowest incidence. The authors demonstrated a significant positive association between temperature and Japanese encephalitis incidence, and a significant negative association between rainfall and Japanese encephalitis incidence. They suggest that modifications in the local climate, related to the dam, are responsible for a Japanese encephalitis increased incidence.

**HEALTHCARE-RELATED INFECTIONS RESULTING IN ENCEPHALITIS**

Between 2004 and 2012, the US Food and Drug Administration received postmarket reports for 20 patients with PCR-confirmed central nervous system (CNS) herpesvirus infections, during or following recent natalizumab treatment [23]. Six cases were also reported in the literature. The median age for all patients was 44 years (30–63 years), 16 (80%) of them being female (probably because of the higher frequency of multiple sclerosis in women). Patients received a median of 21 monthly doses of natalizumab prior to encephalitis. The pathogens and clinical syndromes were five herpes simplex virus (HSV)-1 encephalitis cases, five HSV-2 cases (two encephalitis, two meningitis, and one meningoencephalitis), six HSV nontyped as to HSV-1 or HSV-2 (three encephalitis and three meningitis), and four varicella zoster virus (VZV) infections (two meningitis, one meningoradiculitis, and one meningomyelitis). Two patients died from their infections. The authors of this postmarket study suggest that natalizumab may confer a predilection for CNS herpesvirus infections as follows:

1. Two natalizumab-treated adults developed HSV-2 encephalitis, an unusual finding considering that HSV-2 is more frequently associated with neonatal encephalitis.
2. No reports of HSV-2 CNS infections were retrieved for adults receiving other multiple sclerosis treatment.
3. They also retrieved only two reports of laboratory-confirmed VZV and no cases of HSV CNS infections in patients receiving other multiple sclerosis regimens, compared with 15 cases among natalizumab-treated patients.

This illustrates that HSV and VZV should be considered as opportunistic infections of the brain in natalizumab-treated multiple sclerosis patients. *Acanthamoeba* spp. and *Balamuthia mandrillaris* are the most common causative agents of amebic CNS infections. *Balamuthia* was first recognized in 1986 in the United States during an encephalitis outbreak affecting primates at the San Diego Wild Animal Park. Since then over 150 cases have been reported globally, the majority of them fatal, occurring in immunosuppressed patients (HIV-infected, undergoing immunosuppressive therapy, alcohol abusers or the very old). Recent case reports demonstrate that this agent affects also immunocompetent patients [24,25].

A large outbreak of fungal (*Exserohilum rostratum*) meningitis and other infections occurred in patients who received epidural, paraspinal, or joint injections with contaminated lots of methylprednisolone acetate. A total of 328 patients without peripheral-joint infection were included in an investigation by the US Centers for Disease Control and Prevention; 265 (81%) had CNS infection, and 63 (19%) had non-CNS infections only. This highlights the possibility of nosocomial encephalitis [26].

**NEW PATHOPHYSIOLOGICAL CONCEPTS**

HSV could be involved, as a trigger, in autoimmune encephalitis. In a retrospective study, authors [27] aimed to determine the presence and kinetics of antibodies against synaptic proteins in patients with HSV encephalitis. They analyzed samples of 44 patients with PCR-proven HSV encephalitis for the presence of a panel of onconeuronal and synaptic receptor antibodies. They demonstrated the presence of anti-N-methyl-D-aspartate receptor (NMDAR) antibodies of the immunoglobulin (Ig) subtypes IgA, IgG, or IgM in 13 of 44 patients (30%) in the course of herpes simplex encephalitis (HSE). It suggests secondary autoimmune mechanisms and has implications for the understanding and management of autoimmunity in infectious diseases. In another study [28**, five diagnosed patients with relapsing post-HSV encephalitis in which anti-NMDAR antibodies were identified were included. Antibody synthesis started 1–4 weeks post-HSV encephalitis, preceding the neurological relapse. Three of five patients improved after immunotherapy, one spontaneously, and one has started to improve at the date of the publication.

Moreover, in the same study, a retrospective assessment of 34 HSE patients was performed. It resulted in the identification of two additional patients with anti-NMDAR antibodies, nine with unknown neuronal surface antibodies, and one with anti-NMDAR and unknown antibodies. The three retrospectively identified anti-NMDAR antibody positive patients also had evidence of relapsing post-HSV encephalitis.

These two studies indicate that HSE triggers anti-NMDAR antibodies and potentially other brain
autoimmunity. This is of major importance, if confirmed: should we prescribe corticosteroids early after the onset and diagnosis? Is it an additional explanation for the high rate of sequelae after this infection?

This is obviously a matter for further investigations in the field of infectious encephalitis.

**CONCLUSION**

Ever-changing epidemiology and physiopathology need to stay updated, and encephalitis should be considered as a sentinel for emerging infections. The neurological presentation is spectacular enough to be a good marker for the emergence of an agent in a new geographical area. This demonstrates the importance of close surveillance, as when implanted those diseases are difficult to eradicate.

Fantastic challenges in the future will arise with the demonstrated link between infection and specific autoimmunity. Viruses, HSV in this case, could be a trigger for immune diseases. It raises questions about pathophysiology, and some therapeutic concerns: what could be the place for corticosteroids, for example? This finding is of major importance for the future management of patients and their prognosis.

**Acknowledgements**

None.

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES AND RECOMMENDED READING**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

9. Surveillance is mandatory, as re-emergence is always possible, as demonstrated in Italy.
12. When implanted, a viral disease is very difficult to eradicate. This article describes a model and its expected results.
18. Influenza is responsible for severe neurological presentations. It is an argument to add in favor of vaccination.
20. New viruses are invading countries previously free of them.
27. Climate has an impact on emergence of infectious encephalitis.

This study suggests HSV as a trigger for autoimmune disease. It is of outstanding importance for the treatment and management of sequelae.