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Médecine et maladies infectieuses
Médecine et maladies infectieuses 47 (2017) 221–235

General review

Epidemiology of infectious encephalitis causes in 2016

Épidémiologie des causes d'encéphalites infectieuses en 2016

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Received 14 February 2017; accepted 17 February 2017
Available online 22 March 2017

Abstract

We performed a literature search in the Medline database, using the PubMed website. The incidence of presumably infectious encephalitis is estimated at 1.5–7 cases/100,000 inhabitants/year, excluding epidemics. Infectious encephalitis and immune-mediated encephalitis share similar clinical signs and symptoms. The latter accounts for a significant proportion of presumably infectious encephalitis cases without any established etiological diagnosis; as shown from a prospective cohort study where 21% of cases were due to an immune cause. Several infectious agents are frequently reported in all studies: *Herpes simplex* virus (HSV) is the most frequent pathogen in 65% of studies, followed by Varicella-zoster virus (VZV) in several studies. *Enterovirus*es are also reported; being the most frequent viruses in two studies, and the 2nd or 3rd viruses in five other studies. There are important regional differences, especially in case of vector-borne transmission: Asia and the Japanese encephalitis virus, Eastern and Northern Europe/Eastern Russia and the tick-borne encephalitis virus, Northern America and *Flavivirus* or *Alphavirus*. Bacteria can also be incriminated: *Mycobacterium tuberculosis* and *Listeria monocytogenes* are the most frequent, after HSV and VZV, in a French prospective study. The epidemiology of encephalitis is constantly evolving. Epidemiological data may indicate the emergence and/or dissemination of new causative agents. The dissemination and emergence of causative agents are fostered by environmental, social, and economical changes, but prevention programs (vaccination, vector controls) help reduce the incidence of other infectious diseases and associated encephalitis (e.g., measles).

Keywords: Encephalitis; HSV; VZV; *Enterovirus*; Emerging infections; Epidemiology

Résumé

Nous proposons une revue de la littérature avec des articles sélectionnés par une recherche sur Medline, via le moteur de recherche PubMed. L'incidence des encéphalites présumées infectieuses est estimée entre 1,5 et 7 cas/100 000 habitants/an, hors épidémies. Il existe une similarité clinique entre les encéphalites infectieuses et celles à médiation immune, ces dernières représentant une part importante des encéphalites présumées infectieuses sans diagnostic étiologique établi : dans une cohorte prospective, 21 % des cas étaient attribués à une cause immunitaire. Certains agents

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http://dx.doi.org/10.1016/j.medmal.2017.02.003
0399-077X/

infectieux sont fréquents dans toutes les études : le virus *Herpes simplex* (HSV) est le plus fréquent dans 65 % des études et le virus varicelle-zona (VZV) est souvent le deuxième agent. Les *Entérovirus* sont fréquemment rapportés et constituent les virus les plus fréquents dans deux études et au 2e ou 3e rang dans cinq. Les différences régionales sont importantes, surtout en cas de transmission vectorielle : Asie et virus de l'encéphalite japonaise, Europe de l'Est, du Nord, partie orientale de la Russie et virus de l'encéphalite à tiques européenne, Amérique du Nord et *Flavivirus* ou *Alphavirus*. Des bactéries sont aussi responsables : *Mycobacterium tuberculosis* et *Listeria monocytogenes* étaient les plus fréquentes, après HSV et VZV, dans une étude prospective française. L'épidémiologie des encéphalites est en constante évolution. Elle peut révéler l'émergence et/ou la dispersion de nouveaux agents pathogènes. Les modifications environnementales et socio-économiques les favorisent, mais les programmes de prévention (vaccination, lutte anti-vectorielle) permettent la diminution de l'incidence d'autres maladies infectieuses et encéphalites associées (ex. rougeole).

Mots clés : Encéphalite ; HSV ; VZV ; *Entérovirus* ; Infections émergentes ; Épidémiologie

1. Introduction

Many infectious agents, mainly viral ones, are responsible for encephalitis. However, encephalitis remains a rare complication of most infections. The cause of encephalitis is identified in no more than half of cases.

The incidence of presumably infectious encephalitis is estimated at 1.5–7 cases/100,000 inhabitants/year in published studies and countries, excluding epidemics [1].

2. Methods

We performed a literature search using Medline and PubMed website. We also used experts' references on encephalitis (Fig. 1). We used the search terms "encephalitis AND epidemiology" and "encephalitis AND etiology", with the filters "humans", "adults", and "age > 19 years". We only kept articles published in English and French as literature reviews or case series between January 2000 and July 2015. Clinical Practice Guidelines (CPG) on the "Management of encephalitis in metropolitan France" were issued based on this literature review.

3. Cross-sectional cohort studies and global epidemiology of encephalitis causes

We reviewed 25 cross-sectional studies published between 2000 and 2015 (Table 1, Fig. 2). Cohort studies were either retrospective or prospective based on hospital discharge database (ICD codes) or less frequently on data specifically collected for epidemiological studies. Results in those articles were not compared as they differed in terms of inclusion criteria (adults, children, or both, immune status), case definitions, diagnostic criteria, and study periods. The 25 studies comprised six prospective studies performed in temperate countries [2–8], four in tropical countries [9–12]; and 16 retrospective studies [13–27].

The incidence of encephalitis hospitalization reported in five studies (1.5 to 7.3 hospitalizations/100,000 inhabitants) over time seemed stable although very different between countries [13–17]; it decreased over time in two other studies [18,19]. In the study where results were detailed by age groups or immune status, the incidence was higher in older patients [13,18,20] and in immunocompromised patients [18].

The etiology was identified in 27.5% [27] to 79% [10] of analyzed encephalitis patients. These figures question the performances of and access to the diagnostic tests available at the time each study was performed, and raises issues for the presence of non-infectious etiologies or even unknown infectious agents at the time studies were performed.

It is now well established that infectious encephalitis and immune-mediated encephalitis can present with similar clinical signs and symptoms, suggesting that immune-mediated encephalitis may account for a significant proportion of presumably infectious encephalitis cases without any identified microbial agents. Several studies reported 21% due to an immune cause, 5 to 16% as post-infectious, and 0.1 to 3% as post-immunization encephalitis [4,13,14,19,21].

Herpes simplex virus (HSV) was the most frequent agent, observed in 65% of studies [4–6,10,13,14,16,18,20–24,26]. Varicella-zoster virus (VZV) was the second most frequent agent [4–6,16–19,22–24]. *Enterovirus*es (EV) were also frequently reported and considered the most frequent etiology in two studies [3,11], and the 2nd or 3rd etiology in five studies [6,7,12,25,26]. Both case definitions and study regions used in these studies may explain these differences.

Regional differences shape the epidemiology of encephalitis, especially for vector-borne transmission. The Japanese encephalitis virus (JEV) was frequently reported in Asian studies [11,12]. The tick-borne encephalitis virus (TBEV) was more frequently reported in Eastern and Northern Europe as well as in Russia [7,8]. Other arboviruses, mainly *Flaviviruses* and *Alphaviruses*, were more frequently observed in Northern America [15,21].

Correlatively, a meta-analysis that included 45 studies published between 1950 and 2003, and performed on the five continents, allowed confirming these differences [38]. In Asia, JEV was the most frequently identified infectious agent, and mainly affected children as shown in 10 out of 16 studies. However, HSV was still an important cause of infectious encephalitis, and the results might have been biased by different investigation protocols in the analyzed studies.

Etiologies differed in Europe, with HSV and VZV as the most frequent agents, as well as in America, in addition to EV and

Table 1
Epidemiological studies on encephalitis etiologies.
Études épidémiologiques sur l'étiologie des encéphalites.

Country	Year	Age	Patient's characteristics	Included	Incidence (100,000)	Etiologies	Mortality	Reference
Prospective studies in non-tropical countries								
California (195 H)	1998–2005	C + A	Immunocompetent	1570		37%: EV (17%), HSV (16%), VZV (9%), MTB (1%)	11%	[3]
United Kingdom (24 H)	2007–2008	C + A	Including immunocompromised (15%)	203		63%: HSV (19%), VZV (5%), MTB (5%)	12%	[4]
France (106 H)	2007	C + A	HIV excluded	253		52%: HSV (22%), VZV (8%), MTB (8%), *L. monocytogenes* (5%)	10%	[5]
Spain (17 H)	2008–2009	C + A	Immunocompetent	72		27.6%: HSV (20%), VZV (5.3%), EV (2.6%)		[6]
Finland (18 H)	1995–1996	C + A		1014		46%: VZV (9.5%), HSV (3.5%), EV (2.7%), Influenza A virus (2.6%), TBE (2%)		[7]
Finland (1 H)	1999–2003	A	Immunocompetent	42	2.2	36%: VZV (12%), HSV1 (9%), TBE (9%)		[8]
Retrospective studies based on hospital codes								
Australia (NSW)	1990–2007	C + A	Including immunocompromised	5926	5.2	30%: HSV (13%), VZV (3.8 + 1.8%), *T. gondii* (3.7%), SSPE (1.3%), *L. monocytogenes* (0.5%)	4.6%	[18]
California	1990–1999	C + A	HIV excluded	13,807	4.3	44%: HSV (14.4%), arboviruses (0.64%) MTB (0.2%); *N. meningitidis* (0.9%); *T. gondii* (0.6%); *T. pallidum* (0.1%).		[20]
USA	1988–1997	C + A	Including immunocompromised		7.3	40.5%: 15.5% viral: HSV > *T. gondii* > VZV > arboviruses; ADEM (5.3%)	7.4%	[13]
USA	1998–2010	C + A	Including immunocompromised (HIV: 8.8%)		6.9	50.3%: HSV (15%), WNV (1.5%), ADEM (5.5%)	5.8%	[14]
Alaska/US Indians	1998–2010	C + A	Including immunocompromised (HIV: 3.2%)	436	3.1	46%: HSV (14.6%), WNV (3.6%), ADEM (4.6%)	4.1%	[21]
Canada	1994–2008	C + A	Including immunocompromised	24,028	5.4	50.2%: VZV (17.7%), HSV (9.3%), WNV (3.1%)		[15]
United Kingdom	1989–1998	C + A		6414	1.5 (viral)	40%: HSV (20.8%), VZV (5.2%)	6.5% C 9.5% A	[16]
Ireland	2005–2008	C + A		418	2.49 (viral)	46.7%: HSV (22.1%), VZV (14.4%)	7.9%	[22]
France	2000–2002	C + A	HIV excluded	3598	1.9	20%: HSV (5–13%), VZV (4–7%), arboviruses (0.8–2%), EV (0.2–0.8%)	6%	[17]
Italy	1999–2005	C + A		23,594	5.88	44.4%: HSV (15%), VZV (7%), ADEM (16%), arboviruses (0.5%)		[19]
Norway (Oslo)	2000–2009	A	Including immunocompromised (7%)	70		43%: HSV (14%), VZV (9%)	7%	[23]

Table 1 (*Continued*)

Country	Year	Age	Patient's characteristics	Included	Incidence (100,000)	Etiologies	Mortality	Reference
Other retrospective studies								
Finland	1967–1991	A		322	1.4	49%: HSV (16%), VZV (5%), mumps virus (4%), Influenza virus (4%)	5.6%	[24]
New-Zealand	2005–2009	A			0.5	35%: VZV (14%), HSV (11%), EV (3%)	14%	[25]
Greece	2003–2006	A	Immunocompetent	45	(Viral)	HSV (9%), EV (9%)		[26]
Tunisia	2003–2009			1071	(Viral) (CNS infection)	17.5% including 38 encephalitis: WNV (20), HSV (9), EV (9), Toscana virus (3)		[27]
Prospective studies conducted in tropical countries								
Cambodia	1999–2000	C + A	Including immunocompromised (HIV: 23%)	99		40% (HIV excluded): *Streptococcus* (4.2%), MTB (4.2%), EBV (4.2%), *Cryptococcus* (2%), dengue virus (2%)		[9]
Taiwan	2000–2001	C + A		127		79%: HSV (36%), VZV (13%), MTB (8%), CMV (6%), arboviruses (4%), Influenza virus (0.8%), EV (0.8%)		[10]
Rural Central India	2007	A	Including immunocompromised (HIV: 7 cases)	152	16 (viral)	79%: HSV (36%), VZV (13%), MTB (8%), CMV (6%), arboviruses (4%), Influenza virus (0.8%), EV (0.8%)	36%	[11]
Thailand	2003–2005	C + A	Including immunocompromised (15%)	149		66%: JEV (25%), EV (4%), *Cryptococcus* (2%), *S. pneumoniae* (2%), *H. influenzae* (2%), VZV (1.3%), dengue virus (3%)	10%	[12]

H: hospital; NSW: New South Wales; C: children; A: adults; SSPE: subacute sclerosing panencephalitis; MTB: *Mycobacterium tuberculosis*; HSV: *Herpes simplex* virus; VZV: Varicella-Zoster virus; ADEM: acute disseminated encephalomyelitis; WNV: West Nile Virus; CNS: central nervous system; EV: *Enteroviruses*; EBV: Epstein–Barr virus; CMV: cytomegalovirus; JEV: Japanese encephalitis virus

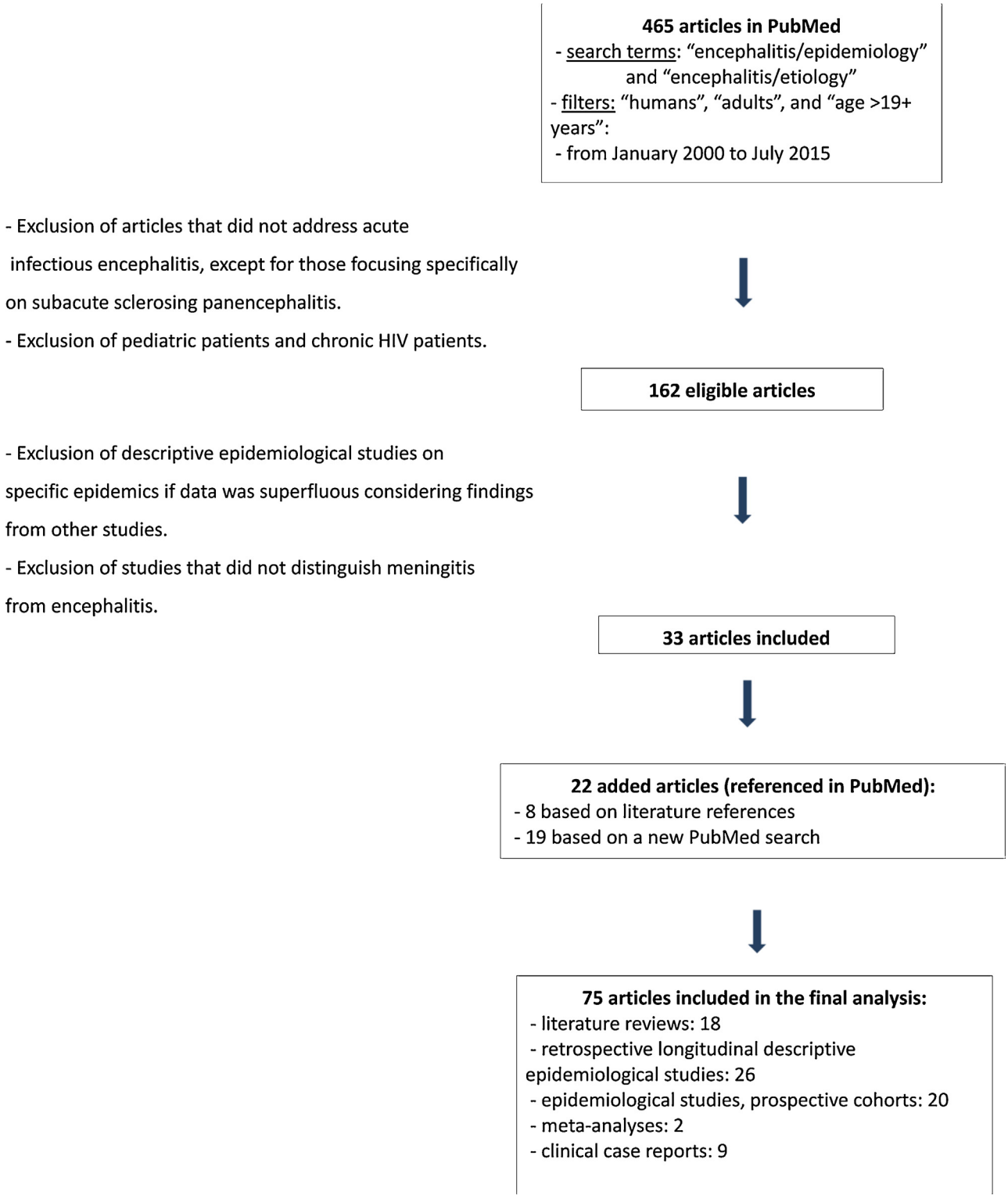

Fig. 1. Flow chart.
Diagramme.

various arboviruses [1]. Interpreting this meta-analysis is, however, difficult due to the heterogeneity of analyzed populations and areas where the studies were performed.

Many other viruses may cause encephalitis. They may represent rare or emergent causes that we will later address in this review.

When considering bacteria, *Mycobacterium tuberculosis* and *Listeria monocytogenes* were the most frequent infectious agents observed in a French prospective study [5]. *Mycoplasma pneumoniae* was also reported in all recent prospective studies [2,4,5]. Several bacteria were responsible for brain abscesses with a symptomatology indicative of

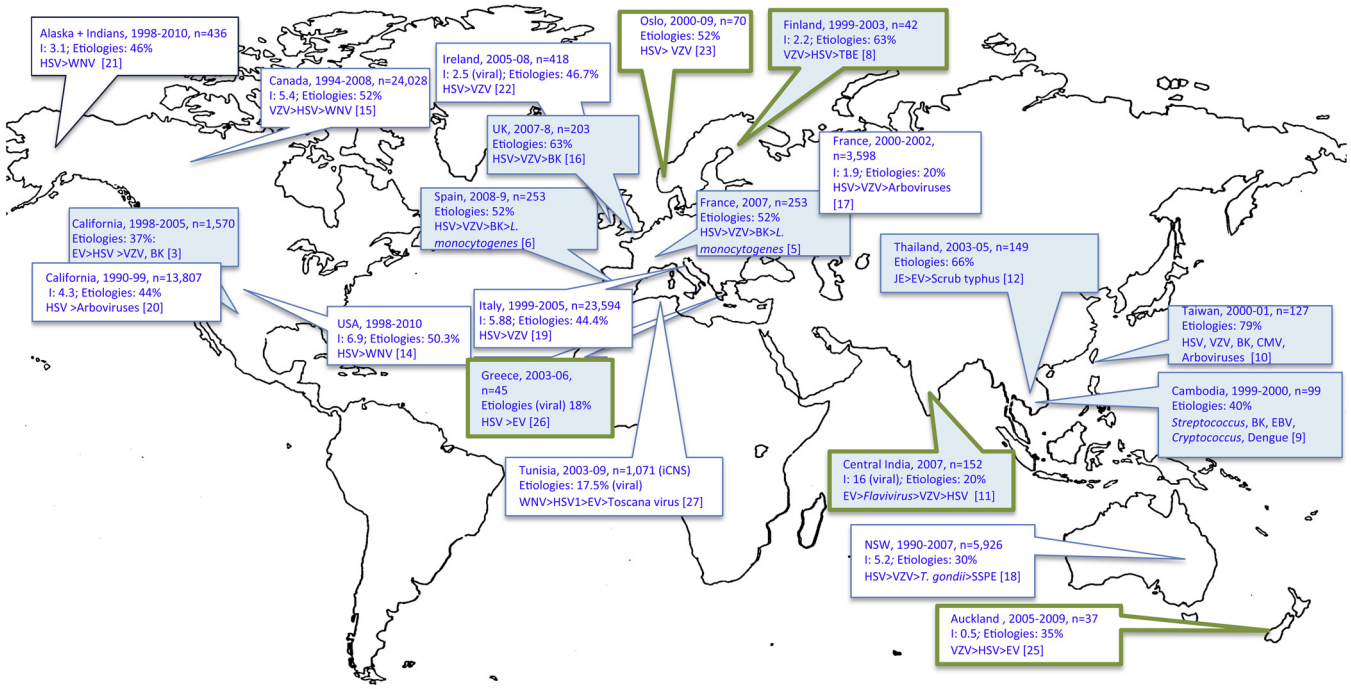

Fig. 2. Map of epidemiological studies on encephalitis etiologies. Blue background: prospective studies; white background: retrospective studies. Green-boxed text: studies including adults; black-boxed text: studies including children and adults. N: number of patients included; I: incidence; iCNS: central nervous system infections.
Carte des études épidémiologiques sur l'étiologie des encéphalites.

encephalitis at the early phase of the infection (*Nocardia*, *Brucella*, etc.).

HSV, VZV, *L. monocytogenes*, and *M. tuberculosis* should be considered the most probable causes of infectious encephalitis in metropolitan France. Consensus therapy against these four infectious agents should be administered as soon as encephalitis is suspected to insure proper patient outcome.

Any recent travel must lead physicians to consider other causes depending on the countries visited, but they should not rule out domestic/native causes. The patient's medical history (immunodeficiency), his/her place of residence (rural or agricultural area), and his/her environment (professional or home) may guide physicians towards specific causes (Table 2).

The epidemiology of encephalitis is constantly changing. Encephalitis may reveal the emergence and/or dissemination of new causative agents. This dissemination is fostered by environmental, social, and economic changes (climate change, population movement, forest fragmentation, urbanization, etc.). Conversely, specific vaccination and vector controls programs should contribute to reducing the incidence of other infectious diseases and associated encephalitis (e.g., measles) [18,19].

4. Causative infectious agents commonly observed in metropolitan France

4.1. Herpes simplex virus (HSV)

HSV1 is the first identified cause of infectious encephalitis. Its estimated incidence is between 2 and 4 cases per million of inhabitants and per year, and considered low when compared with the presence of antibodies in the general population (seroprevalence of 80–90% for HSV1 and 4–40% for HSV2 in adults) [28]. HSV was the most frequently reported etiological agent in 17 of the 25 epidemiological studies (Table 1).

HSV encephalitis was lethal in 5 to 20% of cases (70% before availability of the acyclovir treatment) depending on the recruitment criteria of the studies [3–5,16,24,29]. HSV can trigger an autoimmune encephalitis-associated with clinical neurological relapses or delayed recoveries [30].

The wide implementation of an effective diagnostic test and of a specific effective treatment considerably improved the diagnosis of HSV, its early management, and the prognosis of patients.

4.2. Varicella-zoster virus (VZV)

VZV is the second cause of infectious encephalitis in developed countries. VZV was the first agent reported in pediatric studies [7,15] and in several adult studies [8,25]. Just like HSV, VZV is a DNA virus belonging to the Herpesviridae family. Neurological complications occurred at the end of the primary infection or reactivation of a latent infection, without any associated skin rash in 55% of cases [5]. Immunocompromised patients are at higher risk of encephalitis. Neurovascular damage may be associated with encephalitis: ventriculitis, vasculitis of large vessels complicated by ischemic strokes, vasculitis of small vessels with demyelinating lesions.

Table 2
Main pathogens to consider depending on context.
Principaux agents infectieux à évoquer selon le contexte.

Characteristics/risk factors	Potential infectious agents
Immunodeficiency	All agents are possible but some are more frequently isolated than others: EBV, CMV, HHV6, VZV, EV, *Listeria monocytogenes*, *Mycobacterium tuberculosis*, *Nocardia*, *Cryptococcus neoformans*, JC virus, WNV, LCMV, HEV, measles virus, *Coccidioides*, *Histoplasma capsulatum*, *Aspergillus fumigatus*, *Toxoplasma gondii*, *Acanthamoeba* spp., *Balamuthia mandrillaris*
Monoclonal antibody therapies	Infliximab, etanercept: VZV, *M. tuberculosis*, *Legionella pneumophila*, *Listeria monocytogenes*, *Nocardia*, *Histoplasma capsulatum* Rituximab: EV, JC virus Natalizumab: HSV, JC virus Tocilizumab: VZV, *Mycobacterium tuberculosis*
Following allogeneic hematopoietic stem cell transplantation	HHV6, CMV
Transmission via transplantation/transfusion (infectious agent present in the graft/transfusion)	WNV, rabies virus, LCMV, EBV, CMV, HHV6, TBEV, HIV, JC virus, *Treponema pallidum*, *Anaplasma phagocytophilum*, *Rickettsia*, *Cryptococcus neoformans*, *Coccidioides*, *Histoplasma capsulatum*, *Toxoplasma gondii*, variant Creutzfeldt–Jakob disease (v-CJD)
Unvaccinated patients	Poliovirus, VZV, measles/mumps/rubella viruses, *Mycobacterium tuberculosis*
In endemic areas	Yellow fever virus, JEV, TBEV
Recent vaccination	Yellow fever virus, (measles virus), all
Older age	EEEV, WNV, VZV, HSV, *Listeria monocytogenes*, *Balamuthia mandrillaris*
Pregnancy	LCMV, *Listeria monocytogenes*
Chronic liver disease	*Listeria monocytogenes*
Lifestyle	
Following swimming	EV, *Naegleria fowleri*, Leptospirosis
Speleology	*Histoplasma capsulatum*
Sexual exposure	HIV, *Treponema pallidum*
Travels	
Northern America	WNV, La Crosse virus, SLEV, EEEV, WEEV, California encephalitis virus, Colorado tick fever virus, Powassan virus, Chikungunya virus, rabies virus, EV71, *Rickettsia rickettsii*, *Anaplasma phagocytophilum*, *Borrelia burgdorferi*, *Coccidioides*, *Naegleria fowleri*, *Acanthamoeba* spp., *Balamuthia mandrillaris*, *Baylisascaris procyonis*
South and Central America	VEEV, WNV, EEEV, SLEV, chikungunya virus, dengue virus, yellow fever virus, rabies virus, *Bartonella bacilliformis*, *Rickettsia*, *Taenia solium*, *Plasmodium falciparum*
Asia	JEV, TBEV, Chandipura virus, Nipah virus, EV71, chikungunya virus, rabies virus, *Orientia tsutsugamushi*, *Plasmodium falciparum*, *Angiostrongylus* sp.
Australia/Oceania	MVEV, Kunjin virus, Hendra virus, ABLV, JEV
Europe	TBEV, WNV, Toscana virus, rabies virus *Anaplasma phagocytophilum*, *Borrelia burgdorferi*
Mediterranean region	Toscana virus, WNV, dengue virus, rabies virus
Africa	Chikungunya virus, dengue virus, yellow fever virus, WNV, rabies virus, *Trypanosoma brucei*, *Plasmodium falciparum*, *Schistosoma*
Sting by vectors	
Ticks	TBEV, Powassan virus, Colorado tick fever virus, CTFV, *Borrelia burgdorferi*, *Rickettsia rickettsii*, *Ehrlichia chaffeensis*, *Anaplasma phagocytophilum*, *Francisella tularensis*
Mosquitoes	JEV, WNV, dengue virus, yellow fever virus, chikungunya virus, La Crosse virus, SLEEV, EEEV, WEEV, VEEV, MVEV
Sand flies	Chandipura virus, Toscana virus *Bartonella bacilliformis*
Tsetse flies	*Trypanosoma brucei*
Seasons: spring/autumn	EV, tick-borne and mosquito-borne infections, *Leptospira* sp.
Animals (direct contact or environment contaminated by feces)	
Bats	Rabies virus, Nipah virus, Hendra virus
Monkeys in the Old World	Herpes B virus (Cercopithecine herpesvirus 1)
Carnivores (dogs, cats, ferrets)	Rabies virus, *Bartonella henselae*
Horses	Hendra virus
Pigs	Nipah virus, Influenza virus
Ovines/caprines	*Coxiella burnetii*, *Brucella* (NOT IN FRANCE)

Table 2 (*Continued*)

Characteristics/risk factors	Potential infectious agents
Rodents (wild or domestic)	EEEV, LCMV, La Crosse virus, Powassan virus, VSB1 *Bartonella henselae*, *Rickettsia* spp., *Francisella tularensis*, *Leptospira interrogans*
Raccoons	*Baylisascaris procyonis* (Northern America only)
Lagomorphs, rodents	*Francisella tularensis*
Food exposures	
Poorly or uncooked meat	*Gnathostoma*, *Taenia solium* (cysticercosis), Toxoplasma *gondii*
Unpasteurized milk	TBEV, *Brucella* (in enzootic countries, e.g. not in France), *Listeria monocytogenes*
Crudités	*Toxoplasma gondii*
Sausages prepared with raw pork liver	HEV

4.3. *Mycobacterium tuberculosis (MTB)*

Tuberculosis is a frequent cause of encephalitis in all regions of the world. The severity of the infection and the availability of effective treatments must systematically lead physicians to consider MTB in patients presenting with encephalitis. MTB was reported as the first cause of bacterial encephalitis in several studies: France (8%) [5], England (5%) [4], Cambodia (4%) [9], Taiwan (8%) [10]. Lethality was high (>30%) [4,5]. In France, 20% of patients presenting with MTB encephalitis had a previous or an existing history of tuberculosis. Sixty percent of MTB encephalitis patients had known epidemiological risk factors for MTB [31].

4.4. *Listeria monocytogenes*

Listeriosis develops after ingestion of contaminated food or through contact with an infected animal. The authors of a meta-analysis estimated that 31% of listeriosis case patients worldwide were neurolisteriosis cases [32]. Rhombencephalitis (58%) was the main clinical presentation of *L. monocytogenes* encephalitis in another study [5].

In metropolitan France, *L. monocytogenes* was the 4th identified cause of encephalitis, but only accounted for 5% of cases [5,33]. Several studies even reported a lower proportion of neurolisteriosis cases [4,17,23]. The higher incidence of *Listeria* encephalitis reported in the French study as compared with other national published studies may be explained by a better diagnosis as *L. monocytogenes* is more frequently looked for in encephalitis patients in France mainly due to historical epidemiology. *Listeria* encephalitis might be classified as meningitis in other countries.

A higher lethality was observed in *Listeria* encephalitis patients as compared with other infectious encephalitis (46% versus 10%, $P = 2.10^{-5}$). Identified risk factors for severe *Listeria* infections, which include *Listeria* encephalitis, were older age, cancers, malignant hemopathies, immunodeficiency, chronic hemodialysis, chronic liver disease, and alcohol poisoning [5].

4.5. *European tick-borne encephalitis virus (TBEV)*

TBEV is an arbovirus of the *Flavivirus* genus, which is transmitted to humans by *Ixodes* ticks, and less frequently by ingestion of raw milk from infected cows. TBEV should be differentiated from Powassan virus, often abbreviated as TBE in the United States (please see below).

TBEV is observed in Europe and Asia, from the East of France (Alsace/Rhône-Alpes regions) to Eastern Russia, with the highest incidence in Russia; in Siberia for instance, with an estimated 40 to 80 cases per 100,000 inhabitants. Its incidence is very low in France; 42 cases were reported between 2000 and 2008 in the Alsace-Lorraine region [35].

TBEV disease occurs from April to November, as sporadic cases or outbreaks. Neurological symptoms (acute flaccid paralysis, myelitis, meningitis, and encephalitis) were observed in 20–30% of symptomatic patients [34].

The incidence of TBEV infections seems to have been on the rise for the past 30 years or so in endemic countries. Its distribution area also seems to have grown. The mean annual incidence of tick-borne encephalitis was recently estimated between 1989 and 2007 in 19 endemic European countries to be 8755 cases/year (2805 cases/year, excluding Russia). A 317% (193% excluding Russia) rise in the incidence was observed from 1976 to 1989. However, the incidence has been decreasing in Russia since 1999 as well as in Austria due to the implementation of vaccination (600–700 cases/year before vaccination versus 64 cases/year for the past 10 years) [35].

This increase in incidence is supposedly linked to the higher number of ticks and to the extension of their activity period and human exposure (global warming, higher rainfall rates), and to a better reporting of cases [35].

4.6. *Mycoplasma pneumoniae*

M. pneumoniae infection is frequently associated with encephalitis, especially in children. *M. pneumoniae* is rarely detected in CSF samples, and the diagnosis is often indirect and performed in non-neurological samples, suggesting an immunoinflammatory mechanism rather than a direct infection of the central nervous system (CNS).

In California, only two out of 98 suspected cases of *Mycoplasma* encephalitis were confirmed by CSF PCR [3]. In France in 2007, two probable cases of *M. pneumoniae* encephalitis were diagnosed by seroconversion in blood among the 253 cases included in the study [5].

5. Causative agents of encephalitis frequently observed outside France

5.1. Japanese encephalitis virus (JEV)

JEV is a *Flavivirus* transmitted by *Culex* mosquitoes. It is a major cause of severe encephalitis in Asia, in rice cultivation and pig farming areas [36,37]. Epidemics are observed during the warm season in temperate areas. The infection may also be endemic with a peak during the rainy season in tropical areas. The first cases were reported in China in 1940 and in Southeast Asia. New cases were then described in the West, near Pakistan, and in the East towards Korea. Sporadic cases have been reported since 1995 in Western Pacific and in Central and Northern Australia. The infection is not endemic in Japan, where only rare cases were reported.

A recent meta-analysis estimated the mean annual incidence of the infection in 24 endemic Asian countries between 1998 and 2011 at 1.8/100,000 inhabitants/year (range 0.01 to 10.6/100,000 depending on regions and study periods) [38]. The gross number of cases was estimated at 67,900 cases/year on average. Overall, 81% of cases occurred in areas where vaccination programs had been implemented – cases were thus better detected in these regions – and 50% occurred in continental China. Children accounted for 75% of cases but the mean age was decreasing in areas where vaccination programs had been implemented. A 10 times lower incidence was reported with declarative passive surveillance as compared with laboratory-based surveillance [37]. A total of 8200 cases/year were identified in Mekong countries (Laos, Cambodia, Vietnam, Thailand, Yunnan), of which 563 cases/year in Cambodia, via the surveillance of laboratory results.

The incidence of JEV decreased in various countries (China, Thailand, Korea, Japan, etc.) with the implementation of vaccination and vector controls. A 4 to 8 times decrease in JEV incidence has been observed in Thailand since 2000 [36]. However, the incidence continues to rise in other countries (Bangladesh, India, Nepal, Myanmar, Vietnam, etc.) because of the dissemination of vectors. Many cases have been reported since 2005 in Nepal and in the Uttar Pradesh region of India.

Several studies assessed the risk encountered when traveling to endemic areas. A prospective study, which included 387 adult Australians traveling to Asia for > 7 days from 2007 to 2010, showed that 9% were vaccinated and none contracted JEV [39].

Between 1973 and 2008, among travelers, expatriates, and soldiers, a total of 55 cases were reported, i.e. a mean incidence of 1.5 cases/year and a risk evaluated at less than 0.2 cases/million of American travelers [40].

5.2. Rabies

Rabies viruses belong to the Rhabdoviridae family and to the *Lyssavirus* genus. New viruses are frequently discovered.

Rabies is always fatal (100%) in humans and presents as acute encephalitis following a mean incubation period of 1 to 3 months. Rabies develops after inoculation by a bite/scratch or after a mucous lick by an animal excreting the virus.

Rabies is supposedly responsible for 55,000 deaths/year, mainly in Africa and Asia. Dogs are the infecting animals in 99% of cases and children are mostly affected, especially boys.

In France, terrestrial rabies is no longer observed since 1998 but cases of infected animals, imported from at-risk countries, are regularly detected. A total of 22 fatal cases were declared in France between 1970 and 2014. They were all imported cases, except for one case in French Guiana, and 80% had been contaminated in Africa.

Classical animal rabies is rather well controlled in Western Europe, but historical outbreaks persist in Eastern Europe (Balkan Peninsula, Romania, Poland). Occasional outbreaks may resurface such as in Italy in 2008 among foxes and in Northern Greece in 2011/2013 among wild and domesticated animals. No human case was, however, reported. The virus is present as an enzootic infection in the Balkans, in several European countries (Poland, Ukraine, Moldova, etc.), and in Russia.

Although classical canine rabies is no longer observed in France, EBL1, EBL2 (European bat *Lyssavirus*), and Bokeloh viruses are carried by bats in France. These viruses have only rarely been associated with a human disease (five human cases since 1977 worldwide, including three biologically confirmed) [34].

5.3. West Nile virus (WNV)

WNV is a *Flavivirus* transmitted by *Culex* mosquitoes. Humans and horses are accidental hosts of the virus. Blood-borne transmission (transfusion) or transmission following organ transplantation is possible because of the high number of infected asymptomatic patients (approximately 80% of cases). Neurological presentations (encephalitis, meningitis, acute flaccid paralysis, or myelitis) occurred in less than 1% of cases. Risk factors for neuroinvasive presentations were age (1.5 times increased risk by decade) and immunodeficiency [41].

The disease is present in Eastern and Northern Africa, Asia, Australia (Kunjin virus), and Americas. The virus has regularly been reported in Eastern and Southern Europe (Italy, Greece) over the past 10 years. The United States implemented a surveillance system in 2001; neuroinvasive presentations accounted for 41% of cases, including 63% of encephalitis. Median age of patients presenting with encephalitis was 60 years (range 1 month–99 years) and lethality was 12%. The infection is seasonal in temperate areas, with 93% of cases reported between July and September [41].

In Europe, the first cases were reported in Russia and Eastern Europe, specifically in Romania where a major epidemic occurred in 1996 (352 cases identified, including 44% of meningoencephalitis cases, 40% of meningitis cases, and 16% of encephalitis cases). Major epidemics have been observed since 2010 in the Balkans, with one in Greece between 2010 and 2011, which led to 250 neuroinvasive presentations and a 15% case fatality rate. Sporadic cases have been reported in Italy (three neuroinvasive presentations in 2010 and five in 2012). Seven

human cases – associated with equine cases – including three neuroinvasive presentations were detected in August 2003 in France in the Var region [42, and Public Health France unpublished data]. In 2015, equine cases and one non-neuroinvasive human case were identified in the French Languedoc-Roussillon region. Epidemics were also regularly described in Israel, with more than 250 encephalitis cases and 19 deaths registered in 2000.

There are five lineages of viruses. Lineage 1 is the most frequent, but lineage 2 has emerged in Europe in the early 2000s [42].

Kunjin virus is a subtype 1 of WNV. It was first detected in 1960 in the North of Queensland, Australia, and it then spread to the North and West parts of Australia as well as in Southern Asia. The virus was supposedly responsible for 11% of encephalitis cases observed during the 1974 Murray Valley Virus epidemic. Three encephalitis cases have since been reported in Australia and the virus activity, although not associated with human cases, is regularly reported in Southeast Australia. Clinical presentations seem to be less severe, without any reported deaths [43].

5.4. Enterovirus 71

Enteroviruses belong to the Picornaviridae family. They are often responsible for meningitis in children during the summer and autumn. A total of 3% of neurological presentations are severe encephalitis cases. These RNA viruses have a high rate of spontaneous mutation and the various viral types are responsible for a wide variety of symptoms.

EV71 is a type of *Enterovirus* first isolated in 1969. EV71 infection epidemics have been observed since 1997 in Southeast Asia and in the Pacific. They are responsible for less than a dozen to several hundred thousand cases, mainly pediatric, and usually present as hand, foot and mouth disease. Severe rhombencephalitis was observed in 40% of neurological and cardio-pulmonary presentations of EV71 infections declared in Taiwan between 1998 and 2005. A few EV71 epidemics were reported outside Asia (Australia, United States, Europe, Japan, Brazil) [34,45].

5.5. Bunyaviruses from the California serogroup

Among the California group, La Crosse Virus (LACV) is the most frequently observed in the United States. It is transmitted by *Aedes* mosquitoes. Jamestown Canyon Virus is also responsible for neuroinvasive infections in the United States.

A total of 895 neuroinvasive presentations (encephalitis, meningitis, myelitis) caused by LACV were observed in the United States between 1999 and 2007, i.e. a mean incidence of 0.035 cases/100,000 inhabitants/year, including 88% of cases in patients aged below 20 years and with a sex ratio (M/F) of 1.5. Overall, 87% of cases occurred in seven Central and Eastern States as small outbreaks in forest areas, mainly between July and September. Lethality was 2% and the incidence of sequelae was 10–15% [46].

5.6. Saint-Louis encephalitis virus (SLEV)

This *Flavivirus*, very close to WNV, is transmitted by *Culex* mosquitoes. It was the most frequent arbovirus observed in the United States before the emergence of WNV. The virus is also present in South America and Canada. A three-fold decrease in incidence was observed in the United States between 1990 and 1998. Hypotheses are a host/vector competition with WNV or some ecological cycles influencing the incidence of infections as the disease occurs as epidemics every 10–15 years. A total of 188 neuroinvasive presentations were reported in the United States between 1999 and 2007, i.e. a mean incidence of 0.007 cases/100,000 inhabitants/year. More than 75% of cases occurred in patients aged over 40 years with the proportion of encephalitis increasing with age. Eighty-one percent of cases occurred during summer, with 8% lethality [46].

6. Encephalitis caused by emerging infectious agents

6.1. Powassan virus

Powassan virus is a *Flavivirus* mainly present in Northern America, and is closely related to the TBE virus present in Europe and Asia. Powassan virus is often called TBE in the United States, although it is a different virus.

A total of 37 human cases have been reported between 1958 and 2005, i.e. an incidence of 1.3 case patients/year. Median age was 69 years; 56% were men and 67% of cases occurred between May and July. No death was reported, but six patients had major sequelae [47]. The incidence seems to be on the rise: in 2011, 16 cases were reported to the Centers for Disease Control and Prevention (CDC, USA).

6.2. Nipah virus

Nipah virus belongs to the *Henipavirus* genus. Frugivore *Pteropus* bats are the virus reservoir. It was first detected in 1998 during an epidemic affecting pig breeders in Malaysia and slaughterhouse employees in Singapore. A total of 265 encephalitis cases including 105 deaths were observed in Malaysia and 11 encephalitis cases including one death in Singapore [48].

It is the only Nipah virus epidemic ever observed in Southeast Asia, but more than 12 epidemics and a few sporadic cases have been reported since 2001 in India and Bangladesh. Transmission from bats to humans involved palm juice contaminated by urine or saliva of bats, without any amplifying host (pig). Moreover, in India and Bangladesh, human-to-human transmissions occur and up to five generations of inter-human transmissions were observed in some outbreaks. Among sporadic or epidemic cases observed in Bangladesh between 2001 and 2007, 122 human cases of encephalitis or, less frequently, pneumonia were identified. Mean age of patients was 27 years (range: 2 to 75 years); 61% were men and 71% died [49].

6.3. Hendra virus

Hendra virus is the second member of the *Henipavirus* genus. Frugivore bats are the virus reservoir, and primary hosts are horses. The virus was first described in 1994 during an equine epidemic in Brisbane, Australia. The epidemic led to two human cases of pulmonary infections and one human case of encephalitis. Twelve equine epidemics were observed in Australia and an equine vaccine was developed [43].

Only seven human cases were described in the literature, all in Australia and all in individuals who had occupational contacts with infected horses. They all presented with encephalitis and four patients died.

6.4. Australian bat lyssavirus (ABLV)

Australian bat lyssavirus (ABLV) is close to the rabies virus and is hosted by *Pteropus* bats. It is only observed in Australia. Only two human cases have been described – both fatal – following a bite from a bat. Patients presented with symptoms similar to those of rabies. Rabies vaccines seemed to be only partially effective [43].

6.5. Variegated squirrel bornavirus 1 virus (VSB1)

VSB1 is a *Bornavirus* identified in 2014. In Germany, between 2011 and 2013, three tropical squirrel breeders (from South America, and which possession is subject to regulation in France), who had traded squirrels, presented with acute encephalitis-associated with oculomotor impairment, myoclonic seizures, and an associated venous thrombosis. All three patients died. VSB1 virus was unknown at that time, but was identified from brain biopsies of the three patients and from various organs of squirrels by metagenomics. This cluster remains isolated [50].

7. Infectious agents rarely responsible for encephalitis

7.1. Influenza virus

Rare cases of encephalitis were described during influenza infections.

A prospective study conducted between 2011 and 2013 in the UK reported 25 cases of neurological complications with a positive influenza PCR in the CSF, including 13 patients presenting with encephalitis and one with meningoencephalitis [51]. Overall, 84% were children, including 29% presenting with known underlying neurological diseases, with 16% lethality and 68% of sequelae [51].

7.2. Murray valley encephalitis virus (MVEV)

MVEV is a *Flavivirus* transmitted by *Culex* mosquitoes. The infection presents as encephalitis for 1/500 to 1/1000 infections, with a 15–30% lethality [43].

MVEV is frequent in Australia and New Guinea. The first case was detected in Australia at the start of the 20th century. Six epidemics were then observed; one of them led to 58 cases of encephalitis in 1974 and another one to 17 cases in 2011 [52]. Outside epidemic peaks, two to three human cases are detected every year.

7.3. Herpes B virus or Cercopithecine herpesvirus 1 or Herpes Simian B virus

The virus belongs to the Herpesviridae family and is the only animal herpesvirus known to be pathogenic to humans. The virus reservoir is monkeys from Africa and Asia, mainly macaques, in which the infection is usually asymptomatic or benign. In humans, the virus is responsible for severe encephalitis – that may follow myelitis – following a scratch or a bite by a virus-excreting monkey or following mucous contact with saliva or other feces. Lethality is 50 to 70% and patients usually have major sequelae. A total of 40 human cases have been reported since 1934; they all occurred in laboratory personnel who were in contact with monkeys used for experimental testing. This suggests that viral excretion occurs in stressful conditions [53].

7.4. Alphavirus

Eastern equine encephalitis virus (EEEV) is transmitted by several species of mosquitoes that are very specific to the virus. There are six subtypes; subtype 1 is responsible for most human cases. Sporadic cases and a few epidemics of EEEV have been observed in the Eastern coast of America. A total of 80 patients with neuroinvasive presentations were identified in the United States between 1999 and 2007, i.e. a mean incidence of 0.003 cases/100,000 inhabitants/year. These neuroinvasive presentations affected all age groups, were twice as common in men, and occurred over the summer for 79% of cases. Lethality was 42%, and was higher in children [46].

Western equine encephalomyelitis virus (WEEV) is transmitted by *Culex* mosquitoes. It was responsible for equine and human epidemics during the 20th century in the west of North and South America, but no case has been reported in the United States since 1999 [46].

Venezuelan equine encephalitis virus (WEEV) is transmitted by *Culex* mosquitoes. The virus is currently re-emerging in South America. Epidemics have also been reported in Central America and in the Southeast of the United States. The infection presented as influenza-like illness; encephalitis was only rarely reported (1–4%). Lethality of encephalitis patients was approximately 20%; it was higher among children [54].

7.5. Chikungunya virus

The chikungunya virus is an *Alphavirus* belonging to the Togavirus family. Encephalitis is a rare manifestation of the infection.

During the 2006 epidemic of chikungunya virus (African subtype) in India, 1,400,000 cases were detected (including 57 encephalitis cases). During the 2005 epidemic in Reunion, 12 case patients (6 newborns and 6 adults) presenting with

meningoencephalitis were confirmed among more than 7000 infection cases. No sequelae nor deaths were observed [55].

7.6. Dengue virus

Encephalitis is a rare and atypical complication of dengue virus infection.

A Cambodian prospective study reported confirmed or suspected cases of dengue in five out of 99 patients presenting with encephalitis, including four pediatric cases [9]. The viral genome was detected by PCR in the CSF of four patients [9].

Another prospective study conducted in two Brazilian hospitals (Rio de Janeiro) reported eight suspected cases of dengue among 17 encephalitis case patients (47%). However, only two cases were confirmed (positive PCR or positive IgM in the CSF) [56].

Dengue is considered a potential cause of encephalitis, but the severe presentation is rarely observed in endemic areas or during outbreaks.

7.7. Toscana virus

Toscana virus belongs to the *Bunyavirus* genus. It was first isolated in Central Italy in 1971 from a sand fly, which is the vector and the reservoir of the virus. This virus is the first cause of viral meningitis in Central Italy during summer, and may also be responsible for severe encephalitis. It is present in the whole Mediterranean region, with cases reported in France. Cases have a seasonal distribution based on the activity of sand flies (summer–autumn) [27].

8. Amoeba and parasitic encephalitis

8.1. Naegleria fowleri

Naegleria fowleri is a free-living amoeba ubiquitously distributed worldwide in various warm aquatic environments and soil habitats. It is the causative agent of primary amoebic meningoencephalitis in humans. Transmission to humans occurs by direct contact between nasal airways and water. The amoeba then reaches the brain through the olfactory nerve. The disease is fatal in almost 100% of cases, and death occurs 3 to 7 days after symptom onset. The amoeba is frequently present in the environment, but few individuals are infected. Immunologic and/or genetic risk factors may therefore play a role.

A total of 122 case patients were reported in the United States between 1937 and 2008; 62% were children, with a peak between 10 and 14 years, and 80% were men. Lethality was 99% (1 surviving patient) [57].

8.2. Balamuthia mandrillaris

Balamuthia mandrillaris is a free-living amoeba responsible for acute granulomatous necrotizing hemorrhagic encephalitis in humans. It was first isolated from a monkey in 1986. The infection develops after exposure to contaminated water or following gardening activities (contact with soil). The incubation period lasts several months but once the infection develops patients die within a few days in almost 95% of cases. Immunocompromised individuals (HIV, immunosuppressant drugs, chronic alcohol abuse, etc.) are at higher risk of developing the disease.

Only 100 human cases of *Balamuthia* encephalitis have been reported worldwide since 1986. This figure is probably highly underestimated, as less severe clinical presentations were observed. A total of 46 cases have been described in case reports: 52% in South America, 35% in North America (four cases in the Californian cohort study), 6.5% in Europe, and 2% in Southeast Asia, Japan, and Australia. Overall, 72% were men, 91% were immunocompetent individuals but immunodeficiency factors were probably underestimated, and lethality was 93% [58].

8.3. Acanthamoeba spp.

Just like *Balamuthia mandrillaris*, *Acanthamoeba* sp. is a worldwide free-living amoeba. It is responsible for acute granulomatous necrotizing hemorrhagic encephalitis. This amoeba is ubiquitous in the environment and studies reported a seroprevalence in 85–100% of healthy subjects. Encephalitis presentations are rare, with 18 cases published in the literature since 2000, including 61% of immunocompromised patients and 44% of deceased patients [59].

8.4. Baylisascaris procyonis

Baylisascaris procyonis is a nematode present in 68–82% of raccoons in North America. Severe encephalitis presentations caused by this parasite have been reported in humans following ingestion of dust or soil contaminated by eggs. Other presentations, mainly ocular ones, have also been observed. A total of 13 encephalitis case patients were reported in North America from 1984 to 2002. All patients were young men; five died and survivors presented with major sequelae [60]. Three case patients were also described in the Californian cohort study [3].

9. Nosocomial encephalitis

Several cases of encephalitis for which the infectious agent was transmitted during transplantations have been described.

Rabies cases historically occurred in transplant recipients. In 2004 in Germany, four patients died from rabies following organ transplantations from donors who died from encephalitis of unknown origin.

Lymphocytic choriomeningitis virus (LCMV) was transmitted by infected transplants between 2003 and 2005. In 2008, another *Arenavirus* close to LCMV was transmitted by transplants. LCMV is an *Arenavirus* present in rodents worldwide. It is responsible for asymptomatic or benign infections in immunocompetent patients. It can, however, be responsible for severe infections in immunocompromised patients, especially in patients presenting with meningitis or more rarely encephalitis [44].

A total of 36 cases of WNV infections were reported between 2003 and 2008 in the United States in patients who received a

transfusion or underwent organ transplantation in the previous 30 days [41].

10. Specificity of encephalitis in immunocompromised patients

Immune deficiencies are known to increase the risk of encephalitis following infection, and may also be responsible for encephalitis presentations that are more severe than the ones observed in immunocompetent patients (Table 2).

A prospective British study of 31 immunocompromised patients, including 58% of HIV-infected patients, reported the absence of etiology in 35% of cases. The most frequent pathogen was VZV (19% of cases), followed by *Toxoplasma gondii* (6%), HSV, *M. tuberculosis*, Epstein–Barr virus (EBV), and HHV6 in 3% of cases [4].

In the French prospective study, 30% of patients had comorbidities, including 5.5% of cancer patients [5].

10.1. HHV6

HHV6A and HHV6B viruses belong to the Herpesviridae family. Many cases of HHV6 limbic encephalitis following allogeneic hematopoietic stem cell transplantation have been reported in immunocompromised patients. HHV6 encephalitis is not observed in immunocompetent adult patients.

The HHV6 genome is able to integrate into the human genome, thus allowing its transcription and, correlatively, its detection in various fluids, including CSF. In cases of chromosomal integration, the administration of antiviral drugs does not reduce the viral load (as it is a genome transcription and not an infection). The distinction between chromosomal integration and infection is confirmed by the detection of HHV6 viral genome in skin appendage (nails, hair). Chromosomal integration must be checked when HHV6 encephalitis is suspected. Chromosomal integration is not an antiviral treatment indication.

A retrospective Japanese study reported 23 true HHV6 encephalitis case patients (positive CSF PCR) out of 5484 allogeneic transplantation recipients, i.e. 4/100,000 transplantations. Median time between transplantation and symptom onset was 22 days [61].

Another study reported seven cases of HHV6 encephalitis among 230 allogeneic transplantation recipients, i.e. a cumulative incidence at 70 days of 3%. Encephalitis cases were associated with a peak in blood viral load. The risk of HHV6 encephalitis was higher with umbilical cord cell transplantations than with bone marrow allogeneic transplantations (8% versus 1.2%; $P = 0.008$) [62].

10.2. CMV

CMV encephalitis almost exclusively occurs in highly immunocompromised patients. Among 676 cases included in a study performed between 1965 and 1995, 85% of patients were HIV-infected, 12% presented with another immunodeficiency, and only 21 (3%) were defined as immunocompetent [63]. Many documented cases of CMV encephalitis have been reported in patients who underwent allogeneic hematopoietic stem cell transplantation [64–69], and rare cases have also been observed in immunocompetent patients [70–72].

10.3. JC virus

JC CSF PCR tests have varying degrees of sensitivity depending on the techniques used (types of primers, prior centrifugation of CSF or not). In 44 non-HIV-infected patients presenting with histologically confirmed progressive multifocal leukoencephalopathy (PML), JC PCR in CSF was positive in 19 out of 44 patients (43%) [73]. When the JC PCR is negative in CSF, diagnostic confirmation relies on genome detection on brain biopsy and on histological examination aiming at identifying oligodendrocyte destruction with JC virus nuclear inclusions (electronic microscopy) and multifocal loss of myelin. The plasma PCR may be positive for JC virus. Diagnostic confirmation requires a histological examination to detect the typical lesion of PML. These features were observed in 20/24 of patients included in a study, including eight deceased patients [74].

10.4. Cryptococcus sp.

A French multicenter prospective study reported 230 cases of cryptococcosis, of which 53 were observed in non-HIV-infected patients. Of these patients, 19 presented with malignant hemopathy (36%), 11 had undergone solid organ transplantation (21%), three presented with solid cancer (6%), and 12 with various risk factors (sarcoidosis, diabetes, cirrhosis, corticoid therapy, hypogammaglobulinemia). No underlying immunodeficiency was observed in nine patients (17%) [75]. Central nervous system cryptococcosis cases have been reported by other authors in immunocompetent patients [76].

11. Conclusion

Encephalitis diagnosis is difficult. Many pathogens may cause encephalitis and the etiology remains unknown in approximately half of cases. Specific treatment is rare, but early etiological diagnosis improves the prognosis. Several pathogens, such as HSV and VZV, should thus be rapidly investigated. Patient's characteristics, hobbies, travel, lifestyle, and geographical areas may guide the diagnosis. Four frequent pathogens should always be considered in metropolitan France: HSV, VZV, *L. monocytogenes*, and *M. tuberculosis*. The epidemiology of encephalitis is constantly changing with the discovery of new agents and the emergence or re-emergence of pathogens due to evolutions of the environment or of human activities and at-risk exposures.

Disclosure of interest

The authors declare that they have no competing interest.

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