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Original Article

## **Encephalitis in travellers: A prospective multicentre study**

**Running title:** Encephalitis in travellers

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## Abstract

**Background:** As the epidemiology of encephalitis varies from one country to another, international travel may be an important clue for the diagnostic workout of this puzzling disease.

**Methods:** We performed an ancillary study using the ENCEIF prospective cohort conducted in 62 clinical sites in France from 2016 to 2019. All cases of encephalitis in adults that fulfilled a case definition derived from the International Encephalitis Consortium were included. Travellers were defined as patients who spent at least one night in a foreign country within the last six months.

**Results:** Of the 494 encephalitis patients enrolled, 69 (14%) were travellers. As compared to non-travellers, they were younger (median age, 48 years [interquartile range, 36-69] vs. 66 [49-76],  $P<0.001$ ), less likely to be immunocompromised: 2/69 (3%) vs 56/425 (13%),  $P=0.02$ , and reported more arthralgia: 7/69 (10%) vs. 11/425 (3%),  $P=0.007$ . The risk of poor outcome at hospital discharge (Glasgow outcome scale  $\leq 3$ ), was similar for travellers and for non-travellers after adjustment (aOR 0.80 [0.36 – 1.80],  $P=0.594$ ). Arboviruses were the main causes of encephalitis in travellers: 15/69 (22%) vs. 20/425 (5%) in non-travellers,  $P<0.001$ , and *Herpes simplex virus* (HSV) was the second (9/69, 13%). Of note, in 19% of cases (13/69), the risk of encephalitis in travellers may have been decreased with a vaccine.

**Conclusions:** The two primary causes of encephalitis in travellers are arboviruses, and HSV. Empirical treatment of encephalitis in travellers must include aciclovir. Vaccination may decrease the risk of encephalitis in travellers by up to 19%.

**Key words:** Encephalitis; travellers; herpes simplex virus; arbovirus; prevention

## Background

Encephalitis is defined as an inflammatory process of brain tissue associated with neurologic dysfunction (1). Encephalitis is a rare but debilitating disease with an estimated incidence ranging from 0.06 to 12.6/100,000 persons-year (1,2). Viruses are the most frequent pathogens associated with encephalitis but differential diagnosis include a wide range of infectious and non-infectious causes, including autoimmune, neoplastic and paraneoplastic causes (3–5). As outlined in international guidelines, early diagnosis and appropriate empirical treatment are key factors for outcome (6,7). However, 30-50% of encephalitis cases remain undocumented, which jeopardizes the optimal selection of empirical treatment (8–10).

While some micro-organisms commonly responsible for encephalitis, like *Herpes Simplex virus* (HSV) are ubiquitous, many are unevenly distributed across the world, making international travel an important clue to guide diagnostic workout (11). The epidemiology of encephalitis in travellers may be impacted by the changing profile of travel patterns over years, and by emerging pathogens (12). This changing profile of encephalitis was illustrated by the emergence of West-Nile virus (WNV) and tick-borne encephalitis virus (TBEV) across Europe, in areas where they have not been reported before (13,14). Case reports and series suggest that travellers are more likely to be exposed to unusual causes of encephalitis (11), but these data are limited by small sample size, retrospective design, and publication biases. We report a prospective, multicentre, cohort study, ancillary to the ENCEIF study (9), in which we aimed to describe the characteristics, aetiologies and management of encephalitis in travellers.

## Methods

The ENCEIF multi-centre prospective cohort study enrolled all consecutive patients with encephalitis suspected of infectious origin in 62 participating sites from January 2016 to December 2019 (9). The objective of the ENCEIF study was to describe the epidemiology, the characteristics (clinical, biological, imaging), the management, and the outcome of acute infectious encephalitis in France. All adult inpatients who fulfilled a case definition derived from the International Encephalitis Consortium (1) with no alternative diagnosis were invited to participate in the study (see below).

Briefly, encephalitis was defined as neurologic symptoms of acute onset, for more than 24 h, with no alternative diagnosis, and at least two of the following signs: fever  $\geq 38^{\circ}\text{C}$ , seizure, recent focal neurological symptoms, cerebrospinal fluid (CSF) white cells count  $\geq 5/\text{mm}^3$ , inflammatory brain lesion on magnetic resonance imaging (MRI) or computed tomography (CT)-scan, and suggestive abnormalities on electroencephalogram (EEG). Data were collected on a standardized questionnaire and computerized using a secure, web-based application Voozadoo (Epiconcept©, Paris), in accordance with the French regulation on medical data protection and the European General Data Protection Regulation. Travellers were defined as patients who stayed at least one night in a foreign country within the last six months. Among travellers, a distinction was made between those who usually live in France, but travelled abroad within the last 6 months before encephalitis diagnosis, and those who usually live in a foreign country, but were diagnosed with encephalitis while they were in France (thereafter referred to as foreigners). In-hospital outcome was categorized using the Glasgow outcome scale (GOS), ranging from 1 (death) to 5 (no or minor neuro-psychological deficits with no impact on daily life).

Statistical analyses were performed using the R 4.0.5 software. Categorical variables were described as frequencies and percentages, and quantitative variables as medians and interquartile range. Categorical variables were compared by chi-square or Fisher's exact test as

appropriate, and continuous variables were compared by Mann Whitney test. A  $P$  value  $<0.05$  was considered significant. The odds ratio for poor outcome was computed using a logistic regression analysis and was adjusted for age and immunodeficiency as they were found to be the two major risk factors for poor outcome in previous studies on the same cohort (9).

In accordance with French regulation, we obtained informed non-opposition for the use of medical data from all patients or from relatives responsible for legal matter, or from the attending physician in case of consciousness disorders. In the latter case, this non-opposition to the use of medical data had to be confirmed by patients once they were able to. This work received an authorization of the French Commission for data Protection. This work received an authorization of the French Commission for data Protection (CNIL), and was approved by the National Ethic Committee (No. 915148, authorization obtained on October 20, 2015).

## Results

Of the 494 patients included in the ENCEIF cohort, 69 (14%) were travellers. As compared to non-travellers, travellers were younger (median age, 48 years [interquartile range, 36-69] vs. 66 [49-76],  $P<0.001$ ), more likely to be employed (48.5% vs. 30.5%,  $P=0.004$ ), and less likely to be immunocompromised (3% vs 13%,  $P=0.024$ ), Table 1. Among travellers, 12 (17%) were foreigners.

Travel destinations were diverse, including all five continents. The most frequent were Europe and Africa which is consistent with the known repartition of air traffic in France during the same period, Supplementary figures 1 and 2. Although the ranking of destinations was similar, the repartition was different. Some destinations (Africa and Asia & Oceania) were over-represented while Europe and America were under-represented compared to the “Bulletin statistique du trafic aérien” (15).

On admission, travellers were more likely to present with coma (15% vs 7%,  $P=0.041$ ), headache (59% vs 45%,  $P=0.039$ ), infra-tentorial signs (30% vs 17%,  $P=0.011$ ), including cerebellar syndrome (17% vs 8%,  $P=0.015$ ), and arthralgia (10% vs 3%,  $P=0.007$ ), Table 2. Arboviruses were the primary pathogens in travellers, responsible for 15/69 encephalitis (22%), vs. 20/425 (5%) in non-travellers,  $P<0.001$  (Table 3). The most frequent arboviruses responsible for encephalitis in travellers were TBEV (6/69, 9%), and WNV (4/69, 6%), while TBEV was the only arbovirus encephalitis documented in non-travellers (20/425, 5%). HSV was the second cause of encephalitis in travellers, less frequent than in non-travellers (13% vs 29%,  $P=0.009$ ), as was varicella-zoster virus encephalitis, responsible for 3/69 (4%) of encephalitis in travellers, vs. 62/425 (15%) in non-travellers,  $P=0.032$ . Tuberculosis was more common in travellers, responsible for 6/69 encephalitis (9%), as compared to 5/425 (1%) in non-travellers,  $P=0.002$ . Interestingly, of the 6 cases of tuberculosis encephalitis in travellers, 4 involved foreigners and 5 reported a history of travel to Africa. The proportion of encephalitis of unknown cause was similar in travellers (27/69, 39%), and in non-travellers (143/425, 34%).

The proportion of encephalitis in travellers that can be attributed with certainty to their travel destination was low (15/69, 22%), Table 4. Of note, in 13/69 (19%) cases of encephalitis in travellers, a vaccine recommended for travellers or the general population (ie, TBE, measles, influenza) may have limited the risk of infection. All travellers with encephalitis received aciclovir as empirical treatment (Table 5), with similar time from admission to aciclovir start as compared to non-travellers. In-hospital mortality was 9% (37/425) in non-travellers, as compared to 0/69 in travellers,  $P=0.021$ . However, the risk of poor outcome at hospital discharge (Glasgow outcome scale  $\leq 3$ ), was similar for travellers and for non-travellers after adjustment for age and immunodeficiency (aOR 0.80 [0.36-1.80],  $P=0.594$ ).

## Discussion

The main finding of this prospective, multicentre study, are the followings: i) recent international travel is a common finding in patients with encephalitis, found in 69/494 encephalitis (13%) in France during years 2016-2019, before the COVID-19 pandemic and its travel restrictions; ii) arboviruses are the primary pathogens responsible for encephalitis in travellers (15/69, 22%), primarily TBE and WNV; iii) HSV is the second most frequent pathogen responsible for encephalitis in travellers (9/69, 13%), although less common than in non-travellers (13% vs 29%,  $P=0.009$ ); iv) tuberculosis is more frequently responsible for encephalitis in travellers, than in non-travellers (9% vs. 1%),  $P=0.002$ ; v) according to the etiologies, 19% of encephalitis in travellers may have been prevented, with a vaccine ; vi) encephalitis in returning travellers is not associated with poor outcome at hospital discharge (aOR 0.80 [0.36-1.80],  $P=0.5936$ ).

Despite recent progress in the etiological diagnosis, the management of encephalitis remains a challenge (3,8,16,17), and specific data for sub-populations of interest are warranted. Prospective studies focused on children, and the elderlies (18,19), but to our knowledge, no prospective study on travellers has been reported. Given the importance of appropriate empirical treatment for encephalitis, we aimed to provide specific data for travellers, to better inform therapeutic guidelines in this population (20). Although there is no specific curative treatment for the primary causes of encephalitis in travellers identified in our study, ie arboviruses, our findings have consequences, as these encephalitis might be prevented by vaccine or vector control. TBE is endemic in selected areas within North and Central Europe (21,22), and the ENCEIF cohort study documented its emergence in France during years 2016-2019, becoming the third cause of encephalitis in adults in this country (9). Of note, only 6/26 cases of TBE occurred in travellers during the study period, which confirms that TBE is now endemic in several areas of metropolitan France. Although all cases of WNV encephalitis were



diagnosed in recent travellers, the risk of an outbreak due to WNV infections in France is real, as sporadic transmission of WNV has been documented in horses, and humans, in France. In addition, WNV lineage 2 is now well established in Europe, responsible for domestic outbreaks every year in neighbouring countries, over recent years (23–25). No case of rabies was reported in this prospective cohort. In Europe, the 18 consecutive cases of rabies reported during years 2006-2019 were all travel-related, mostly from Asia and Africa (26).

The low proportion of cases attributed to travel (22%) highlights the need to keep the same first-line work-up and probabilistic treatment in travellers presenting with encephalitis. This is especially relevant given that HSV is the first treatable etiology in travellers as well as in non-travellers, with a dramatic impact of early treatment with aciclovir. Finally, it is important to keep in mind that encephalitis in travellers is a rare event, we report 69 cases over 4 years in 62 centres in France while over 145 million air travels happened each year during the study period.

The proportion of possibly preventable encephalitis (19%) in our study highlights the importance of pre-travel consultation that tackles vector protection and evaluates the need for vaccination, especially TBE vaccine (27,28). Unfortunately, we have no information on the vaccination status and use of repellents in the travellers' patients included in our study. The small number of arboviruses encephalitis did not allow for in-depth analysis of clinical features of arboviruses, and a previous study on the whole ENCEIF cohort using a factor analysis of mixed data could not identify any distinctive pattern or cluster of cases (29). The better prognosis of encephalitis in travellers may be mostly related to the lower proportion of comorbidities, and the younger age, of this population. Due to limited sample size, and the absence of any fatal outcome among travellers with encephalitis, our study was not powered to identify independent prognostic factors.

This study has limitations: first, despite the large initial cohort, the number of returning travellers makes for a small sample size. As it only included adult patients with encephalitis managed in France during years 2016-2019, our findings may not be generalized to children, to other countries, and to other period of times. However, to the best of our knowledge, this is the first prospective cohort study on encephalitis in travellers, and by far the largest to date. With a large number of participating sites, the enrolment of all consecutive cases of encephalitis, and the use of international inclusion criteria, our study provides robust data that may be of interest for other settings. Inclusions stopped in December 2019, immediately before the COVID-19 pandemic, and travel patterns were similar to the general population in France during the study period, with Europe (76.7%), and Africa (12.0%) as the two main destinations for intercontinental travel (15).

In conclusion, a recent history of travel abroad in patients with encephalitis should not change the preliminary work-up, and the empirical treatment, which must include aciclovir pending HSV encephalitis is ruled out. However, arbovirus encephalitis, and tuberculosis, both more common in travellers than in non-travellers, must be suspected early in the process. Pre-travel consultation should address the risk of arbovirus encephalitis for selected destinations, and consider specific vaccinations, and/or vector control advices.

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**Author contributions**

The authors confirm contribution to the paper as follows: study conception and design: Alexandra Mailles, Jean-Paul Stahl, Pierre Tattevin ; data collection: The investigator's group ; analysis and interpretation of results: Pierre Fillâtre, Léa Picard ; draft manuscript preparation: Léa Picard, Pierre Tattevin, Alexandra Mailles, Pierre Fillâtre, Jean-Paul Stahl. All authors reviewed the results and approved the final version of the manuscript.

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**Conflict of interest**

The authors have declared no conflicts of interest.

**Data availability**

The data underlying this article cannot be shared due to privacy concerns for the individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

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**Table 1.** Demographic characteristics of patients with encephalitis, travellers (n=69) vs. non-travellers (n=425), Enceif cohort, France 2016-19

	<b>Travellers</b> n=69	<b>Non-travellers</b> n=425	<b>P</b>
<b>Demographics</b>			
Age, years	48 [36-69]	66 [49-76]	<b>&lt;0.001</b>
Gender, male	46 (66.7%)	257 (60.6%)	0.409
<b>Professional status</b>			
			<b>0.002</b>
Active, unemployed	9 (13.2%)	35 (8.4%)	
Active, employed	33 (48.5%)	128 (30.5%)	
Student	4 (5.9%)	14 (3.3%)	
Retired	22 (32.4%)	242 (57.8%)	
<b>Co-morbidities</b>			
Diabetes	4 (5.8%)	63 (15.0%)	0.062
Cancer	3 (4.3%)	36 (8.5%)	0.342
Hemopathy	4 (5.9%)	23 (5.5%)	1
Immunodepression	2 (2.9%)	56 (13.2%)	<b>0.024</b>
Chronic neurological disorders	1 (1.4%)	28 (6.7%)	0.151
Chronic psychiatric disorders	1 (1.4%)	27 (6.5%)	0.167

Qualitative data presented as number (%), quantitative data as median [interquartile range]



**Table 2.** Clinical characteristics of encephalitis on admission, travellers (n=69), vs. non-travellers (n=425), **Enceif cohort, France 2016-19**

	<b>Travellers</b> n=69	<b>Non-travellers</b> n=425	<b>P</b>
<b>Clinical findings</b>			
Coma	10 (14.5%)	28 (6.6%)	<b>0.041</b>
Altered mental status	30 (43.5%)	167 (39.3%)	0.599
Confusion	36 (52.2%)	270 (63.5%)	0.095
Epilepsy	7 (10.1%)	67 (15.8%)	0.302
Headache	41 (59.4%)	192 (45.2%)	<b>0.039</b>
Supra-tentorial signs	26 (37.7%)	180 (42.4%)	0.55
Motor deficit	11 (15.9%)	48 (11.3%)	0.366
Speech disorders	18 (26.1%)	152 (35.8%)	0.152
Infra-tentorial signs	21 (30.4%)	71 (16.7%)	<b>0.011</b>
Cranial nerve palsy	9 (13.0%)	46 (10.8%)	0.736
Cerebellar syndrom	12 (17.4%)	32 (7.5%)	<b>0.015</b>
Fever	58 (84.1%)	325 (76.5%)	0.213
Rash	6 (8.7%)	45 (10.6%)	0.79
Respiratory signs	7 (10.1%)	48 (11.3%)	0.94
Digestive symptoms	15 (21.7%)	79 (18.6%)	0.65
Arthralgia	7 (10.1%)	11 (2.6%)	<b>0.007</b>
<b>Cerebrospinal fluid</b>			
Erythrocytes, per mm <sup>3</sup>	11 [2-80]	15 [4-60.5]	0.978
White cells, per mm <sup>3</sup>	75 [19.5-243.5]	114 [32-273.5]	0.152
Protein, g/L	0.87 [0.60-1.41]	0.90 [0.62-1.44]	0.749

Qualitative data presented as number (%), quantitative data as median [interquartile range]

**Table 3.** Causes of encephalitis, travellers (n=69), vs. non-travellers (n=425), Enceif cohort, France 2016-19

	Travellers, n=69	Non-travellers, n=425	P
<b>Human herpes viruses</b>			
Herpes simplex virus	9 (13.0%)	123 (28.9%)	0.009
Varicella-zoster Virus	3 (4.3%)	62 (14.6%)	0.032
Epstein-Barr Virus	0	6 (1.4%)	1
Cytomegalovirus	1 (1.4%)	0	0.14
<b>Arboviruses</b>	15 (21.7%)	20 (4.7%)	<0.001
Tick-borne encephalitis	6 (8.7%)	20 (4.7%)	0.238
West-Nile virus	4 (5.8%)	0	<0.001
Japanese encephalitis	2 (2.9%)	0	0.019
Zika virus	1 (1.4%)	0	0.14
Toscana virus	1 (1.4%)	0	0.14
Chikungunya	1 (1.4%)	0	0.14
<b>Other viruses</b>			
Enterovirus	1 (1.4%)	5 (1.2%)	0.597
Influenza	1 (1.4%)	10 (2.4%)	1
Measles	1 (1.4%)	2 (0.5%)	0.364
<b>Bacteria</b>			
Tuberculosis	6 (8.7%)	5 (1.2%)	0.002
<i>Listeria monocytogenes</i>	3 (4.3%)	20 (4.7%)	1
<i>Mycoplasma pneumoniae</i>	0	4 (0.9%)	1
<i>Bartonella henselae</i>	1 (1.4%)	0	0.14
<i>Francisella tularensis</i>	1 (1.4%)	0	0.14
<i>Borrelia burgdorferi</i>	0	3 (0.7%)	1
<b>Miscellaneous*</b>	0	22 (5.2%)*	0.057
<b>Unknown</b>	27 (39.1%)	143 (33.6%)	0.452

Data presented as number (%); \* Miscellaneous : Cryptococcosis (n=4), JC virus (n=3), HHV-6 (n=2), *Capnocytophaga* sp. (n=2), Leptospirosis (n=2), Whipple disease (n=2), primary HIV infection, syphilis, *Coxiella burnettii*, Parvovirus B19, *Anaplasma* sp., *Rickettsia* sp., *Legionella pneumophila* (one patient each)

**Table 4.** Encephalitis in travellers: travel destinations and travel-associated etiology, Enceif cohort, France 2016-19

	<b>Total</b>	<b>Travel-associated etiology</b>
<b>Travellers</b>	69	15 (21.7%)
Tourists	57	11 (19.3%)
Foreigners	12	4 (33.3%)
<b>Travel destination</b>		
<b>Africa</b>	21	7 (33.3%)
North Africa	9	2 (22.2%)
East Africa	3	3 (100%)
Sub Saharan Africa	9	2 (22.2%)
<b>America</b>	5	0
North America	4	0
South America	0	0
Central America	1	0
<b>Asia &amp; Oceania</b>	11	4 (36.4%)
Middle East	2	0
Central Asia	1	1 (100%)
South-East Asia	5	2 (40%)
East Asia (continental)	2	0
Oceania	1	1 (100%)
<b>Europe</b>	38	4 (10.5%)
North of Europe	5	0
Central Europe	16	1 (6.2%)
South of Europe	18	3 (16.6%)

Data presented as number (%)

**Table 5.** Encephalitis in travellers (n=69) vs. non-travellers (n=425): Treatment and outcome, Enceif cohort, France 2016-19

	<b>Travellers</b> n=69	<b>Non-travellers</b> n=425	<b>P</b>
Time from symptoms onset to aciclovir start, days	3 [1-6]	2 [1-5]	0.297
Time from hospital admission to aciclovir start, days	0 [0-1]	0 [0-1]	0.316
Glasgow outcome scale (GOS) $\geq 3$	8 (11.6)	82 (19.5)	0.162
In-hospital mortality	0 (0.0)	37 (8.8)	<b>0.021</b>

Qualitative data presented as number (%), quantitative data as median [interquartile range]