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Central nervous system infections in a tropical area: Influence of emerging and rare infections

H. Chaumont\textsuperscript{a,b,c}, E. Roze\textsuperscript{c,d}, B. Tressières\textsuperscript{e}, F. Lazarini\textsuperscript{f}, and A. Lannuzel\textsuperscript{a,b,c,e}

\textsuperscript{a}Centre Hospitalier Universitaire de la Guadeloupe, Service de Neurologie, Pointe-à-Pitre/Abymes, French West Indies, France
\textsuperscript{b}Faculté de Médecine de l’université des Antilles, French West Indies, Pointe-à-Pitre, France
\textsuperscript{c}Faculté de Médecine de Sorbonne Université, Institut National de la Santé et de la Recherche Médicale, U 1127, CNRS, Unité Mixte de Recherche (UMR) 7225, Institut du Cerveau et de la Moelle épinière, ICM, Paris, France
\textsuperscript{d}AP-HP, Hôpital de la Pitié-Salpêtrière, Département de Neurologie, Paris, France
\textsuperscript{e}Centre d'investigation Clinique Antilles Guyane, Inserm CIC 1424, Pointe-à-Pitre, France
\textsuperscript{f}Institut Pasteur, Perception and Memory Unit, Centre National de la Recherche Scientifique, Unité Mixte de Recherche 3571, Paris, France

Corresponding author: Hugo Chaumont, MD, Department of Neurology, University Hospital of Guadeloupe, 97139, Pointe-à-Pitre/Abymes, French West Indies, France. Tel.: +590 590 891 430; fax: +590 590 891 431; e-mail: hugo.chaumont@chu-guadeloupe.fr

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Disclosure of conflict of interests

H. Chaumont: received travel grants from PEPS development, Roche and Pfizer. E. Roze: served on scientific advisory boards for Orkyn, Aguettant, Merz-Pharma; received honoraria for speeches from Orkyn, Aguettant, Merz-Pharma, Medday-Pharma, Everpharma, International Parkinson and Movement disorders Society; received research support from Merz-Pharma, Orkyn, Aguettant, Elivie, Ipsen, Everpharma, Fondation Desmarest, AMADYS, Fonds de Dotation Brou de Laurière, Agence Nationale de la Recherche; received travel grant from Vitalair, PEPS development, Aguettant, Merz-Pharma, Ipsen, Merck, Orkyn, Elivie, Adelia Medical, Dystonia Medical Research Foundation, International Parkinson and Movement disorders Society, European Academy of Neurology, International Association of Parkinsonism and Related Disorders. A. Lannuzel: received research support from France Parkinson, PSP France, Agence Nationale de la Recherche, Fonds européen de développement regional, French Ministry of Health, University Hospital of Guadeloupe; received honoraria from Association des Neurologues du Québec and travel grants from Vitalair, PEPS development, Merz-Pharma, International Parkinson and Movement disorders Society. B. Tressières and F. Lazarini have nothing to declare.
Abstract

Background and purpose: The frequency of infectious encephalitis and the distribution of causative pathogens in the tropical areas are poorly known and may be influenced by emerging and rare infections. The aim was to characterize a large series of acute infectious encephalitis and myelitis in immunocompetent patients from the Caribbean island of Guadeloupe identifying clinical, biological and radiological features according to pathogens.

Methods: Using a hospital database, we retrospectively collected detailed information on a comprehensive series of immunocompetent patients with acute infectious myelitis and encephalitis over the 2012-2018 period.

Results: From 259 suspected cases with acute central nervous system (CNS) infection, we included 171 cases for analysis, comprising 141 encephalitis, 22 myelitis, and eight encephalomyelitis. The annual incidence peaked at 15.0/100 000 during the Zika 2016 outbreak. Children accounted for 22.2% of cases. Eight adults died during hospital stay, all encephalitis. Seventeen infectious agents, two of which had never been described in Guadeloupe so far, were identified in 101 cases (59.1%), including 35 confirmed cases (34.7%), 48 probable cases (47.5%), 15 possible cases (14.9%) and three clinical cases (3.0%). The most frequent etiologic agents were zika virus in 23 cases (13.5%), herpes simplex in 12 (7.0%), varicella-zoster virus in 11 (6.4%), dengue virus in 11 (6.4%) and leptospirosis in 11 (6.4%).

Conclusions: Zika outbreak had a major influence on the annual incidence of acute CNS infection. Acute neuroleptospirosis is over-represented in our series. Further efforts are mandatory to develop new diagnostic tools for pathogen profiling.

Introduction

The incidence of infectious encephalitis in temperate countries in immunocompetent subjects is estimated at 1.9 to 4.3 cases per 100,000 inhabitants per year (1,2). In North America and Europe, viruses of the Herpes group (Herpes Simplex (HSV), Varicella-zoster (VZV) and Epstein-Barr virus (EBV)) are the first cause of infectious encephalitis accounting for 25 to 32 % of the cases (3–5). In tropical area, prospective epidemiological studies report a higher incidence of 14/100 000 in Thailand and 50/100 000 in India (6,7). The distribution of causative pathogens
differs from that observed in Europe or North America. Arboviruses may represent up to 28% of cases (6). The causative infectious agent remains undetermined in most cases (ranging from 40% to 50% in large prospective studies) (3,4). Causes and incidence of acute infectious myelitis are poorly studied and there is no large series of patients.

To characterize the full spectrum of infectious agents causing encephalitis, myelitis and their outcome, we retrospectively collected detailed information on a series of consecutive patients with acute CNS infection in the Caribbean island of Guadeloupe over a seven-year period (2012-2018).

**Methods**

**Patients and study design**

We extracted all cases registered as infectious encephalitis or myelitis from the database of the University Hospital of Guadeloupe (UHG) between January 2012 and December 2018. Patients were seen in the departments of Neurology, Infectiology, Intensive care, Pediatrics, and General Medicine in the UHG, the only tertiary center in an Archipelago counting 420,000 inhabitants. In 2016 during the last population census, the age distribution in the Guadeloupean population was: 0-14 years old (21.5%); 15-29 years old (17.4%); 30-44 years old (19.9%); 45-59 years old (21.5%); 60-74 (13.1%), 75 years old and more (6.6%).

**Standard protocol approvals, registrations, and patient consents**

According to the French regulation, the retrospective use of our hospital database was approved by the National Commission of Information Technology and Civil Liberties (declaration number 2171956 v 0). The local IRB (“EREGIN”, University Hospital of Guadeloupe), reviewed and approved the study protocol. The study was classified as an observational study according to the rules of the French regulation. As local ethic committee did not require to get written consent for this observational study, oral informed consent was obtained from all participants after providing them written explanations, and the study was performed according to the approved protocol.

**Diagnosis of encephalitis and myelitis**

We included patients aged at least one month with acute manifestations of encephalitis or myelitis persisting over 24h, and no other diagnosis than infection. For encephalitis, at least one major criterion and two minor criteria were necessary. Major criteria were: consciousness or vigilance disorder, behavioral disorder, one or several partial or generalized seizures non attributable to a pre-existing seizure disorder, a recently appeared focal neurological symptom.
Minor criteria were: a temperature over 37.8°C, a biological anomaly of the cerebrospinal fluid (CSF) (CSF leukocyte count ≥4 x 10^6 cells/l, CSF protein concentration ≥40 mg/dl), a cerebral imaging suggesting a recently appeared encephalitis, an anomaly evoking encephalitis detected through electroencephalogram (EEG) and non-attributable to another pathology. EEG abnormalities ranged from nonspecific generalized slowing to distinctive patterns suggestive of specific entities, including repetitive sharp wave complexes over the temporal lobes or periodic lateralizing epileptiform discharges or bilateral synchronous periodic sharp and slow waves. For acute myelitis, patients had i) sensory/motor manifestations or dysautonomia attributable to the spinal cord, ii) a signal abnormality or contrast enhancement on spinal cord MRI or an abnormal CSF (leukocyte count ≥4 x 10^6 cells/l or a protein level in CSF ≥40 mg/dl) was required, iii) progression to nadir of under 21 days following the onset of symptoms.

The exclusion criteria were positive human immunodeficiency virus (HIV) status; meningitis with no argument supporting cerebral parenchyma damage; acute pyogenic meningoencephalitis (classically excluded in series of infectious encephalitis); cerebral, brainstem, cerebellar abscesses; intramedullary and epidural abscess of the spinal cord.

The patients were listed as “confirmed” when the pathogenic agent or its genome was found inside the CSF, or if there was a seroconversion inside the CSF. The affection was “probable” if the agent or its genome was found outside the CSF, or if there was a seroconversion outside the CSF, or a high single immunoglobulin M (IgM) measure was found inside the CSF. It was “possible” if a high single immunoglobulin M (IgM) measure was found outside the CSF. It was of high clinical presumption, referred to as “clinical cases” if massive clinical arguments in favor of an infectious etiology were retained, without biological proof. The remaining cases were classified as “undetermined”.

Nineteen neurozika patients were comprehensively described in a previous publication (8).

**Statistical analyses**

Quantitative variables were summarized as median with interquartile range (IQR) and compared across groups using Mann-Whitney non-parametric test. Categorical data were expressed as percentages and compared between groups using Chi-square test or Fisher exact test, depending on the sample size. For each year of the study period, the incidence rates were calculated by dividing the number of incident cases per year by the number of inhabitants in Guadeloupe estimated by INSEE (Institut National de la Statistique et des Etudes Economiques). The 95% confidence intervals (CI) were calculated assuming a Poisson distribution. Odds-Ratios (OR) and their 95% confidence intervals were calculated using logistic regressions to identify clinical and biological factors associated with the occurrence of zika virus (ZIKV) and dengue.
virus (DENV) encephalitis in adult population (≥ 16 years old) (crude Odds-Ratios) and the need for mechanical ventilation during hospitalization (adjusted Odds-Ratios). Statistical analyses were performed using SPSS (v. 21, IBM SPSS Statistics, Chicago, IL); significance was considered at the 5% level.

Data availability
Some data will be made available from the corresponding author, upon reasonable request. The data are not publicly available because they contain information that could compromise the privacy of our patients.

Results

Population
We included for analysis 171 patients presenting an acute infectious myelitis/encephalitis in 2012-2018 (Fig. 1).

The annual incidence peaked at 15.0/100,000 in 2016 during the Zika outbreak (Fig. 2). Zika virus (ZIKV) infection, but neither dengue virus (DENV) nor chikungunya virus (CHIKV) outbreak had a significant influence on incidence rate of infectious encephalitis or myelitis.

General characteristics of the patients are shown in Table S1. Children accounted for 22.2% of cases. Encephalitis were more frequent in men (59.6%), women having more myelitis (68%) and encephalomyelitis (75%). Half of the patients with encephalitis had a normal brain MRI.

Etiology
Although acute CNS infection was suspected in all cases included for analysis, infectious agents were identified reliably in only 101 cases (59%). In 35 of them (34.7%) an infectious agent was detected in the CSF (confirmed cases). Forty-eight patients (47.5%) were probable cases (22 with identified pathogen out of CSF or 26 with seroconversion in the serum). Possible cases or clinical cases represented respectively 14.9% (n = 15) and 3.0% (n = 3).

The infectious causative agent was a virus in 75 patients (74.3%), a bacterium in 21 (20.8%), a fungus in 4 (4.0%) and a parasite in one (1%). Seventeen different etiologic agents were identified (Table S2). The five most frequent were ZIKV in 23 cases (13.5%), HSV in 12 (7.0%), VZV in 11 (6.4%), DENV in 11 (6.4%) and leptospirosis (LEPT) in 11 (6.4%) (Table S3). VZV was the most frequent pathogen in children (13.2%). The 12 other infectious agents in the remaining 33 cases (19.3%) were: enterovirus (EV, n = 8), Mycoplasma pneumoniae (n = 5), Syphilis (n = 4), CHIKV (n = 3), Cryptococcus neoformans (n = 3), EBV (n = 3), cytomegalovirus

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(CMV, n = 2), *Angiostrongilus cantonensis* (n = 1), *Aspergillus sp* (n = 1), human influenza A virus (n = 1), human T-Cell leukemia virus (HTLV, n = 1) and *Listeria monocytogenes* (n = 1).

**Arboviruses**

A flavivirus (ZIKV, DENV) or an alphavirus (CHIKV) was involved in 37 cases (21.6%). CHIKV was responsible for two myelitis (Fig. 3A) and one encephalitis, DENV for two myelitis (Fig. 3B), eight encephalitis, two of which resulting in a fatal outcome (Fig. 3C), and one encephalomyelitis. ZIKV was responsible for 14 encephalitis, one of them fatal, six myelitis and three encephalomyelitis.

Spinal location causing myelitis or encephalomyelitis was more frequent in patients with flavivirus infection (ZIKV and DENV) than those in the herpes virus group (HSV/VZV/EBV) (*P* = 0.035) (Table S4). The other factors associated with flavivirus infection versus herpes virus infection were: female sex (*P* = 0.037), rash (*P* = 0.025), arthritis (*P* < 0.001), abdominal pain (*P* = 0.031). Inversely low natremia (*P* = 0.010) and altered consciousness (*P* = 0.007) were predominantly associated to herpes virus infections (Table S4). Rash (OR 20.0, 95% CI 6.33, 66.20), arthritis (OR 27.38, 95% CI 7.86, 95.35), conjunctivitis (OR 33.69, 95% CI 3.87, 293.10), absence of altered consciousness (OR 2.70, 95% CI 1.02, 7.14) were associated with ZIKV CNS infection (Table S5).

**Leptospirosis**

Leptospirosis was identified in 11 adult cases (6.4%), including ten men. Detailed characteristics of these patients are shown in Table S6. Diagnosis was probable in eight cases, possible in two cases and one patient was a "clinical case". The median age was 59 (IQR, 56-62). Three patients, all men, were employed as farmers or working with animals. Imaging showed an acute stroke in two patients (patient 6 and 10), and a transverse myelitis in one (patient 11, Fig. 3D). The factors associated with neuroleptospirosis (Table S7) were male sex (OR 9.44, 95% CI 1.15, 77.78), icterus (OR 4.41, 95% CI 1.91, ∞), abdominal pain (OR 5.14, 95% CI 1.20, 22.05), breathing dysfunctions (OR 4.43, 95% CI 1.06, 18.55), AST >120 U/l (OR 12.38, 95% CI 2.29, 66.95), ALT >103 U/l (OR 28.87, 95% CI 2.93, ∞), creatinine >106 µmol/l (OR 8.00, 95% CI 1.90, 33.63) and platelets <150 x 10⁹ cells/l (OR 7.08, 95% CI 1.81, 27.67).

**Rare etiologies - Clinical features and management**
A diabetic 85 years old woman was admitted with confusion, aphasia, altered level of consciousness, dysexecutive syndrome, behavioral disorders and cerebellar syndrome. Brain MRI showed diffuse bilateral abnormalities (Fig. 3E). CSF analysis showed white cell count at $4 \times 10^6$ cells/l, protein level was 104 mg/dl, and glucose level was normal at 3.1 mmol/l. *Aspergillus* sp. was detected by RT-PCR in the CSF. Aphasia and altered level of consciousness were slowly improved after introduction of Voriconazole IV. There was no post-discharge follow-up.

A 10 months old boy was admitted with altered consciousness, urinary retention, lower limb and back pain, flaccid tetraplegia with areflexia. Two days before he had presented rash, asthenia, anorexia, limbs edema and fever. Spinal MRI showed cervical and lumbar spinal cord abnormalities (Fig. 3F). CSF showed a meningitis with white cell count at $280 \times 10^6$ cells/l (lymphocytes 63%, eosinophils 30%, macrophages 4%, PNN 3%), protein level at 111 mg/dl and low glucose at 1.0 mmol/l. *Angiostrongylus cantonensis* RT-PCR was positive in CSF. Albendazole IV was combined with corticosteroid therapy and patient slowly improved. He has gait disorder sequelae.

**Patient management, outcome and risk factors**

Duration of the stay in hospital was shorter in children (8 days, IQR, 4-11) than in adults (14 days, IQR, 9-23, $P < 0.001$). Fifty-seven patients (33.3%) including three children were admitted in intensive care unit (Table S1). Mechanical ventilation was required in 35 cases, including two children. In multivariate analysis, altered level of consciousness (OR 7.64, 95% CI 2.06, 28.34), seizures (OR 4.11, 95% CI 1.65, 10.20), and abnormal MRI (OR 2.68, 95% CI 1.08, 6.65) were risk factors of mechanical ventilation (Table S8). Eight adults died during hospital stay, all encephalitis including three from unidentified pathogen. Six died of brain disorders and two of additional sepsis. DENV was responsible for two fatal outcomes and ZIKV for one fatal.

**Discussion**

Over a seven-year period, we collected 171 cases of acute CNS infection in the Caribbean island of Guadeloupe, comprising 141 encephalitis, 22 myelitis, and eight encephalomyelitis. We found that Zika 2016 outbreak had a major influence on the annual incidence of acute CNS infection, further indicating a particular tropism of ZIKV towards the CNS in children and adults. Significant adjustments in health care organization are required during epidemic zika periods. Leptospirosis was found in 6.4% of cases, and was predicted by sex (male), icterus, abdominal pain, breathing dysfunctions, increased liver enzymes and creatinine, and reduced platelet count. This is...
important for clinical practice since acute neuroleptospirosis has a good prognosis when treated early (9). Specific treatment of leptospirosis can also prevent chronic neuroleptospirosis (10).

Our study has limitations. First, due its retrospective approach, and because the annual incident rate may have been underestimated as some mild cases may not have been referred to the hospital. Second, we decided to widen the major diagnostic criteria of the International Encephalitis Consortium (11) due to the retrospective nature of clinical records and lack of information on possible alteration of mental status of certain patients. Indeed, some patients had only new onset of focal neurological findings or generalized/focal seizures mentioned in clinical records while a pathogen was detected in the CSF. Third, cross reactions between flavivirus renders the diagnosis of recent infection difficult in patients already exposed to a previous infection with a flavivirus. In our study, except during Zika outbreak, diagnosis of arboviruses was largely based on serology, as RT-PCR was not performed systematically. We think flaviviruses are implicated in a large part of the undetermined cases.

The annual incidence of acute CNS infection was tripled during the Zika outbreak (Fig. 2). Within this period (2016), proven zika-related CNS infection accounted for 40% of the cases but we suspect this percentage may largely underestimate the actual proportion of zika-related CNS encephalitis or myelitis. Indeed, the annual incidence of cases of acute CNS infection of undetermined etiology increased concurrently with the emerging of the Zika outbreak, possibly reflecting difficulties to diagnose ZIKV infection at the acute phase of neurological manifestations (12). The sudden and major increase in the number of acute CNS infections may be beyond the response capacity of the local health care system, requiring transient and rapid adjustments during Zika outbreak. During the study period, the population was exposed to a CHIKV outbreak with attack rate similar to that of ZIKV outbreak (around 60% and 50% respectively) (13,14). However, this outbreak had only a minor influence on the annual incidence of acute CNS infections (Fig. 2). This further suggests that ZIKV has a particular tropism towards the CNS in addition to its well-known role in the pathogenesis of Guillain-Barré syndrome in the peripheral nervous system (8). CNS tropism of ZIKV has been largely reported during the prenatal period (15–17). In post-natal individuals, encephalitis, myelitis, encephalomyelitis represent nearly 20% of neurological manifestations of ZIKV infection (8,18), and 16% of patients may have a mixed disorder involving both the central and peripheral nervous system (8). Experimental works and post-mortem analysis of affected neonates suggest that early CNS infection by ZIKV during development results in neuronal death and impairs neurodevelopment (19–21). More recently, the susceptibility of mature neuronal cells and adult human brain tissues was also demonstrated, using dedicated experimental paradigms (22).
In our study a pathogen was detected or highly suspected in 59% of cases. West-Nile virus (WNV) might be a candidate pathogen in some of the cases of unknown origin. This highly neurotropic flavivirus, which circulates in animals, was discovered in 2002 in Guadeloupe, particularly in horses (23). WNV serology was routinely performed only during Zika outbreak but no case was detected. This can be explained by cross-reactions (24), which can lead to a misinterpretation due to the concomitant rise of non-specific IgM for these two flaviviruses. We suggest that the detection of WNV by PCR or culture be performed in all suspected cases of encephalitis/myelitis in the Caribbean. Given the possible similarities between the two entities, infectious and autoimmune encephalitis, we cannot formally exclude that a small number of our cases of indeterminate etiology, could be autoimmune encephalitis mimicking an infectious encephalitis or being associated with infection.

Encephalitis or myelitis due to leptospirosis are extremely rare, and only isolated cases have been reported whereas aseptic meningitis is more common (9). In our series, leptospirosis represented the third cause of CNS infections, together with VZV and DENV. The incidence rate of LEPT in temperate regions has been estimated between 0.01 and 0.17/100 000 per year (25), as compared to 69.4/100 000 per year in Guadeloupe (26). We advocate that leptospirosis be tested systematically in the French West Indies and other countries of the Caribbean area, when infectious encephalitis or myelitis is suspected. Indeed delayed diagnosis and treatment can result in poor outcome during the acute phase or lead to chronic neuroleptospirosis (10). In the tropical area, the upsurge of this disorder could be partly explained by the presence of animal reservoirs other than rats (27). In our study, 10 of 11 cases concerned were men. Leptospirosis mainly affects men (28) because of their professional activities (farmers, breeders, sewer workers). It is noteworthy that in our series only three patients were employed as farmers or working with animals.

We found two rare pathogens responsible for one encephalitis and one myelitis. *Aspergillus* is a classical cause of meningitis, vasculitis, and brain abscess in immunosuppressed patients (29) but diffuse encephalitis as observed in our case is very unusual, particularly in immunocompetent subjects (30). Myelitis caused by infection of *Angiostrongylus cantonensis* is a rare condition (31) although it is the most common eosinophilic meningitis worldwide.

Given the large variety of causal agents and the high number of cases with unknown etiology, we advocate for greater access to diagnostic technics allowing direct and specific detection of multiple pathogens, particularly in tropical areas.

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**Supporting Information**

Additional Supporting Information may be found in the online version of this article:

**Table S1.** General characteristics of patients with acute infectious myelitis or encephalitis, 2012-2018.

**Table S2.** Pathogens identified in 59% of cases, 2012-2018.

**Table S3.** Characteristics of the 68 patients with acute CNS infection due to ZIKV, DENV, VZV, HSV, and leptospirosis, 2012-2018.

**Table S4.** Comparison between flaviviruses (dengue and zika) and herpes viruses (HSV, VZV, EBV).

**Table S5.** Factors related to zika virus.

**Table S6.** Detailed characteristics of the 11 patients with CNS leptospirosis, 2012-2018.

**Table S7.** Factors related to neuroleptospirosis.

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Table S8. Risk factors to mechanical ventilation.

Figures Legends

Figure 1. Flow chart of the selection process, 2012-2018.

Figure 2. Number of cases of acute CNS Infections, 2012-2018.

Figure 3. MRI findings in encephalitis and myelitis, 2012-2018.

(A) CHIKV myelitis in a 68 years old man: sagittal T1 Gadolinium sequence showing posterior contrast enhancement of the lumbar cord; (B) DENV myelitis in a 25 years old woman: sagittal T1 gadolinium sequence showing multiple contrast enhancement of the spinal cord (C5-C6, T3-T4, T6-T7); (C) DENV encephalitis in a 45 years old woman: Fluid-attenuated inversion recovery (FLAIR) imaging demonstrates bilateral hyperintensities in temporal lobes. (D) LEPT myelitis in a 33 years old man (patient 11, Table S6): sagittal T1 Gadolinium sequence showing multiple posterior contrast enhancement in thoracic cord (T6-T8). (E) Aspergillus sp. encephalitis in an 85 years old woman: FLAIR imaging showing multiple and bilateral hyperintensities in temporal, parietal and frontal lobes. (F) Angiostrongilus Cantonensis myelitis in a 10 months old boy: multiple contrast enhancement and swelling in the cervical and lumbar cord in a sagittal T1 Gadolinium sequence.