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The Place of Viral Etiology in Encephalitis and Meningoencephalitis

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Abstract:

Introduction : Encephalitis and meningoencephalitis are inflammatory disorders of the brain tissue responsible for neurological dysfunction, sometimes of infectious or non-infectious origin. They may follow an acute, subacute or chronic course. Infectious encephalitis is more frequent in young children, individuals over 65 years of age and immunocompromised patients. The objective of this study was to describe the Algerian epidemiology by demonstrating the frequency of viral etiologies.

Materials and methods: A prospective study was conducted using a broad testing approach. We used a case definition compatible with those employed in previous studies, namely acute cerebral dysfunction and signs of inflammation, including patients who also had meningeal inflammation with an encephalic component (meningoencephalitis). Patients were recruited from three departments (intensive care, infectious diseases and paediatrics); data were collected according to the case definition using a standardised form. We sought to identify etiological pathogens using a standardised procedure based on SPILF recommendations, while describing the epidemiological, clinical, biological and etiological characteristics. Risk factors associated with in-hospital death were evaluated by multivariate logistic regression.

Results: A total of 141 patients with acute infectious encephalitis were included in the study. A viral etiology was determined in 73/141 (51.8%); it was confirmed for 29 (39.7%) patients, considered probable for 42 (57.3%) and possible for 2 (2.7%). Epstein–Barr virus (EBV) 14 (19.2), herpes simplex virus (HSV) 14 (9.9%), cytomegalovirus (CMV) 11 (15.1%), adenovirus 6 (4.3%) and coronavirus 12 (16.4%) were the most frequently identified pathogens.

Twenty-three patients (16.3%) (69% of whom were older than 16 years) died. Risk factors associated with death were: admission to intensive care ($p < 10^{-3}$), age ≥ 65 years ($p = 0.005$), initial level of consciousness ($p = 0.04$), Glasgow Coma Scale score < 8 ($p < 10^{-3}$), status epilepticus ($p = 0.022$), hydrocephalus ($p = 0.024$), involvement of the parietal lobe ($p = 0.046$), length of hospital stay < 5 days ($p = 0.006$), rhinovirus infection ($p = 0.032$), CMV infection ($p = 0.013$) and coronavirus infection ($p = 0.013$).

Conclusion: This study highlights a “cocktail” of numerous pathogens, most of which were potentially preventable. We observed a high proportion of EBV, which could probably be explained by the high prevalence of nasopharyngeal cancer in our setting.

Keywords: virus, EBV, encephalitis, meningoencephalitis, HIV-negative

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1 Introduction

Meningoencephalitis is a severe infectious condition (1), notably because involvement of the brain (whether or not associated with meningeal and/or spinal cord involvement) is characterised, in addition to an infectious syndrome, by disturbances of consciousness, autonomic dysfunction, psychiatric symptoms and sometimes status epilepticus. These manifestations result from direct aggression of the grey matter by infectious agents or from immune-mediated lesions of the white matter. They remain a real challenge in terms of etiological diagnosis and medium- and long-term management.

Viral infections are the most common etiologies of acute meningoencephalitis. The main mechanism corresponds to direct involvement of the central nervous system (CNS), which is invaded either via the haematogenous route (for example, arboviruses) or via retrograde neuronal spread (for example, herpes simplex virus or rabies virus) (2–5).

The elementary neuropathological lesions observed predominate in the grey matter and schematically combine cellular lesions and an inflammatory reaction of variable intensity with a predominantly perivascular distribution, microglial proliferation and astrocytic gliosis of variable intensity. Demonstration of the virus or its components in brain tissue (by immunofluorescence or immunohistochemistry) and culture from a brain biopsy is sometimes possible (2).

Herpetic meningoencephalitis is the leading recognised cause of viral meningoencephalitis, accounting for 12–14% of diagnosed viral meningoencephalitis cases in Europe (2).

Acute meningoencephalitis related to arboviral infections is frequent in the Americas and Asia. The most common etiology is Japanese encephalitis (around 20,000 cases per year, nearly half of them in China) (6). These meningoencephalitides are very rare in France and are mainly observed in patients returning from areas endemic for these viruses. In Tunisia, 173 cases of West Nile virus infection were reported in 1997 and 233 cases in 2003 (7).

HSV-1 and HSV-2, arboviruses and rabies virus are responsible for the highest mortality (4, 5, 8–10).

Despite advances in pathophysiological knowledge and the widespread use of molecular biology techniques, the etiology of encephalitis remains unknown in the majority of cases. Their incidence, patient prognosis in the short and medium term and the persistence and severity of sequelae remain incompletely defined (11).

The objective of this study was to describe the Algerian epidemiology by demonstrating the frequency of viral etiologies.

2 Method

This prospective, longitudinal and exhaustive study included patients older than 28 days with symptoms suggestive of encephalitis and meningoencephalitis, hospitalised in three departments (intensive care, infectious diseases and paediatrics) during the period from 1 April 2012 to 31 August 2015, with assessment of epidemiological, clinical, radiological and etiological parameters.

Selected patients were those presenting with disturbances of consciousness, seizures, central or peripheral neurological signs, autonomic dysfunction, with fever ≥ 38 °C and cerebrospinal fluid (CSF) showing at least one abnormality: ≥ 4 cells/mm³ or protein concentration ≥ 0.4 g/L. Patients older than 28 days hospitalised for neurological signs and/or radiological signs of febrile encephalitis with normal CSF were also included, given the frequency of post-infectious encephalitis.

Clinical exclusion criteria were: HIV-positive status, brain abscess and non-infectious CNS disorders.

Data collected on a technical form included: sociodemographic characteristics; suggestive circumstances; geographical origin; season; vaccination status; history of contact with animals and other vectors; history of travel; immunosuppression status; personal medical history; signs suggestive of tuberculosis; mode of onset; general signs; functional signs; physical signs; neurological and extra-neurological manifestations; and short- and medium-term outcomes.

Biological, bacteriological, virological and parasitological examinations were performed systematically for all recruited patients, including standard laboratory tests, blood cultures, cytobacteriological and biochemical examination of CSF with direct examination and culture on Schöler medium for turbid CSF and testing for soluble antigens, culture on Löwenstein–Jensen medium in cases of suspected tuberculosis, and screening for haematozoa (blood smear from EDTA tube, stained with RAL) in cases of suspicion.

In the event of a contraindication to lumbar puncture, the etiology was sought from other specimens, notably serum or secondary localisations.

All data concerning HIV-negative patients in our study were recorded on a standardised form completed at admission. In addition, for the purposes of further microbiological investigations, samples were collected and immediately frozen at –80 °C for subsequent analyses (whole blood in EDTA tube [5 mL] or clotted blood in a dry tube [5–10 mL], pharyngeal swab, CSF [1 tube of 15 drops each]). These samples were complemented by blood in an EDTA tube (5 mL) or dry tube (5 mL) collected at discharge.

Lumbar puncture (LP) was performed in 131 (92.9%) patients. LP was not performed in 10 patients (7.1%) because 4 had papilloedema, 2 had spondylodiscitis and 4 had cerebral malaria.

Due to insufficient volume, CSF glucose was measured in only 129 samples (98.47%) and CSF protein in 124 samples (94.65%).

Additional analyses (PCR, viral culture and serological tests) were carried out subsequently at the Institut des Agents Infectieux (IAI) of Lyon University Hospital. Molecular analyses were performed according to the standards of the IAI microbiology laboratories. Samples were extracted on a NucliSENS EasyMAG system (bioMérieux). After extraction, various real-time PCR/RT-PCR assays were performed for detection of viruses and bacteria.

The etiological work-up was performed in accordance with SPILF recommendations for the management of patients with encephalitis (12). The recommended diagnostic procedure (12) is divided into three successive stages according to the frequency of infectious agents as causes of encephalitis and the need to start early treatment for certain pathogens.

Ethical rules related to medical confidentiality and patient agreement with respect to prescribed therapeutic measures were respected throughout the study. Patient or family consent for the lumbar puncture was obtained verbally.

A case classification system was created to specify the level of evidence linking the microbiological result obtained from analysed specimens to the observed encephalitis. According to the result, the etiology identified for each case was classified as confirmed, probable, possible or unknown, in line with SPILF recommendations (12). More than one etiology could be assigned to a given case. The classification system took into account the nature of the etiological agent and the strength of a given positive laboratory test result as a cause of encephalitis or otherwise. Interpretation of results may be difficult and must be undertaken in light of the clinical context, the virus identified and knowledge of the patient's immune status (13).

We were able to test 2,671 samples by PCR, perform 404 direct examinations and bacterial cultures, 219 viral cultures and 380 serological tests. The number of pathogens investigated per patient included in this study ranged from 1 to 31. For 13 patients, only a single test was performed because it was immediately positive. The mean number of agents investigated was 15.01 in patients with a diagnosis and 20.17 in patients without a diagnosis.

For arboviruses commonly associated with encephalitis (i.e., Japanese encephalitis virus [JEV] or West Nile virus), documentation of acute infection in paired serum samples was considered the diagnostic gold standard and therefore regarded as confirmation.

Risk factors associated with death during hospitalisation were assessed by multivariate logistic regression.

3 Results

Overall, among the 141 HIV-negative patients with encephalitis and/or meningoencephalitis who met the inclusion and exclusion criteria of our study, 111 had at least one suggested etiological diagnosis; 73 (51.8%) had at least one suggested viral etiology, representing 65.8% of identified etiologies (29 definite, 42 probable and 2 possible). In 21 patients (28.7%), evidence of infection by several pathogens was found, suggesting possible co-infections; among them, 10 (13.7%) had more than two detected pathogens.

Table 1. Summary of viral etiology identified per patient (n = 73/141)

Etiology (n = 73)	**Confirmed (n = 29/73)**	**Probable (n = 42/73)**	**Possible (n = 2/73)**	**Total n (%)**
EBV	12 (including *Streptococcus D*–HSV, 1 coronavirus–HSV–tuberculosis, tuberculosis, coronavirus, *Listeria*, enterovirus)	4 (CMV, varicella–zoster virus [VZV], HSV-1–facial palsy)	–	16 (21.9)
CMV	5 (EBV)	4 (2 tuberculosis, tuberculosis)	–	9 (12.3)
Coronavirus	–	14 (*Listeria*, *Streptococcus pneumoniae*–*Mycoplasma*, tuberculosis–CMV, EBV–*Chlamydia*, *Mycoplasma*, tuberculosis, tuberculosis–*Chlamydia*, tuberculosis–*Mycoplasma*, tuberculosis)	–	14 (19.2)
Adenovirus	4 (HSV-1)	2 (1 human herpesvirus 6 [HHV-6], parvovirus B19–coronavirus–Lyme disease)	–	6 (8.2)
Enterovirus	3 (EBV, *S. pneumoniae*)	2 (2 rhinovirus)	–	5 (6.8)
HSV-1	2 (*Chlamydia*)	6 (Lyme disease, *S. pneumoniae*–*Listeria*, HHV-6, tuberculosis, *Coxiella* I, II)	–	8 (10.9)
HHV-6	–	3 (*Rickettsia typhi*, facial palsy)	–	3 (4.1)
Mumps virus	1	–	–	1 (1.4)
Rubella virus	2 (*S. pneumoniae*–HSV)	1	–	3 (4.1)
Influenza A	–	2 (1 EBV)	–	2 (2.8)
Influenza B	–	1 (1 coronavirus)	–	1 (1.4)
VZV	–	2 (Lyme–*Chlamydia*, *Mycoplasma*)	1 (*Chlamydia*)	3 (4.1)
BK virus	–	1 (tuberculosis)	–	1 (1.4)
West Nile virus	–	–	1 (HSV-1)	1 (1.4)
Total number of patients	29	42	2	73 (100)
Total pathogens isolated	38	55	3	96

Among the 73 patients with at least one viral etiology, a monoviral etiology was identified in 28/73 (38.4%) patients, and a treatable etiology in 38/73 (52.1%) cases.
In other words, among the 96 identified etiological diagnoses:

1. The 38 confirmed cases were due to: HSV-1, EBV, CMV, enterovirus, adenovirus, mumps virus and rubella virus.
2. The 55 probable cases were due to: HSV-1, HSV-2, EBV, CMV, VZV, adenovirus, enterovirus, HHV-6, rubella virus, parvovirus B19, influenza A, influenza B, rhinovirus, coronavirus and BK virus.
3. The 3 possible cases were due to: West Nile virus, VZV and HSV.

These raw results are presented in Table 1. Etiology was confirmed or probable in 94/96 (97.9%) and possible in 2 cases (2.1%).
Among the confirmed etiologies (29 patients, 39.7%), the leading agent was EBV, 12 cases (16.5%), followed successively by CMV 5 (6.9%), adenovirus 4 (5.5%), enterovirus 3 (4.1%), HSV 2 (2.8%), 2 cases (2.8%) of rubella virus and 1 case (1.4%) of mumps virus.
There were five confirmed co-infections, including one viral–viral co-infection (4.4%) "EBV–enterovirus".
Diagnosis was considered probable for 42 (57.5%) patients, with 13 (17.8%) probable co-infections. Among probable etiologies, the leading agent was coronavirus, 14 cases (19.2%), followed by 6 cases of HSV (8.2%), 4 cases (5.5%) of CMV, 4 cases (5.5%) of EBV, 3 cases (4.1%) of VZV, 3 cases (4.1%) of HHV-6, 2 cases (2.8%) of adenovirus, 2 cases (2.8%) of enterovirus, 2 cases (2.8%) of influenza A, 1 case (1.4%) of influenza B, 1 case (1.4%) of rubella virus, 1 case (1.4%) of BK virus and one parvovirus B19 co-infected with adenovirus and coronavirus.
A possible etiology was identified in 2 patients; one probable–possible co-infection "HSV–West Nile virus".

Table 2. Aggregated clinical data according to viral etiology

Clinical signs / Etiology	EBV (n = 20) %	HSV (n = 14) %	CMV (n = 11) %	Enterovirus (n = 6) %	Adenovirus (n = 6) %	HHV-6 (n = 5) %	VZV (n = 4) %	Other viruses (n = 12) %
Abrupt onset	16 (80)	8 (57.1)	4 (36.4)	6 (100)	3 (50)	5 (100)	2 (50)	6 (50)
Progressive onset	4 (20)	6 (42.9)	7 (63.6)	–	–	–	2 (50)	6 (50)
Headache	11 (55)	12 (85.7)	6 (54.5)	3 (50)	4 (66.7)	2 (40)	4 (100)	8 (66.7)
Neck stiffness	13 (65)	5 (35.7)	3 (27.3)	5 (83.3)	3 (50)	2 (40)	1 (33.3)	3 (25)
Initial Glasgow score < 8	–	3 (21.4)	3 (27.3)	0	2 (33.3)	–	–	2 (16.7)
Behavioural disturbances	12 (60)	7 (50)	6 (54.5)	5 (83.3)	2 (33.3)	3 (60)	3 (75)	5 (41.7)
Seizures	8 (40)	4 (28.6)	7 (63.6)	–	–	–	0	7 (58.3)
Neurological deficits	11 (55)	11 (78.6)	6 (54.5)	2 (33.3)	5 (83.3)	–	3 (75)	4 (33.4)

Cranial nerve involvement	5 (25) I, 3 III, VI, VII	4 (28.6) I, III, VI, VII	2 (18.2) VII	2 (33.3) I, VII, IX, X	2 (33.3) VII, IX, X	–	1 (25) III, VII	2 (16.7) I, II, IX, X
Aphasia	4 (20)	3 (21.4)	2 (18.2)	0	1 (16.7)	–	0	1 (8.3)
Amnesia	0	1 (7.1)	0	0	–	–	0	1 (8.1)
Cerebellitis	2 (10)	2 (14.3)	1 (9.1)	0	1 (16.7)	–	2 (50)	–
Myelitis	3 (15)	2 (14.3)	1 (9.1)	1 (16.7)	–	1 (20)	1 (25)	2 (16.7)
Psychiatric disorders	2 (10)	3 (21.4)	0	1 (16.7)	–	–	0	1 (8.3)

Aggregated biological data by viral etiology

Table 3. Aggregated biological data in patients with viral etiologies

Biological parameter	**Confirmed and probable viral (n = 71) %**	**Possible viral (n = 2) %**
Pleocytosis ≥ 4 cells/mm³	57 (77)	1 (50)
Elevated CSF protein	39 (52.7)	1 (50)
Hypoglycorrhachia	21 (28.4)	1 (50)
C-reactive protein negative or weakly positive	51 (68.9)	2 (100)
Positive procalcitonin	39 (52.7)	0
Hyponatraemia	28 (37.8)	0

Table 4. Aggregated CSF data according to pathogen

CSF results / Etiology	**EBV (n = 20) %**	**HSV (n = 14) %**	**CMV (n = 11) %**	**Enterovirus (n = 6) %**	**Adenovirus (n = 6) %**	**HHV-6 (n = 5; LP = 4/5) %**	**VZV (n = 4) %**	**Other viruses (n = 12) %**
Pleocytosis ≥ 4 cells/mm³	17 (85)	9 (64.3)	6 (54.6)	6 (100)	4 (66.7)	4 (80)	4 (100)	7 (58.3)
Lymphocytic predominance	12 (60)	7 (50)	7 (63.6)	4 (66.7)	3 (…)	3 (60)	3 (75)	7 (58.3)
Neutrophilic predominance	3 (15)	5 (35.7)	1 (9.1)	1 (16.7)	1 (16.7)	–	–	3 (25)
Mixed	3 (15)	1 (7.1)	2 (18.2)	1 (16.1)	1 (16.7)	1 (20)	1 (25)	1 (8.3)

Elevated CSF protein	13 (65)	7 (50)	6 (54.6)	6 (100)	2 (33.3)	1 (20)	2 (50)	7 (58.3)
Hypoglycorrhachia	9 (45)	6 (42.9)	2 (18.2)	2 (33.3)	0	1 (20)	1 (25)	2 (16.7)
Hyponatraemia	5 (25)	6 (42.9)	5 (45.5)	3 (50)	1 (16.7)	3 (60)	0	4 (33.3)

Global clinical and biological description

The median age of the study population was 28 years [0–83 years]. Forty-two patients (57.5%) were male. Twenty-two patients were aged 28 days to 15 years; 43 (58.9%) were 16–64 years old; and 8 (11%) were older than 65 years. A total of 57 patients (78.1%) were vaccinated against measles. In 39.7% of cases, admission occurred in 2013; 32.9% of cases occurred in winter, with some variation according to season (spring, summer). Seventy patients (95.9%) reported having lived in an urban area during the previous three months.

A total of 16 patients (21.9%) had an underlying disease (1 cancer, 4 diabetes mellitus, 2 thyroid dysfunction); 5.4% were receiving immunosuppressive therapy or corticosteroids. Twelve patients (16.4%) were smokers, with a mean cumulative tobacco exposure of 13.3 pack-years.

Abrupt onset was observed in 42 patients (57.5%). Rhinorrhoea was present in 17.8% of cases. Respiratory involvement was found in 28.8% of patients. Nine patients (12.3%) had a rash (morbilliform in 6.8%, vesicular in 4.1%). Hepatic involvement was documented in 14 patients (19.1%), and cardiac involvement in 4.1% of cases.

Fifty patients (68.5%) had headaches. Neck stiffness was found in 32 (43.8%), whereas the predominant neurological manifestations were disturbances of consciousness in 48 (65.8%), of whom 15.1% had a Glasgow Coma Scale score < 8; confusion in 4 (5.5%); hallucinations in 10 (13.7%); aphasia in 9 (12.3%) cases; behavioural disturbances in 41 (56.1%); motor deficits in 42 (57.6%); and seizures in 30 (41.1%).

A non-negligible proportion of patients (8.2%, 6 cases) presented with psychiatric disorders at the onset of encephalitis. However, in our study, 2 patients (2.7%) had a prior psychiatric history, and only one of them presented with psychiatric symptoms at the onset of the clinical picture.

Pleocytosis was found in 52/68 (76.5%) CSF samples; of these, 65.7% showed lymphocytic predominance, 17.9% neutrophilic predominance and 16.4% mixed cellularity. Hypoglycorrhachia was noted in 21 cases (31.8%). Elevated CSF protein was observed in 39 cases (60.9%). Nineteen cases (26%) had CRP levels > 50 mg/mL. Procalcitonin was positive in 39 (53.5%) cases. Leukocytosis was found in 26 (35.6%) cases. Hyponatraemia was present in 26 (35.6%) cases.

From an imaging perspective, frontal lobe involvement was observed in 17 patients (23.6%), 64.7% of which were bilateral. Temporal involvement was found in only 10 cases (13.9%), with bilateral involvement in 60%. Parietal lobe involvement was evident in 15 cases (20.8%), with bilateral involvement in 46.7%. Hydrocephalus was present in 14 cases (19.4%). Rhombencephalitis was documented in 3 patients (4.2%). EEG findings compatible with encephalitis (categories not mutually exclusive) were present in 17/32 (53.2%) patients, and electrical temporal lobe involvement accounted for 58.9%.

The median length of hospital stay was 17 days (1–874 days).

A total of 23 patients (16.3%) died; the median age of those who died was 34 years (0–83), and 69.6% were older than 16 years, with a predominance of males (sex ratio 1.3). Criteria for admission to intensive care (30.1%) were: Glasgow Coma Scale score < 8 (36.1%), status epilepticus (22.2%), neurological complications (27.1%), hydrocephalus (6.6%) and haemodynamic instability (12.9%). Viral etiologies significantly associated with death were CMV, rhinovirus and coronavirus. Risk factors associated with death were: admission to intensive care ($p < 10^{-3}$), age ≥ 65 years (p = 0.005), initial level of consciousness (p = 0.04), Glasgow Coma Scale score < 8 ($p < 10^{-3}$), status epilepticus (p = 0.022), hydrocephalus (p = 0.024), involvement of the parietal lobe (p = 0.046), length of hospital stay < 5 days (p = 0.006), rhinovirus infection (p = 0.032), CMV infection (p = 0.013) and coronavirus infection (p = 0.013).

Twelve patients (16.4%) had sequelae persisting for more than six months: psychomotor delay in 2 cases; epilepsy in 4 cases; behavioural disorders in 4 cases; memory disorders in 2 cases; intellectual impairment in 4 cases;

hydrocephalus in 1 case; blindness in 1 case; motor deficit in 2 cases; paraparesis in 1 case; and sensorineural deafness in 1 case.

Table 5. Aggregated imaging data according to viral etiology

Imaging / Etiology	**EBV (n = 20) %**	**Coronavirus (n = 18) %**	**HSV (n = 14) %**	**CMV (n = 11) %**	**Enterovirus (n = 6) %**	**Adenovirus (n = 6) %**	**HHV-6 (n = 5) %**	**VZV (n = 4) %**	**Other viruses (n = 12) %**
Temporal involvement	1 (5)	1 (5.6)	3 (21.4)	2 (18.2)	1 (16.7)	–	–	0	3 (25)
Frontal involvement	3 (15)	3 (16.7)	3 (21.4)	3 (27.3)	4 (66.7)	2 (33.3)	–	0	4 (33.3)
Parietal involvement	1 (5)	1 (5.6)	4 (28.6)	6 (54.5)	1 (16.7)	3 (50)	–	1 (25)	1 (8.3)
Occipital involvement	0	1 (5.6)	0	1 (9.1)	–	–	–	0	–
Bilateral involvement	3 (15)	4 (22.2)	3 (21.4)	3 (27.3)	4 (66.7)	3 (50)	–	0	4 (33.3)
Bilateral frontal lesions (n = 34)	4 (11.8)	5 (14.7)	6 (17.6)	4 (11.8)	4 (11.8)	1 (2.9)	–	–	5 (14.7)
Bilateral temporal lesions (n = 35)	4 (11.4)	4 (11.4)	4 (11.4)	4 (11.4)	4 (11.4)	3 (8.6)	–	–	6 (17.1)
Bilateral parietal lesions (n = 39)	4 (10.3)	4 (10.3)	5 (12.8)	7 (17.9)	4 (10.3)	3 (7.7)	–	1 (2.6)	5 (12.8)
Bilateral occipital lesions (n = 29)	4 (13.8)	5 (17.2)	3 (10.8)	3 (10.3)	4 (13.8)	3 (10.3)	–	–	5 (17.2)
Oedema and signs of herniation	2 (10)	0	4 (28.6)	0	1 (16.7)	1 (16.7)	2 (40)	0	2 (16.7)
Hydrocephalus	5 (25)	0	2 (14.3)	5 (45.5)	1 (16.7)	1 (16.7)	0	0	1 (8.3)
Rhombencephalitis	2 (10)	–	2 (14.3)	–	0	–	–	–	1 (8.3)

Ischaemic lesions	2 (10)	1 (5.6)	1 (7.1)	0	1 (16.7)	1 (16.7)	–	–	1 (8.3)
ADEM	0	1 (5.6)	0	0	0	1 (16.7)	–	0	1 (8.3)
Myelitis	0	0	1 (7.1)	0	1 (16.7)	0	–	0	2 (16.7)
Normal imaging	9 (45)	8 (44.4)	4 (28.6)	2 (18.2)	3 (50)	2 (33.3)	2 (40)	2 (50)	3 (25)

(ADEM: acute disseminated encephalomyelitis)

Discussion

In Batna, a wide range of pathogens cause acute encephalitis. In this study, using a comprehensive approach and advanced diagnostic methods, an etiology was identified in 111 cases, of which 73 (65.8%) had a viral etiology, versus 66.4% in France (2007) (12), 43.8% in England 2005–2006 (14), 21.3% in California 1998–2005 (15), 19.9% in the French PMSI 2000–2002 (16) and 63.3% in Thailand 2003–2005 (17).

Table 6. Comparison of identified etiologies in encephalitis and meningoencephalitis (n = 141)

	Our study 2012–2015 (n = 141) %	**California 1998–2005 (n = 1,570) %**	**France 2007 (12) (n = 253) %**	**PMSI 2002 (n = 3,598) %**	**England 2005–2006 (n = 203) %**	**Thailand 2003–2005 (n = 149) %**
Encephalitis without etiology	30 (21.7)	1,236 (78.7)	122 (48)	2,897 (79.9)	75 (37)	51 (34.2)
Etiology identified	111 (78.7)	334 (21.3)	131 (52)	701 (19.5)	128 (63.1)	98 (65.8)
HSV	14 (9.92)	53 (3.5)	55 (22)	62 (5)	38 (19)	1 (0.7)
VZV	4 (2.8)	27 (2)	20 (8)	43 (3)	10 (5)	2 (1.3)
West Nile virus	1 (0.7)	19 (1.2)	1 (0.4)	0	–	–
Enterovirus	6 (4.3)	43 (2.8)	3 (1)	5 (0.4)	3 (1)	30 (20.1)
EBV	20 (14.2)	17 (1.1)	3 (1)	0	1 (0.5)	3 (2.1)
CMV	11 (7.8)	–	6 (2)	24 (2)	–	–
Adenovirus	6 (4.3)	14 (1)	0	1 (0.02)	0	7 (4.7)
HHV-6	5 (3.5)	–	–	–	1 (0.5)	–
Rubella virus	3 (2.1)	0	0	0	0	4 (2.7)
Measles virus	0	0	0	5 (0.4)	0	10 (6.7)
Mumps virus	1 (0.7)	0	0	0	0	8 (5.7)
Parvovirus B19	1 (0.7)	0	0	0	0	0

Coronavirus	18 (12.8)	0	0	0	0	0
Influenza A	2 (1.4)	22 (1.4)	0	0	2 (1)	6 (4)
Influenza B	1 (0.7)	0	0	0	0	0
Rhinovirus	2 (1.4)	0	0	0	0	0
BK virus	1 (0.7)	0	0	0	0	1 (0.5)

In our work, we noted only minor differences between our results and those of other studies (see Table 6) regarding seizures, Glasgow Coma Scale scores and personality disorders. However, we observed a high frequency of focal neurological deficits (57.6%) versus 37% in France 2007 (12), 36% in England 2005–2006 (14) and 34.2% in Thailand (17). Given the co-infections with 5 cases (3 confirmed, 2 probable) of tuberculosis and 2 cases of *Listeria monocytogenes*, this higher frequency may be explained by the fact that focal signs are more frequent in *Listeria* meningoencephalitis (18–20), but also in *Mycobacterium tuberculosis* infection (21).

A non-negligible proportion of patients (8.2%) presented with psychiatric disorders at the onset of encephalitis. In a Swedish study, 2.5% of 236 patients with HSV encephalitis were reported to have a psychiatric disorder before encephalitis (22). In our study, 5 patients (3.5%) had a psychiatric history, but only 2 of them presented psychiatric symptoms at the onset of the clinical picture. Among the 8.2% of patients with psychiatric disorders, 2 had HSV infection with two co-infections (HSV-1–*Chlamydia*, HSV-2–tuberculosis), 2 had EBV infection (one of them co-infected with coronavirus) and 1 patient had enterovirus infection. The interval between onset of neurological signs and hospitalisation did not differ from that of patients receiving psychotropic treatment.

In light of our data, the 17.9% of cases with neutrophilic predominance in CSF may represent a transient early pattern for some viruses. However, we found that 3/12 of these cases were co-infected with a confirmed or probable bacterial etiology, and 2 cases with a possible bacterial etiology. Similarly, among the 16.4% of cases with mixed CSF cellularity, 4/12 cases were co-infected with a confirmed or probable bacterial etiology and 3 with a possible bacterial etiology. Likewise, among the 21 cases (31.8%) with hypoglycorrhachia, 9 were co-infected with a confirmed or probable bacterial etiology and 6 with a possible bacterial etiology.

In our cohort, among the 19 cases (26%) with CRP > 50 mg/mL, 3 were co-infected with a confirmed or probable bacterial etiology and 4 with a possible bacterial etiology. Similarly, among the 39 cases (53.5%) with positive procalcitonin, 9 were co-infected with a confirmed or probable bacterial etiology and 8 with a possible bacterial etiology. Among the 26 cases (35.6%) with leukocytosis, 6 were co-infected with a confirmed and/or probable bacterial etiology.

Hyponatraemia was present in 26 cases (35.6%), of whom 37.8% had confirmed or probable viral infection, and 9 were co-infected with a confirmed or probable bacterial etiology. Neuroimaging was abnormal in 46 cases (63%). In our cohort, among the 17 cases (23.6%) with frontal involvement, 64.7% were bilateral, whereas temporal involvement was observed in only 10 (13.9%) cases, 60% of which were bilateral. Among the 14 cases (19.4%) with hydrocephalus, 35.7% were co-infected with a confirmed or probable bacterial etiology.

In our study, taking co-infections into account, the most frequently identified viral etiological agent was EBV, 20 cases (14.2%), followed by HSV 14 (9.9%) and CMV 11 (7.8%). In comparison, the French study (12) reported frequencies of HSV 55 (22%) and VZV 20 (8%). In England (14), the most frequent etiology was HSV 38 (19%) and VZV 10 (5%). The California study (15) reported 25% enterovirus and 24% HSV, and the PMSI 2000–2002 study (16) reported HSV 62 (5%), VZV 43 (3%) and CMV 24 (2%). These results are therefore quite heterogeneous.

The leading agent in our series was EBV, 20 cases (14.2%) (13 confirmed, 7 probable), versus 17 (1.1%) in California 1998–2005 (15), 3 (1%) in France, 1 (0.5%) in England 2002–2006 (14) and 3 (2.1%) in Thailand 2003–2005 (17).

The second most frequent agent was HSV, 14 cases (9.9%), including 2 confirmed and 12 probable cases, compared with 53 (3.5%) cases in California 1998–2005 (15), 55 (22%) in France 2007 (12), 38 (19%) in England 2002–2006 (14), 62 (5%) in PMSI 2002 (16) and 1 case in Thailand 2003–2005 (17).

In contrast to other studies (12, 16), which reported a high frequency of herpes, the number of HSV infections detected in our study was low. According to Weil et al. (23), false-negative results may occur in patients of any age who have a first negative LP but a second positive one at day 4–7. In our study, one patient had an initially negative PCR that became positive on a second LP performed on day 4 because of clinical non-improvement. This finding is supported by several other reports (Akhan Infection 2001, McCabe Neurology 2003, Tyler HERPES 2004, Boivin HERPES 2004, Kennedy J Neurol 2005, Whitley Antiviral Res 2006, Espy Clin Microbiol Rev 2006, Kimberlin HERPES 2007), often involving early LP during the first neurological signs or minimally inflammatory CSF, as well as possible technical issues (PCR inhibitors, inadequate sample storage, haemorrhagic LP) (24–26). Another cause of false negatives is the presence in CSF of haemoglobin degradation products (porphyrins) (27, 28).

De Tiège et al. (CID 2003) described 8 initially negative PCRs (before day 3) among 33 children, associated with CSF white blood cell counts < 10/mm³ and normal protein concentrations; a similar case was observed in our study. The diagnosis can be definitively ruled out if HSV PCR is also negative on a second CSF sample collected on or after day 4, even if there are clinical or radiological signs compatible with temporal lobe involvement, allowing acyclovir to be discontinued (23).

HSV-2 may cause benign recurrent meningitis (Mollaret meningitis) (29) and is only rarely responsible for encephalitis in adults (26, 30, 31). Our case concerned a 25-year-old woman with HSV-2 co-infected with tuberculosis.

CMV occupied the third position in our series, with 11 cases (7.8%), compared with 6 cases (2%) in France (12) and 24 cases (2%) in the PMSI study (16). Among the 5 confirmed cases (one co-infected with EBV in serum), there were also 6 probable cases, some co-infected with (1 EBV, 1 BK–coronavirus, 2 BK [CSF], 1 BK possible).

We observed a low proportion of encephalitis due to enterovirus, 6 cases (4.3%), compared with other studies: 43 cases (2.8%) in California 1998–2005 (15), 3 cases (1%) in France (12), 5 cases (0.4%) in PMSI 2000–2002 (16), 3 cases (1%) in England (14) and 30 cases (20.1%) in Thailand 2003–2005 (17). We had only 3 confirmed cases (1 isolated in CSF and pharyngeal swab), 2 of which were co-infected (1 EBV, 1 *S. pneumoniae*), and 3 probable cases (1 echovirus 4, 1 echovirus 9, others not sequenced).

Although adenovirus exceptionally causes encephalitis, we identified 6 cases (4.2%) in our cohort, compared with 1 case (0.02%) in PMSI 2000–2002 (16), 7 cases (4.7%) in Thailand 2003–2005 (17) and 14 cases (1%) in California 1998–2005 (15). Among these 6 cases, 4 were confirmed, 2 probable, and 3 were co-infections (1 HSV, 1 HHV-6, 1 parvovirus–coronavirus–Lyme). Our results are surprising in view of their rarity in the literature and their usual occurrence in immunocompromised hosts with a high mortality (32, 33).

HHV-6 was detected in 5 cases (3.5%) in serum, compared with 1 case (0.5%) in England (14).

We observed a low proportion of VZV, 4 cases (2.8%), compared with 20 cases (8%) in France (12), 10 cases (5%) in England (14), 27 cases (2%) in California 1998–2005 (15), 43 cases (3%) in PMSI 2000–2002 (16) and 2 cases (1.3%) in Thailand 2003–2005 (17). The cases described included 3 probable cases, 2 co-infected with *Borrelia burgdorferi*–*Chlamydia*–*Mycoplasma*, EBV, and 1 possible case co-infected with *Chlamydia*.

Our findings are consistent with the cohort of Glaser et al. 1998–2005, in which VZV was identified in 27/1,570 (2%) cases (15), and with reports indicating that VZV PCR is positive in CSF in only one-third of cases (34, 35), while remaining useful for early diagnosis. Thus, a diagnosis of VZV meningoencephalitis can only be excluded when both IgG testing and PCR are negative (29).

We also report 3 cases of influenza: 2 cases of influenza A (1 H1N3, 1 non-typed) compared with 2 cases (1%) in England (14), 22 cases (1.4%) in California 1998–2005 (15), 6 cases (4%) in Thailand (17) and 4 cases in Dallas County, Texas, between 18 and 28 May 2009 (36). One case of influenza B (Yamagata) was observed, compared with no cases reported in other studies. Most cases reported in the literature have involved Asian children younger than 15 years (37, 38).

In our cohort, we were struck by the frequency of coronavirus infection, with a total of 18 cases, 4 of which were monoviral. Our data are supported by a study published on 2 May 2018 in Beijing, China, in which, among 183 and 236 children hospitalised with acute encephalitis syndrome alone or associated with respiratory tract infection, anti-coronavirus IgM antibodies were detected in 22/183 (12.02%) and 26/236 (11.02%) children, respectively, during the period May 2014–April 2015 (39, 40).

We identified one case of mumps meningoencephalitis, with neutrophilic CSF predominance, normal glucose and elevated protein, and normal inflammatory markers.
Finally, we observed 3 cases (2.1%) of rubella virus infection, compared with 4 cases (2.7%) in Thailand 2003–2005 (17): 2 confirmed (co-infected with *S. pneumoniae*) and 1 probable case.
Other pathogens identified were 2 cases of rhinovirus HRV-C44 (none previously reported), 1 parvovirus B19, 1 West Nile virus and 1 BK virus.
None of the samples was positive for measles virus, in contrast to 5 cases (0.4%) in PMSI and 10 cases (6.7%) in Thailand 2003–2005 (17). Likewise, no cases of parechovirus were identified.
The median hospital stay was 17 days (1–874), compared with 20 days (2–284) in France 2007 (12).
An unfavourable course was observed in 22 (30.1%) of our patients, with 23/73 (16.3%) deaths, among whom the viral factors significantly associated with mortality were rhinovirus (p = 0.034), CMV (p = 0.013) and coronavirus (p = 0.013).

3.1 Conclusion

Although this study excluded HIV-positive patients and we did not investigate non-infectious forms of encephalitis (such as encephalitis due to anti–N-methyl-D-aspartate receptor antibodies or voltage-gated potassium channel antibodies), which have recently been shown to cause encephalitis (14, 41), it illustrates the complexity of managing suspected encephalitis in view of the multiplicity of etiologies. It also highlights the specific features of the Algerian epidemiology and thus the need for an approach adapted to the national context, in terms of the incidence of the different pathogens and adjustment of the priority of targeted etiologies by tier according to the results obtained in our cohort.
The implementation of on-site diagnostic tools (real-time PCR, serology) and improved intensive care management will certainly have an impact on mortality and should contribute to optimising patient outcomes.

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