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Médecine et maladies infectieuses 47 (2017) 236–251

General review

Infectious encephalitis: Management without etiological diagnosis 48 hours after onset

Encéphalite infectieuse : diagnostic étiologique non fait à 48 heures, conduite à tenir

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Received 20 February 2017; accepted 22 February 2017
Available online 15 March 2017

Abstract

Introduction. – The etiological diagnosis of infectious encephalitis is often not established 48 hours after onset. We aimed to review existing literature data before providing management guidelines.

Method. – We performed a literature search on PubMed using filters such as "since 01/01/2000", "human", "adults", "English or French", and "clinical trial/review/guidelines". We also used the Mesh search terms "encephalitis/therapy" and "encephalitis/diagnosis".

Results. – With Mesh search terms "encephalitis/therapy" and "encephalitis/diagnosis", we retrieved 223 and 258 articles, respectively. With search terms "encephalitis and corticosteroid", we identified 38 articles, and with "encephalitis and doxycycline" without the above-mentioned filters we identified 85 articles. A total of 210 articles were included in the analysis.

Discussion. – Etiological investigations must focus on recent travels, animal exposures, age, immunodeficiency, neurological damage characteristics, and potential extra-neurological signs. The interest of a diagnosis of encephalitis for which there is no specific treatment is also to discontinue any empirical treatments initially prescribed. Physicians must consider and search for autoimmune encephalitis.

Keywords: Infectious encephalitis; HSV; VZV; Listeria; Tuberculosis

Résumé

Introduction. – L'absence de diagnostic étiologique après 48 heures de prise en charge d'une encéphalite infectieuse est fréquente. Nous avons voulu faire le point de la littérature existante avant de donner des recommandations de prise en charge.

Méthode. – Dans PubMed, nous avons utilisé les filtres « *since 01/01/2000* », « *human* », « *adults* », « *English or French* » et « *clinical trial/review/guidelines* », ainsi que les mots clés Mesh « *encephalitis/therapy* » et « *encephalitis/diagnosis* ».

Résultats. – Les mots clés Mesh « *encephalitis/therapy* » et « *encephalitis/diagnosis* » aboutissent respectivement à 223 et 258 articles. Les mots clés « *encephalitis and corticosteroid* » aboutissent à 38 articles et « *encephalitis and doxycycline* » sans les filtres sus-cités à 85 articles. Au total, 210 articles ont été retenus.

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http://dx.doi.org/10.1016/j.medmal.2017.02.004
0399-077X/

Discussion. – Les recherches étiologiques doivent être guidées par les notions de voyages, d'expositions animales, l'âge ou l'immunodépression, ainsi que par les caractéristiques de l'atteinte neurologique et les éventuels signes extra-neurologiques. L'intérêt du diagnostic des encéphalites qui ne disposent pas de traitement spécifique est également d'arrêter les traitements probabilistes initialement mis en route. Les encéphalites auto-immunes doivent être recherchées.

Mots clés : Encéphalite infectieuse ; HSV ; VZV ; Listeria ; Tuberculose

1. Introduction

On the third day of encephalitis patient management, first-line diagnostic test results may not lead to etiological identification when the Herpes simplex virus (HSV), Varicella zoster virus (VZV), and Enterovirus PCR tests and CSF and blood cultures are negative. This is quite frequent as, even after extensive and standardized etiological investigations, the causative agent is documented in only 38–52% of cases [1,2]. Metabolic or toxic encephalopathy diagnosis must be reconsidered when the CSF analysis is normal. The aim of this literature review is to better characterize clinical presentations of infectious encephalitis and understand etiological test performances to improve the diagnostic and therapeutic management of patients. We will assume that an amoxicillin and acyclovir treatment was prescribed at the start of patient management.

2. Material and methods

We identified 223 and 258 articles, respectively, using PubMed filters such as "since 01/01/2000", "human", "adults", "English or French", and "clinical trial/review/guidelines", and Mesh search terms "encephalitis/therapy" and "encephalitis/diagnosis". We also took into consideration articles mentioned in the selected articles, without using filters for publication dates. We identified 38 articles with the search terms "encephalitis and corticosteroid", and 85 articles with "encephalitis and doxycycline" without using the above-mentioned filters.

We included a total of 210 articles in the literature analysis.

3. Therapeutic management

3.1. Should acyclovir be continued when the HSV PCR is negative?

HSV encephalitis is the most frequent cause of viral encephalitis [1–3]. Therapeutic delays impact vital and functional prognoses [4,5]. It is thus recommended to initiate an empirical treatment with acyclovir when patients present with signs and symptoms of encephalitis before receiving results of the CSF HSV PCR test [6,7].

Typical clinical signs and symptoms described in retrospective studies included fever in 76 to 91% of cases [8–10]. Consciousness disorders were observed in 90% of cases [8], with a mean Glasgow score of 13.2 ± 3.1. Only a minority of patients had a Glasgow score < 8 (8.6% in Raschilas' study) [9]. Disorientation was observed in 76–81% of cases, behavior disorders in 41–66%, language disorders in 33–57%, seizures in 33–55%, and focal neurological disorders in 24–26% [9].

CSF analysis of infectious encephalitis patients revealed lymphocytic meningitis with a median CSF cell count between 83 and 237 nucleated cells (NC)/mm^3, of which 77–80% were lymphocytes and 4–12% were neutrophils [9,10]. Neutrophil predominance was rare (2.2% of patients with 69% of neutrophils maximum) [9]. CSF cell count was < 10 NC/mm^3 in 15% of patients [10]. CSF protein level was moderately high, between 0.67 and 0.83 g/L [9,10]; a CSF protein level > 1 g/L was only observed in 25% of patients [10].

Radiological findings described in a study of 93 patients presenting with HSV encephalitis were temporal lesions for 49 patients (53%) or fronto-temporal lesions for 34 patients (36%). Other lesions were also described in 8 patients (9%) with occipital presentations [9]. These extra-temporal presentations seem to be mainly reported in immunocompromised patients [11], although documented cases have been reported in immunocompetent patients [12]. Only 5% of patients have normal MRI results [8]. The authors of a recent retrospective study observed that initially bilateral lesions and extra-temporal lesions on MRI were associated with a lower risk of HSV encephalitis than other etiologies (OR 0.38 [0.18–0.79] and 0.37 [0.18–0.74], respectively) [13].

CSF HSV PCR test is currently the reference diagnostic method for HSV encephalitis. Its sensitivity is 98%, when compared with brain biopsy [14]. It is, however, important to keep in mind that PCR results may be negative during the first few days. The authors of a retrospective study of 38 children presenting with HSV encephalitis reported negative results in 8/33 (24%) children before Day 3 of disease evolution. Diagnostic sensitivity was 74% and 79% at Day 0 and Day 3, respectively. These negative results were significantly associated with a lower CSF protein level and with the absence of associated meningitis (with a cut-off value at 10 leukocytes/mm^3 in this study) [15]. The authors of another study of 11 patients presenting with < 3-day history of HSV encephalitis observed that three patients (27%) had an initially negative CSF HSV PCR that turned positive 4 to 7 days later, even after initiating the acyclovir treatment [16]. Negative PCR was not just observed in patients presenting without associated meningitis as the authors of this study reported that the CSF cell count of the three negative CSF PCR tests performed during the first lumbar punctures was 90, 330, and 720 leukocytes/mm^3, respectively. Other studies reported negative PCR tests performed on early CSF samples collected after onset of clinical signs [17–19]. It should, however, be noted that

this is rare. The authors of a French prospective study of 253 encephalitis patients observed that 55/55 of patients presenting with HSV encephalitis had an initially positive CSF HSV PCR, even though performed within two days of clinical sign onset for 27/55 patients [2].

The CSF HSV PCR usually remains positive for 5 to 7 days following antiviral treatment initiation [20]. Another study showed that PCR results remained positive between Day 0 and Day 7 of treatment for 49/50 CSF samples (98%), between Day 8 and Day 14 for 8/17 CSF samples (47%), and beyond Day 15 for 4/19 CSF samples (21%) [14]. Nevertheless, in this old study, patients whose PCR results remained positive the first week were more often treated with vidarabine than acyclovir. The authors reported that patients had to remain longer on vidarabine treatment to obtain negative PCR results [21].

The benefit of CSF HSV PCR depends, like all diagnostic tests, on pre-test probabilities. These probabilities are calculated based on radiological and clinical presentations and on CSF analysis. Thus, post-test probabilities – calculated with Bayesian statistics – of obtaining an HSV encephalitis diagnosis despite a negative PCR differ in patients presenting with confusion and fever who are admitted to the emergency department and receive an acyclovir empirical treatment (with a pre-test probability of 5%) and in patients presenting with typical signs and symptoms (with a pre-test probability of 60%). The diagnosis may reasonably be ruled out with a negative PCR in the first type of patients as the post-test probability is 2/1000, while for the second type of patients the post-test probability is 6% and must lead to further investigations before ruling out HSV encephalitis diagnosis [22].

3.2. Should acyclovir be continued when the VZV PCR is negative?

VZV encephalitis was reported as the second [2,3] or third [1] cause of encephalitis in the most recent French and Anglo-Saxon studies. VZV encephalitis was probably underdiagnosed, especially as it may occur without any associated skin lesions [23–27].

VZV is reportedly responsible for encephalitis, as well as for central nervous system vasculitis and infarctions [25,28,29]. Two-thirds of patients presenting with VZV central nervous system vasculitis also present with moderate lymphocytic pleocytosis (< 100 NC/mm^3), moderately high CSF protein level, and normal CSF glucose level [30]. The sensitivity of the CSF VZV PCR is moderately satisfactory. Results may be negative depending on the type of CNS lesions as well as during the first few days following symptom onset [31], although this is less documented than with HSV. The authors of a literature review of 20 patients presenting with encephalitis but without any associated vasculitis observed that 16 patients (80%) were diagnosed using VZV PCR; the four remaining patients presented or previously presented with vesicular rash [32]. Another study reported a positive CSF VZV PCR in only two of three encephalitis patients (66%) and in 12 of 27 (44%) patients presenting with meningoradiculitis and shingles [27]. However, the authors of a literature review of VZV central nervous system vasculitis observed that VZV PCR was less sensitive than intrathecal secretion of anti-VZV antibody test ($P < 0.001$), as the PCR test was positive for only 9 of 28 patients (30%) who all tested positive for intrathecal secretion [25]. The authors of another literature review reported the same results with the same sensitivity ranges [28].

Sensitivity differences depend on pathophysiology: for encephalitis, the PCR test may be positive before intrathecal secretion of immunoglobulins; conversely, VZV vasculitis onset is observed a few weeks after viral infection at a stage where only the intrathecal secretion of immunoglobulins remains positive [33]. It should be noted that studies reporting the clear superiority of the detection sensitivity of anti-VZV antibodies versus VZV PCR were performed by the same team (Nagel and Gilden, Colorado). Although American guidelines recommend anti-VZV antibody detection test [34], there is no consensus method to perform this analysis. Interpretations are not standardized. A cross-reaction also occurs between anti-HSV and anti-VZV antibody detection tests [35]. The detection test for antibodies against VZV glycoprotein E (gE) seems to be more specific, but it is not available in routine practice [36].

3.3. Should amoxicillin be continued?

The authors of the French multicenter prospective study "Encephalitis 2007" reported that *Listeria monocytogenes* is the second bacterial cause of encephalitis after *Mycobacterium tuberculosis* [2]. However, *Listeria monocytogenes* is associated with the highest lethality (46%) in patients presenting with severe comorbidities. CNS damage, and especially brainstem damage are the most frequent localization of invasive listeriosis in adults, except for pregnant women [37].

The risk of *Listeria monocytogenes* invasive infection exponentially increases with age or occurs in very specific patients such as those presenting with severe immunodeficiency or pregnant women. The authors of a study of 1959 listeriosis case patients documented between 2001 and 2008 in France observed an incidence of 0.05/100,000/year before the age of 65, of 0.38/100,000/year for the 65–74-year age group, and of 0.96/100,000/year for patients aged above 75 years. The highest incidence was observed in patients presenting with chronic lymphocytic leukemia (55/100,000/year) [38].

CSF analysis reveals meningitis (310 to 660 NC/mm^3), usually mixed and showing lymphocytic predominance, with high CSF protein level (0.9 to 2.3 g/L) and low CSF glucose level in 21-89% of cases [2,39,40]. The authors of a literature review of 110 rhombencephalitis patients [39] reported 14% and 42% sensitivity for Gram-staining microscopic examination and culture, respectively. Sensitivity was 28% and 90% in case of meningitis. Blood cultures were positive in two-thirds of cases.

The sensitivity of the *Listeria* PCR depends on the primers used. The authors of a 1992 study reported that the PCR test targeting the *iap* gene was positive in only 14/17 *Listeria* cases confirmed by culture and that it allowed for identifying three of seven meningitis cases with negative cultures. This primer was associated with a lack of specificity as four positive PCR tests were obtained in CSF cultures positive for *Haemophilus influenzae* [41].

Since 2011, RT-PCR amplifying the *hly* gene encoding *L. monocytogenes* listeriolysin O in CSF has been developed and tested in the CSF samples of 214 patients suspected of having *L. monocytogenes* CNS infection [42]. In addition to the nine cases confirmed by culture, the PCR was also highly positive in five patients – despite negative cultures – who received antibiotics within 1 to 5 days before lumbar puncture. The specificity of this primer seemed to be much better as no false positive results were reported. However, its sensitivity was not excellent as 10/24 PCR tests were negative in patients presenting with a documented infection (by associated bacteremia or anti-LLO antibody seroconversion) [42].

3.4. Should a trial of antituberculosis treatment be implemented?

The main risk factors for tuberculosis are prolonged stay in an endemic area [43], chronic alcoholism, solid cancers, prolonged corticoid therapy, and anti-TNF treatments [44]. Thwaites developed an algorithm to differentiate bacterial meningitis from tuberculous meningitis based on clinical (age, rapidity of clinical evolution) and paraclinical criteria (CSF cell count and percentage of neutrophils, elevated white blood cell count), with a 97% sensitivity and a 91% specificity [45]. This algorithm has since been prospectively evaluated in 205 patients presenting with meningitis and a low CSF glucose level. It was associated with an excellent negative predictive value (99%), thus allowing to reasonably rule out the diagnosis with a score > 4. It should be noted that a CSF with > 900 NC/mm^3 and > 75% of neutrophils is already associated with a score of 3 and 4, respectively [46]. The algorithm has been validated in South-East Asia [47], where the prevalence of tuberculous meningitis is high. It should now be evaluated in countries with a lower prevalence. The algorithm does not seem to be discriminating in countries with a high prevalence of HIV [48].

A trial of antituberculosis treatment is recommended if clinical signs and symptoms and paraclinical examinations match. Treatment should be initiated before diagnostic confirmation, especially as it is often delayed due to the time required for cultures [44]. A delayed treatment is highly associated with poor prognosis [49–51], especially in elderly patients and in patients presenting with initial consciousness disorders, hydrocephalus, or cerebral ischemia [52]. When an empirical antituberculosis treatment has been initiated and when cultures remain negative, British guidelines recommend continuing the antituberculosis treatment in the absence of any other etiologies (grade BIII). Guidelines specify that the decision to continue or discontinue the trial of treatment should not be based on the improvement of the patient's condition (or lack of it) on antituberculosis drugs (grade BIII) [44]. Data on CSF evolution during antituberculosis treatment is scarce, but the quantity of lymphocytes and CSF protein level seem to take much longer to normalize than CSF glucose level [53].

The antituberculosis treatment must be combined with a systemic corticoid therapy. The authors of a meta-analysis of seven randomized studies (1140 patients) reported a reduced mortality in patients receiving corticoids (relative risk 0.78 [0.67–0.91]) and a better functional prognosis [54]. The corticoid therapy is thus recommended in the guidelines for grade A-I in non-HIV-infected patients [44].

Diagnostic test sensitivity data is extrapolated from available data on tuberculous meningitis because very few studies have been conducted on tuberculous encephalitis. The authors of a prospective study of 132 tuberculous meningitis adult patients performed in Vietnam in 2004 managed to obtain a microbiological diagnosis for 82% of patients. The microscopic examination and CSF cultures were positive for 58 and 71% of cases, respectively [55]. The sensitivity of the CSF microscopic examination was influenced by:

- the number of samples evaluated per patient, with a sensitivity ranging from 37 to 87% when one to three CSF samples were analyzed, despite antituberculosis treatment initiation;
- the volume of CSF available (from 10 to 15 mL at best);
- the examination of the CSF sediment.

The authors of a large European retrospective study (14 countries, 506 patients presenting with central nervous system tuberculosis selected based on: (i) a positive microscopic examination by Ziehl-Neelsen staining; (ii) and/or a positive CSF culture on Lowenstein medium; (iii) and/or a positive BK PCR) observed that CSF cytology yielded 320 ± 492 NC/mm^3, with a predominance of lymphocytes (67 ± 26%), CSF protein level at 3.1 ± 4.2 g/L, and CSF glucose level/glycemia ratio of 0.28 ± 0.15.

Culture sensitivity on Lowenstein medium was 72.6% and the sensitivity of the microscopic examination was 27.3% [56].

Several authors suggested using CSF adenosine deaminase (ADA) titration as a criterion to discriminate tuberculous meningitis from other bacterial meningitis types, despite low level of evidence. The authors of a meta-analysis performed in 2010 reported sensitivity and specificity of ADA titration of 79% and 91% in the diagnosis of central nervous system tuberculosis, with positive and negative likelihood ratio of 6.85 and 0.29, respectively [57]. Another study reported a lower sensitivity for ADA titration (55%) [58]. Nevertheless, the recent European study reported a positive ADA in routine practice in only 41/137 cases (29.9%) [56]. The benefit of this test is thus limited.

The authors of a 2013 study of 235 South African patients (majority of HIV-infected individuals) presenting with meningitis observed that the quantitative Xpert MTB/RIF PCR, versus culture and/or Amplicor PCR, was associated with a better sensitivity than that of a clinical score or the CSF microscopic examination (Gram and auramine staining): 62% versus 30% and 12%, respectively ($P = 0.001$). A better sensitivity was observed when the CSF sample had previously been centrifugated (82% vs 47%), which required 3 mL of CSF (instead of 1 mL). South Africa is an endemic country for tuberculosis; PPV and NPV of the Xpert MTB/RIF test were 90 and 77% [59]. The authors of a meta-analysis published in 2014, and including 18 studies, observed that the sensitivity and specificity of the Xpert MTB/RIF test in CSF, as compared with culture, were 81 and 98%, respectively [60]. The authors of the multicenter European study observed a 57.3% sensitivity for BK PCR [56].

This sensitivity was measured using the analysis of heterogeneous PCR techniques: PCR-hybridization (Cobas® Amplicor, Grenzach-Whylen, Roche, Germany), RT-PCR (ProbeTec®, Becton Dickinson, Oxford, UK; GeneProof®, GeneProof, Brno, Czech Republic; GeneExpert®, Cepheid, Sunnyvale, CA, USA), which does not allow for evaluating the sensitivity of each of these techniques. The authors also highlighted the possibility of performing a blood IGRA test (QuantiFERON®-TB Gold Test In-Tube), and reported good results: 37 positive results out of 41 tested (sensitivity of 90.2%). The authors of the European study suggested the following explanation for the lower diagnostic sensitivity of these techniques: the quantity of tuberculous bacilli in the studied sample was probably much more significant in South-East Asia because of a longer time between clinical sign onset and hospital admission.

3.5. Should a corticoid therapy be implemented?

No evidence-based data supports the benefit of a systemic corticoid therapy for most encephalitis types. A few authors of clinical case reports mention the benefit of corticoids in patients presenting with consciousness disorders. This is due to the non-specific reduction in cerebral edema [61,62]. Corticoid therapy is, however, very important in patients presenting with ADEM [63,64] and autoimmune encephalitis [65], or in patients presenting with an associated vasculitis [30,66]. The same can be said for patients presenting with tuberculous meningitis combined with encephalitis [44]. For HSV encephalitis, non-randomized studies highlighted the benefit of an adjuvant corticoid therapy with an acyclovir treatment [67]. Its definitive role could not be clarified for lack of inclusion in an initial randomized prospective study [68], but another international randomized study is currently being designed (T. Solomon, unpublished data).

3.6. Should a trial of doxycycline treatment be initiated?

No study has evaluated the efficacy of such treatment when empirically administered.

Nevertheless, because of diagnostic difficulties of some encephalitis caused by intracellular bacteria, doxycycline may here be useful thanks to its broad-spectrum activity against these bacteria. Authors of clinical case reports and short-term studies called to mind that this molecule is effective against *Rickettsia* [69], *Coxiella burnetii* [70,71], *Mycoplasma* [72], and typhus-associated encephalitis [73,74]. Although doxycycline is not a first-line option, it is included in the therapeutic armamentarium of *Brucella* [75–78], *Bartonella henselae* [79], *Tropheryma whipplei* [80], and *Ehrlichia* encephalitis [81], and even of Lyme neuroborreliosis [82] and toxoplasmosis [83].

4. Diagnostic management

In a second-line context, other etiologies may need to be investigated depending on exposures, patient's characteristics or clinical presentation of the infection, especially for diagnoses with consequences on patient management (specific treatment or prevention measures for relatives). These main criteria are detailed in Table 1.

Table 1
Causative agents to consider based on context and corresponding diagnostic tests.
Pathogènes à évoquer en fonction du contexte et tests diagnostiques correspondants.

Context	Causative agents	Diagnostic tests
Sexually transmitted infections	HIV	Plasma serology, plasma HIV RNA
	Syphillis	Blood TPHA VDRL, CSF VDRL
Children/young adults	*Mycoplasma pneumoniae*	Plasma/CSF serology, PCR in nasopharyngeal secretions
	Influenzae virus	PCR in nasopharyngeal secretions
	Epstein-Barr virus	Plasma serology, plasma/CSF PCR
No vaccination	Measles	Plasma/CSF serology, CSF PCR
	Mumps	Plasma/CSF serology
	Rubella	Plasma/CSF serology
Immunodeficiency	*Cytomegalovirus*	Plasma/CSF PCR
	Human herpesvirus 6	Plasma/CSF PCR
	JC virus	CSF PCR
	Cryptococcus	Plasma antigen, CSF microscopic examination/antigen/culture
	Toxoplasma gondii	Plasma serology, CSF PCR
Travels	Arboviruses	Plasma/CSF serologies, plasma PCR

HIV: human immunodeficiency virus; CSF: cerebrospinal fluid; PCR: polymerase chain reaction; TPHA: *Treponema pallidum* hemagglutination; VDRL: venereal disease research laboratory.

4.1. Specific cases of sexually transmitted infections, to always consider

4.1.1. Should HIV encephalitis be considered despite an initially negative serology?

Between 11 and 17% of neurological manifestations are reported in patients presenting with symptomatic HIV primary infection [84,85]. However, encephalitis presentations at the stage of primary infection are rare. The authors of a study of 23 patients presenting with HIV primary infection and neurological damage observed that 13 patients (57%) had peripheral neuropathy, eight (35%) had isolated lymphocytic meningitis, and two (9%) had acute encephalitis [84]. Reported central neurological damages included encephalitis [85–88] and ADEM [89], which were sometimes life-threatening [90,91]. Patients presenting with neurological symptoms at the primary infection stage seemed to contract AIDS more rapidly [84]. As even the combined HIV serological tests (detection of antibodies and AgP24) lack sensitivity in the very first days of the primary infection [92], these tests should be repeated and plasma RNA-HIV [93,94] should be searched for in patients presenting with severe neurological symptoms. When these tests are positive, the plasma viral load must be completed with a CSF viral load.

4.1.2. Should syphilis be considered?

The incidence of syphilis has considerably increased in France since 2000, especially in men who have sex with men. Neurosyphilis may present as encephalitis [34]. CSF analysis usually indicates pleocytosis, but it may be normal in < 10% of cases (especially for tertiary syphilis and tabes). CSF protein level is moderately high (normal in 34% of meningovascular syphilis). The diagnosis of neurosyphilis relies on a positive serum serology (active syphilis), associated with at least two CSF abnormalities among the following:

- positive Venereal Disease Research Laboratory (VDRL);
- meningitis (NC > 5/mm^3);
- high CSF protein level [95,96].

4.2. Enterovirus

Enterovirus is a frequent cause of meningitis in children and adults, but there is usually no associated encephalitis. Two situations should, however, be distinguished from one another:

- the epidemiological context (traveling back from China and South-East Asia mainly), with the possibility of an Enterovirus 71 infection associated with a risk of severe encephalitis, especially in children
- some immunodeficiency types: x-linked agammaglobulinemia and severe hypogammaglobulinemia which increase the risk of chronic infections caused by *Enterovirus* associated with encephalitis, including *Enteroviruses* considered non-encephalitogenic in the general population.

Regardless of the context, when the *Enterovirus* CSF PCR test is positive in patients presenting with encephalitis, the sample should be sent to the *Enterovirus* national reference center for a better characterization of the strain.

The authors of a study of 138 patients reported that the *Enterovirus* (EV) CSF PCR (Amplicor test, Roche®) had better sensitivity than the cell culture (98.6% vs 55.8%). The rapidity of result availability (5–6 hours) was also of advantage compared with culture (3–5 days) [97]. The authors of a 2005 retrospective study of 34 patients observed that the sensitivity of the EV PCR in the diagnosis of EV meningitis (non-EV71) was 76% and 96% in CSF and stool samples, respectively. The sensitivity of the CSF PCR decreased two days after disease onset, while the sensitivity of the stool PCR remained high up to 16 days after disease onset [98]. A persistently positive stool PCR was reported in other studies [99]. In the absence of any CSF PCR analysis (or if it comes back negative), a positive EV PCR in the stool or throat samples of patients presenting with neurological symptoms must lead physicians to consider an EV diagnosis [100].

4.3. Especially in children and young adults

Two etiologies, for which the causative agent is only rarely detected in the CNS, must be considered. Diagnostic confirmation may be obtained by PCR in nasopharyngeal secretions or blood serology. The absence of direct documentation on CSF samples is indicative of the post-infectious impairment, just like in ADEM [63,64].

4.3.1. Mycoplasma pneumoniae

M. pneumoniae encephalitis is mainly reported in children [101]. The authors of a prospective study of 1988 patients addressed to the California Encephalitis Project for encephalitis without any etiological diagnosis observed signs of recent *M. pneumoniae* infection (serum IgM, seroconversion, or CSF or respiratory secretion PCR positive for *M. pneumoniae*) in 111 patients, of whom 84 were children (76%). Diagnosis only relied on serological tests for 80% of these 84 pediatric case patients (serum IgM or seroconversion). Among all adult and pediatric patients, *M. pneumoniae* PCR in CSF and respiratory secretions was positive in 29% and 2% of cases, respectively [102]. In a large review of *Mycoplasma pneumoniae* encephalitis, CSF abnormalities were reported in 40 to 60% of patients, usually with 10–200 NC/mm^3 and lymphocytic predominance in 90% of cases. A high CSF protein level was observed in 35 to 50% of cases, and CSF glucose level was normal [72]. The limitations of current diagnostic tests are persistently positive serum IgMs and respiratory PCR test several months after initial infection, thus calling into question the responsibility of *M. pneumoniae* in cases where documentation only relies on one of these tests (as compared with seroconversion or with CSF antibody detection) [103].

4.3.2. Influenza virus

Physicians may look for the influenza virus during endemic periods. The authors of a literature review of influenza virus neurological manifestations reported that a positive CSF pleocytosis was only observed in 9 to 22% of cases [104,105]. CSF protein level and CSF glucose level are usually within normal values, although significantly high CSF protein levels have been reported [106]. Detecting influenza A or B-specific RNA fragments in CSF samples or brain biopsy plates by RT-PCR has been documented in encephalitis cases as early as 1 or 2 days following infection onset [106]. However, although some studies reported positive influenza CSF PCR tests with five positive cases out of six patients presenting with encephalopathy and influenza A [107], the virus was rarely detected in CSF samples in most other studies [104,106,108]. The virus was not detected by cultures or immunostaining technique in the reported autopsy cases, but a diffuse edema without any inflammatory infiltrate nor specific cytopathogenic effect was observed [109].

4.3.3. Epstein-Barr virus (EBV)

Physicians must consider EBV in children presenting with acute encephalitis without any etiological diagnosis. Clinical signs and symptoms are varied, including fever, cephalgia, seizures, behavior disorders, cerebellar syndromes, or rhombencephalitis [110–112]. Cases in young adults have also been reported [113]. Diagnosis relied on plasma serology and molecular biology techniques (serum or CSF PCR); the authors of a study reported a 78% sensitivity for molecular biology

techniques [113]. Many coinfections have also been reported; the authors of a study of 32 patients with a positive EBV CSF PCR observed that 47% of them had another infection [114].

4.4. In the absence of vaccination

For measles, mumps, and rubella, diagnosis relies on the serological detection of an acute infection, possibly confirmed by CSF PCR (negative in cases of post-infectious encephalitis).

Measles is responsible for three types of neurological complications. Post-infectious acute encephalitis usually occurs 3 to 10 days after rash onset, with a prevalence of 1 to 3 case patients per 1000 measles cases [115]. This presentation is associated with ADEM. As described in the following chapter, the virus is never detected in CSF samples as it is a post-infectious inflammation. Focal neurological disorders, seizures, and fever are usually reported. The infection is associated with a poor prognosis as 25% of patients die and 33% have severe sequelae [115]. The two other presentations of encephalitis are acute inclusion body encephalitis, only occurring in highly immunocompromised patients between five weeks and six months after rash onset, and sclerosing subacute panencephalitis which occurs several months after rash onset and is linked to the virus persistence within the brain [115].

Mumps virus infection presents as parotiditis, meningitis, or encephalitis in 95%, 0–10%, and 0–1% of cases, respectively [116]. Clinical signs and symptoms include fever, seizures, and consciousness disorders. Prognosis is usually favorable with a lethality of 1 to 5% and a low morbidity rate. CSF analysis reveals a predominantly lymphocytic pleocytosis with normal or slightly elevated CSF protein level, and a usually normal CSF glucose level [116]. Approximately 1 rubella patient in 6000 also presents with encephalitis. Clinical signs and symptoms are non-specific. Lethality could reach 20%, but clinical signs and symptoms are usually self-limiting after 1 to 3 weeks and do not lead to any sequelae. Diagnosis relies on plasma and CSF serology [117].

4.5. Immunocompromised patients

4.5.1. CMV

CMV encephalitis almost exclusively occurs in highly immunocompromised patients. The authors of a literature review of 676 case reports published between 1965 and 1995 reported that 85% of patients were HIV-infected, 12% presented with another form of immunodeficiency, and only 21 (3%) were immunocompetent [118]. Many documented cases of CMV encephalitis have been reported in patients who underwent allogeneic hematopoietic stem cell (AHSC) transplantation [119–124], and rare cases have also been observed in immunocompetent patients [125–127]. Diagnosis relies on CMV CSF PCR and the initial treatment should be based on the combination of foscavir and ganciclovir (class IV of evidence). This dual combination therapy seems to be associated with a better prognosis for CMV encephalitis patients [128].

4.5.2. HHV-6

The diagnosis of HHV-6 encephalitis should not be considered without first ruling out the possibility of viral genome integration within the host's chromosomes [129], defined by a high concentration of viral DNA in serum (>3.5 $\log^{10}$ copies/mL) or in whole blood (> 6.0 $\log^{10}$ copies/mL). This may lead to wrongly interpret the presence of HHV-6 DNA in CSF [130]. In cases of chromosomal integration, parts of the viral genome are massively replicated when the usual host's DNA replication occurs, without triggering infectious virus production and without any associated symptoms. Another diagnostic means of chromosomal integration consists in looking for HHV-6 genome in tissues devoid of living cells such as the hair (not hair follicles) or nails. True HHV-6 encephalitis mainly occurs in patients who underwent allogeneic hematopoietic stem cell (AHSC) transplantation [131]. For these patients, detected viral loads are far lower than those of patients in whom chromosomal integration is detected. CSF cytological analysis may be normal [132]. The main subtype of HHV-6 associated with encephalitis is HHV-6B, with predominantly limbic presentations [133]. The presence of HHV-6A in the CSF of immunocompetent patients is therefore rather indicative of chromosomal integration than true infection [131]. True encephalitis treatment is ganciclovir or foscavir [128]. Chromosomal integration should not be treated.

4.5.3. JC virus

Several studies of non-HIV-infected patients presenting with progressive multifocal leukoencephalopathy (PML) have been conducted. Their authors reported that the CSF analysis usually revealed normal cytology with rare cases of highly moderate pleocytosis, minor elevation of CSF protein level (< 1 g/L), and normal CFS glucose level [134,135]. JC CSF PCR tests have varying degrees of sensitivity depending on the techniques used (types of primers, prior centrifugation of CSF). The authors of a study of 44 non-HIV-infected patients presenting with histologically confirmed PML observed that the CSF PCR was positive in 19/44 patients (43%) [136]. When the CSF PCR is negative, diagnostic confirmation relies on genome detection by brain biopsy and on histological examination to identify oligodendrocyte destruction with nuclear inclusions of JC virus (electron microscopy) and multifocal loss of myelin. The plasma PCR test may be positive for JC virus [134]. Diagnostic confirmation requires a histological examination to be performed to look for the typical lesion of PML. These features have been observed in 20/24 of patients, including 8 deceased patients [135]. There is no effective specific treatment and only the substantial decrease in immunosuppressant drug dose may impact the functional and vital prognosis [137].

4.5.4. Cryptococcus sp.

The authors of 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 hemopathy (36%), 11 had undergone solid organ transplantation (21%), 3 presented with solid cancer (6%), and 12 with various risk factors (sarcoidosis, diabetes, cirrhosis, corticoid therapy, hypogammaglobulinemia). No underlying

immunodeficiency was identified in nine patients (17%) [138]. Central nervous system cryptococcosis cases have been reported by other authors in immunocompetent patients [139]. Signs and symptoms were non-specific in non-HIV-infected patients with fever observed in 29/53 of patients (55%), consciousness disorders or signs of focalization in 20/53 (38%), and meningitis in 20/53 (38%). The authors observed that the CSF cell count of non-HIV-infected patients presenting with CNS cryptococcosis was higher ($P < 0.05$) with a median of 82 [16–160] NC/mm^3, a moderately elevated CSF protein level at 0.9 [0.7–1.2] g/L, a frequently low CSF glucose level with a mean CSF/blood ratio of 0.35 ± 0.24 [138]. Diagnosis relied on a positive microscopic examination after CSF staining with India ink or on the detection of cryptococcal antigens by CSF analysis or culture, with 100% sensitivity for both techniques. The serum antigen test was positive in 25/29 of cases (86%); thus indicating the dissemination of the fungal infection [138].

4.5.5. Toxoplasmosis

Plasma IgG serology must be prescribed because immunodeficiency is associated with a risk of cyst reactivation and brain damage [6,34]. Diagnosis relies on an immunodeficiency context and on MRI findings. Rare encephalitis presentations without any abscesses have been reported. The toxoplamosis CSF PCR has an 86% sensitivity and 100% specificity [140,141].

4.6. Etiologies

On the basis of recent travels and criteria described in the "epidemiology" section, the following etiologies must be investigated.

4.6.1. Parasitosis

Trypanosomiasis and cerebral malaria must be considered in patients traveling back from endemic areas, even if these are not considered true encephalitis presentations [34].

4.6.2. Arboviruses

Several arboviruses must be investigated depending on the geographic area and context [142].

Serological diagnostic tools for *Flavivirus* (especially dengue, Murray Valley encephalitis, yellow fever, tick-borne encephalitis, Saint Louis or West Nile viruses) and *Phlebovirus* (Toscana virus, Sandfly fever Naples and Sandfly fever Sicilian viruses) are poorly specific. Seroneutralization must therefore be performed by the reference laboratory using the so-called "plaque-reduction neutralization test" (PRNT) technique because of cross-reaction between species. Similarly, prior vaccination against a *Flavivirus* (TBE, Japanese encephalitis, yellow fever) may compromise the serology interpretation. Detecting intrathecal immunoglobulin secretion [143,144] or using PRNT techniques may thus be required.

4.6.2.1. Japanese encephalitis. The ELISA detection method of IgM in CSF or blood samples of patients suspected of Japanese encephalitis is sensitive. In a study, most patients had antibodies at the time of hospital admission and almost all patients had antibodies three days after disease onset [145]. The PCR test may also be performed on CSF samples, but this technique is only profitable the first four days after disease onset [146,147]. The authors of a 2005 Thai study of 144 patients presenting with serologically confirmed Japanese encephalitis observed that the frequency of specific IgM detection using the ELISA test was:

- in serum: 26/44 (59%) between 1 and 4 days, 31/44 (70%) between 5 and 8 days, and 23/26 (88%) between 9 and 12 days following first symptom onset;
- in CSF: 60/66 (91%) between 1 and 4 days, and 65/66 (98%) beyond 7 days after symptom onset.

Diagnosing Japanese encephalitis by IgM detection in CSF samples is therefore a sensitive method, no matter when the initial symptoms appear, while the serological diagnosis is only reliable nine days after disease onset [148]. The authors of a literature review observed that the presence of anti-Japanese encephalitis virus IgM antibodies in CSF samples a few days after disease onset had >95% sensitivity [149].

4.6.2.2. Tick-borne encephalitis (TBE). CSF analysis often reveals pleocytosis, usually < 100 NC/mm^3, with a predominance of neutrophils at the initial phase and of lymphocytes at a later stage. Fluid is often hemorrhagic with a high CSF protein level in 80% of cases [144,150,151]. CSF IgM appear within 6 days of CNS impairment onset and disappear after 6 weeks, when IgG appear in CSF [152]. In rare cases, the CSF PCR test may be positive at the early phase of meningitis combined with encephalitis or in very rare chronic presentations [153]. Its benefit is therefore limited [151].

4.6.2.3. West Nile Virus (WNV). The CSF analysis of patients presenting with CNS impairment related to WNV reveals pleocytosis in 95% of cases, usually with < 500 NC/mm^3, a moderately high CSF protein level, and a normal CSF glucose level. CSF is often hematic, with > 50 RBC/mm^3 in 25% of cases [154–156]. Diagnosis relies on anti-WNV antibody detection (IgG and IgM) in CSF or blood samples. Detecting positive IgM in CSF samples is pathognomonic of a CNS infection as these antibodies do not cross the blood-brain barrier. IgM sensitivity in CSF is good, reported at 94% (89% if sampled < 8 days) [156], while it usually is negative in blood the first 15 days after symptom onset [157]. Antibodies remain in the CSF for a long time after the end of the infection, for more than two months in 50% of patients [155,158] and may even stay longer as specific IgM were detected in the CSF samples of three patients 110, 141, and 199 days following WNV encephalitis [159]. Viral genome detection by PCR may also be performed, but its sensitivity is lower: 57% in CSF and 14% in plasma [156]. Combining plasma PCR and serological tests helps improve diagnostic sensitivity at the acute phase of the infection, as showed in a study where plasma PCR alone had a 45% sensitivity, IgM serology alone had a 58% sensitivity, and both of these techniques combined had a 94% sensitivity [160].

4.6.2.4. Dengue virus (DV). DV-related neurological damages are varied and may be life-threatening. The authors of a retrospective study of 84 patients who died from DV infection observed that 41 patients had CNS impairment with 46.3% of encephalitis cases, 34.1% had meningitis combined with encephalitis, and 19.5% had meningitis [161]. The diagnosis was confirmed by CSF RT-PCR for seven patients, by CSF IgM detection test for 27 patients, and by CSF NS1 antigen detection test for 22 patients [161]. The authors of a Vietnamese prospective study of 21 patients presenting with DV-related neurological manifestations (including 9 encephalitis patients) observed that three patients had a CSF set pressure > 20 cm H_20, three patients had pleocytosis (> 5/mm^3), and seven had high CSF protein level (> 0.45 g/L). No patient presented with low CSF glucose level. Baseline and discharge serum serology led to establishing diagnosis in 14 and 15 patients, respectively. The diagnosis was based on CSF serology for six patients, and was confirmed by viral culture of serum for seven patients, and by CSF viral culture for two patients. Finally, the diagnosis was established by serum PCR and CSF PCR for five and three patients, respectively [162].

4.6.2.5. Murray Valley encephalitis virus. This virus is endemic in some areas of Northern Australia, in Papua New Guinea, and on the Java Island. CSF analysis usually reveals pleocytosis, a rather lymphocytic one. The diagnosis relies on the detection of viral genome by PCR, but only at the viremic phase, which lasts less than 14 days after inoculation. The CSF PCR test is usually negative. IgM appear in serum between Day 4 and Day 9. When using serological tests, a cross-reaction is observed with the other *Flavivirus*, and even with a post-yellow fever or Japanese encephalitis vaccine immunity [163].

4.6.2.6. Powassan virus (PV). Powassan virus (PV) diagnosis relies on the detection of serum or CSF specific IgM. Confirmation is usually obtained by PRNT. CSF RT-PCR may also help in confirming diagnosis [164].

4.6.2.7. Toscana virus. The CSF analysis usually reveals lymphocytic pleocytosis, normal CSF glucose level, and a moderately high CSF protein level (< 1 g/L) [165,166]. The PCR test is more sensitive than IgM detection or culture [165]. A real-time PCR technique was developed in 2011 for use in the diagnosis of Toscana virus infection, regardless of the native and/or imported nature of the virus. A new lineage of Toscana virus, different from the strain found in Italy, has indeed been observed in Spain [167]. Cell culture seems to be poorly sensitive in detecting the virus as it was only isolated from 14% of CSF samples (plated onto Vero cells) for which the PCR test was positive for Toscana virus [165].

Various bunyaviridae viruses may be considered. Multiplex RT-PCR is able to target preserved and common areas within the heterogeneous family of Bunyaviridae viruses (including 300 members). This technique has been validated for the detection of Bunyaviruses responsible for encephalitis (California encephalitis virus, La Crosse virus, Rift Valley fever virus, Sandfly fever Naples virus, Toscana virus, Sandfly fever Sicilian virus) [168]. The most common diagnostic tool is the IgM detection test in CSF samples. For La Crosse virus, the detection of anti-La Crosse virus IgM by ELISA test is enough to confirm the encephalitis diagnosis [169]. Powassan virus infection diagnosis is based on the detection of serum or CSF specific IgM. Confirmation is usually obtained by PRNT or CSF RT-PCR [164].

4.7. Specific risk exposure to zoonoses

Specific etiologies must be considered depending on the type of exposure. These rare etiologies are detailed in Table 2.

4.8. Specific cases of amoebic encephalitis

Free-living amoeba encephalitis is reported in immunocompetent and immunocompromised individuals [183]. Clinical signs are non-specific, but their evolution is usually subacute. Concomitant skin lesions are reported in >50% of cases with possible documentations on these skin lesions [184]. Most case patients have been reported in Northern or Latin America; a few anecdotal case patients have been reported in Asia, Australia, and Europe [183].

Studies reporting cases of amoebic encephalitis caused by *Balamuthia mandrillaris* or *Acanthamoeba* also reported pleocytosis (usually lymphocytic), high CSF protein level (often > 1 g/L), and low CSF glucose level [184–186]. Serology helped in establishing diagnosis, but it had limitations as results could be negative in immunocompromised patients, with cases confirmed by brain biopsy while the serology was negative [185]. Besides, in exposed patients, serology could be positive even though no sign of amoebic encephalitis was observed. The serology cut-off value was 1:64 [185]. The diagnosis is usually hard to establish and must lead to stereotactic brain biopsy with microscopic examination by hematoxylin and eosin staining in case of a positive serological test to look for cysts and trophozoite forms. Diagnostic confirmation may be done by PCR or culture [186]. When a CSF 16S RNA PCR test and a brain biopsy PCR were combined to diagnose free-living amoeba encephalitis, the sensitivity was excellent (5/5 cases with a positive PCR test on at least one of the two samples) [187]. The typical brain lesion observed in *Balamuthia* or *Acanthamoeba* amoebic encephalitis patients was a granulomatous amoebic encephalitis, although the absence of granuloma at histological examination did not rule out the diagnosis [188]. Amoeba usually looks like a ring and are located in the perivascular space of brain vessels [185].

Naegleria fowleri is an amoeba responsible for meningitis combined with encephalitis in immunocompetent patients, following fresh water swimming. Clinical signs and symptoms are similar to those of fulminant and usually fatal hemorrhagic encephalitis [189,190]. Cases have been reported in the United States, South America, South-East Asia, Africa as well as in Turkey and Italy [191,192]. The diagnosis relies on CSF analysis revealing pleocytosis and high CSF protein level that may sometimes be above 5 g/L. Microscopic examination may yield free-living amoeba. Diagnostic confirmation of *Naegleria fowleri* infection may be done by immunofluorescence technique

Table 2
Causative agents by animal exposures and diagnostic tests.
Pathogènes impliqués en fonction des expositions animales et tests diagnostiques.

Animal	Causative agents	Diagnostic tools	Sensitivity	Specificity	Comments	References
BatsDog bite	*Lyssavirus*	Saliva RT-PCR Biopsy of the neck skin	63.2% 98%	70.2% 98.3%	100% sensitivity if 3 successive saliva samples	[145,170]
Cats	*Bartonella henselae*	Plasma serology Brain biopsy PCR	NS	NS	<2% of *Bartonella* infections with neurological presentation	[171–174]
OvineBovine	*Coxiella burnetii*	Plasma serology	NS	NS	Rare cases reported	[71,175,176]
	Brucella	Plasma serology CSF serology Blood cultures CSF cultures	75% 77% 25% 29%	NS NS NS NS	Sensitivity measured based on a sample of 215 patients presenting with meningitis combined with encephalitis or *Brucella* meningitis	[78]
Ticks	*Rickettsia*	Plasma serologies Blood PCR	NS NS	NS NS	Seroprevalence of 11–26% in endemic areas Appearance of antibodies between Day 7 and Day 15	[177]
	Borrelia	Plasma serology CSF serology	∼100% ∼100%	WB WB	Rare encephalitis presentations	[178]
Game	*Francisella tularensis*	Plasma serologies CSF PCR	NS	NS	Rare cases of encephalitis or rhombencephalitis reported	[2,179]
Rats	Leptospirosis	Urine PCR Serologies	NS NS	NS NS	Meningitis in 5–18% of cases Encephalitis cases less frequently observed	[180–182]

RT-PCR: reverse transcriptase polymerase chain reaction; CSF: cerebrospinal fluid; WB: western blots; NS: non-significant.

with anti-*N. Fowleri* antibodies, or by molecular biology using a specific PCR test.

4.9. Should autoimmune causes be considered?

Autoimmune encephalitis and paraneoplastic encephalitis are caused by the presence of an antibody targeting CNS antigens that may be common to antigens expressed by a tumor tissue. Clinical presentations are non-specific and may mimic all symptoms of infectious encephalitis, although some clinical presentations, such as anti-NMDA-R antibody encephalitis, have specific presentations. Knowledge on this topic is rapidly growing and reference centers need to work together in that respect. New specific presentations of new antibodies are regularly being reported (such as anti-GABA receptor antibody encephalitis responsible for status epilepticus, reported in 2014 [193]).

The immunoglobulin class of autoantibodies targeting neuronal membrane receptors is associated with specific clinical presentations. All antibodies associated with autoimmune encephalitis are of the IgG class. The detection of IgA or IgM antibodies targeting these antigens has poor diagnostic or clinical significance [194–196]. For instance, although IgG antibodies against NMDA-R GluN1 are specific to anti-NDMA-R encephalitis (anti-N-methyl-D-aspartate receptor), up to 10% of healthy subjects have anti-NMDA-R serum IgA or IgM antibodies [194].

CSF detection of antibodies is therefore fundamental because:

- except for a few rare cases of anti-LGI1 and CASPR2 antibodies, all encephalitis cases are associated with the presence of CSF antibodies. Relevant antibodies, absent from serum, are also frequently detected in CSF [197];
- for anti-NDMA-R antibody encephalitis, for instance, CSF antibody levels are better correlated with clinical evolution than serum concentrations [197];
- detection techniques of serum antibodies induce an important background noise which is hard to interpret, and may trigger false positive results [194,198].

However, the background noise is insignificant in the CSF.

Only anti-NMDA-R antibody encephalitis is described in the present article as it is the most frequent and best characterized type of encephalitis.

Anti-NMDA-R encephalitis: typical clinical signs and symptoms are those of a combination of psychiatric disorders, seizures, and consciousness disorders [199,200]. The authors of a monocentric study have reviewed 505 charts of patients aged 18 to 35 years admitted to the intensive care unit (ICU) during a 5-year period for encephalitis without causative agent. Serum and CSF samples of patients presenting with a combination of psychiatric disorders, seizures, and meningitis were retrospectively analyzed for NMDA-R antibodies. Six patients out of seven had CSF anti-NMDA-R antibodies with a specific cytopathogenic effect [201]. CSF antibodies must be looked for as approximately 3% of false negative results are observed in serum [200].

Retrospective studies on anti-NMDA-R encephalitis reported lymphocytic pleocytosis in >90% of cases [200,202,203], an inconstantly high CSF protein level (usually < 1 g/L), and CSF oligoclonal band in 36–67% of cases. CSF serology performed to detect anti-NMDArR antibodies is very sensitive [197,202,204], and more specific than that performed in serum. These antibodies have a specific cytopathogenic effect. Immunocytochemical analysis of cells that have been transfected to express the antigen of interest is usually performed (e.g., GluN1 – NMDA receptor subunit). This test is usually performed in a cell lineage of human kidney (HEK cells) [202].

The authors of a 2012 retrospective study included 44 patients presenting with PCR-confirmed HSV encephalitis. They detected anti-NDMA-R IgG, IgA, and IgM antibodies able to modify the *in vitro* expression of synaptic proteins in the CSF or serum samples of 13 patients (30%). These antibodies have not been identified in control patients (VZV and EV encephalitis). Authors hypothesized that CNS infections could trigger the production of these antibodies [205].

4.10. Should post-infectious causes be considered? Cases of acute disseminated encephalomyelitis (ADEM)

The typical clinical presentation of ADEM is acute neurological symptoms occurring 2 to 30 days after a viral or bacterial infection, or following vaccination. Symptoms are varied and combine consciousness disorders that may lead to coma, and signs of focalization (77–85% of cases) or seizures (4–30% of cases). Patients sometimes present with fever (15–70% of cases).

The pathophysiology is probably an autoimmune response against a myelin antigen triggered by the infection or the prior vaccination. Patients present with abnormalities on brain or spine MRI with multiple demyelinating lesions in hypersignal T2 and FLAIR sequences, usually showing contrast enhancement following gadolinium injection. There is no predefined diagnostic criteria; differentiating an initial flare of multiple sclerosis from ADEM is thus difficult [206]. Retrospective studies of ADEM reported a normal CSF in less than 20% of cases. Authors reported moderate pleocytosis (50–90 NC/mm^3) with a predominance of lymphocytes, high CSF protein level between 0.6 and 1.3 g/L, and intrathecal secretion of immunoglobulins in 37.5 to 58% of cases [64,207,208].

ADEM has multiple etiologies with post-infectious etiologies observed in 42 to 72% of cases, and with post-vaccine etiologies [64]. Although the time relation between the infection and ADEM onset has already been proven, pathogens are never detected on neurological specimens (negative CSF PCR, negative brain biopsy), except for a few cases of EBV or *Mycoplasma pneumoniae* infection [209,210]. The authors of a 2005 literature review presented the main causes of ADEM. The main viral causes are measles with 100 ADEM patients per 100,000 measles case patients, and rubella and VZV (10 to 20 ADEM patients per 100,000 infections). ADEM cases have been reported at the end of infections caused by *Coronavirus*, Coxsackie, Dengue, EBV, HAV, HCV, HIV, HHV-6, mumps, and parainfluenza viruses. Some authors reported cases of ADEM after HSV encephalitis. Cases have also been reported after bacterial infections (*Borrelia burgdorferi*, *Chlamydophila* sp., *Legionella* sp., *Mycoplasma pneumoniae*, *Rickettsia rickettsii*, *Streptococcus* sp.) as well as a few days after the following vaccinations: measles (0.1 cases per 100,000 vaccinations), mumps (0.6 to 1.4 cases per 100,000 vaccinations), pertussis (0.9 cases per 100,000 vaccinations), and Japanese encephalitis (0.2 cases per 100,000 vaccinations) [64].

5. Conclusion

The diagnostic and therapeutic management of patients presenting with encephalitis without any documented etiology following first-line tests must take into consideration the potential main causes of the infection, their diagnostic tools, and the potential treatments. Etiological investigations must be guided by recent travels, animal exposures, age, immunodeficiency, neurological damage characteristics, and potential extra-neurological signs. When investigations cannot be comprehensive, physicians should keep in mind all possible etiologies for which a specific intervention is indicated, whether it is curative treatments (tuberculosis, encephalitis caused by intracellular bacteria, autoimmune encephalitis) or preventive treatments (patient isolation, close contact vaccination). The benefit of a diagnosis of encephalitis that does not require the administration of a specific treatment is also to discontinue any empirical treatments initially prescribed.

Disclosure of interest

The authors declare that they have no competing interest.

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