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General review

Management of adult infectious encephalitis in metropolitan France

Prise en charge thérapeutique des encéphalites infectieuses de l'adulte en France métropolitaine

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Abstract

Infectious encephalitis is a severe disease leading to a high mortality and morbidity. The most frequent causes include *Herpes simplex* virus, Varicella Zoster virus, *Listeria monocytogenes*, and *Mycobacterium tuberculosis*. Urgent treatment is required (anti-infective therapy and nonspecific supportive care). The aim of this study was to define treatment strategy, empirical and after microbiological documentation at 48 hours, through a systematic literature review.

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

Résumé

L'encéphalite infectieuse est une maladie grave pouvant être responsable d'une morbi-mortalité importante. Les étiologies les plus fréquemment rencontrées sont le virus *Herpes simplex*, le virus varicelle-zona, *Listeria monocytogenes* et *Mycobacterium tuberculosis*. Sa prise en charge thérapeutique réalisée en urgence se doit d'être adaptée à l'épidémiologie et comporte des traitements anti-infectieux, symptomatiques et adjuvants. Le but de ce travail est de faire le point sur la stratégie thérapeutique immédiate (probabiliste) et après 48 h quand le diagnostic est documenté, à la lumière de la revue systématique de la littérature.

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

1. Introduction

Encephalitis is an infectious or non-infectious central nervous system disorder, with various presentations and levels of

severity. Encephalitis is associated with a high morbidity and mortality. Infectious encephalitis combines neurological symptoms, indicative of brain parenchymal damage, with nonspecific symptoms (mainly fever). Encephalitis onset is usually acute or subacute.

Rapid treatment initiation is required because of the potential severity of encephalitis. The various presentations and the sometimes hard-to-establish diagnosis, especially when confronted with bacterial meningitis, stress the need for an urgent, optimal, and standardized management.

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Clinical practice guidelines (CPG) have thus been drafted under the aegis of the French Infectious Diseases Society (French acronym SPILF), collectively with other scientific societies.

We aimed to summarize literature data on the initial (most often empirical) and secondary therapeutic management of infectious encephalitis when its cause has been identified. This document is not intended as guidelines; it does not necessarily represent the authors' views. It is rather a factual literature analysis allowing readers to appraise literature data.

2. Material and methods

We performed a literature search in December 2014 using several databases (PubMed and The Cochrane Library). We searched for articles published over a 10-year period. We also included original articles or articles published before 2004 that we deemed important. We first performed a general search using the keyword “encephalitis”, combined with “infectious”, “viral”, “diagnosis”, “guidelines”, “treatment”, and “management” (MeSH terms). We then looked for the most frequent causes of encephalitis using the search terms “herpes virus” (including HSV, CMV, VZV, HHV6, EBV), “enterovirus”, “arbovirus”, “influenzae”, “measles”, “HIV”, “Japanese encephalitis”, “tick-borne”, “West Nile virus”, “mycoplasma”, “*Listeria* OR listeriosis”, “*Borrelia burgdorferi*”, and “tuberculosis or mycobacteria”. Treatment-related terms were associated with the search words when needed: “acyclovir”, “amoxicillin”, “aminoglycosides”, “gentamicin”, “steroids”, “hypothermia”, “intracranial hypertension”, “status epilepticus”, “epilepsy”, “anticonvulsant”, “decompressive craniectomy”. Specific searches were performed on areas of interest. Encephalitis in immunocompromised patients, especially in HIV-infected patients, was not specifically addressed. To avoid compromising the completeness of our analysis, we did not consider this an exclusion criterion. We assessed all prospective studies (clinical trials, meta-analyses, comparative studies, observational studies) and gave priority to the most informative ones using the GRADE approach [1]. We only took into consideration studies with evidence-based data (grade A = level 1: well-powered comparative studies, meta-analysis of randomized comparative studies, and grade B = level 2: low-power comparative studies, well-conducted non-randomized comparative studies, cohort studies). We also took into consideration a few retrospective studies and case-series when other articles on the same field of interest were not available (grade C = level 3). We also included literature reviews. We did not take into consideration reports of a single or a few isolated cases of infectious encephalitis. Experimental studies were not included in the analysis, except for the evaluation of antibiotic therapy prescribed for neuroinvasive listeriosis. Finally, we only used articles written in English or French.

3. Results

3.1. Initial therapeutic management (first 48 hours)

Initial management must be implemented as soon as the infectious encephalitis diagnosis is suspected based on the following

criteria: clinical signs and symptoms, imaging results, CSF, and EEG. Treatment must be initiated rapidly. Physicians must concomitantly assess the severity of the infection and decide on the hospitalization ward (ICU or medical), anti-infective treatments, symptomatic treatments, and even on adjuvant treatments.

3.1.1. Initial hospitalization ward

Although the hospitalization ward of patients suspected of encephalitis has never been studied, hospitalization is the standard approach. The choice of hospital ward is jointly decided by emergency physicians or infectious disease specialists or neurologists and intensive care unit (ICU) physicians. Fifty percent of encephalitis patients have to be admitted to the ICU, at least temporarily [2,3].

Patients presenting with:

- severe neurological damage (at least two seizures or status epilepticus; Glasgow score < 13);
- other organ failures (shock, respiratory distress syndrome, etc.);
- behavior disorders preventing hospitalization in a standard unit must be hospitalized in the ICU or in a continuous monitoring unit.

Less severe patients suspected of encephalitis must be hospitalized in a medical ward with a continuous monitoring capacity, because of the risk of complications (mainly neurological) especially in the early course of the disease.

3.1.2. Initial anti-infective treatment

The potential severity of some infectious encephalitis requires the urgent initiation of an empirical anti-infective treatment. The benefit of an early treatment on mortality has already been confirmed, especially for herpes simplex virus (HSV) encephalitis [4,5]. An anti-infective treatment active against the most frequent causative agents of infectious encephalitis (HSV, Varicella zoster virus [VZV], *Listeria monocytogenes*) must be immediately initiated after blood culture and lumbar puncture have been performed to rule out purulent meningitis (clear fluid, negative Gram-staining direct examination). When the CSF is turbid or when a bacterial meningitis partially treated with a previous antibiotic therapy is suspected, the initial treatment must take into consideration the likelihood of bacterial meningitis, as per guidelines issued by the SPILF [6]. As for other cases (clear fluid), the first-line empirical treatment must include IV acyclovir 10 mg/kg/8 hrs and amoxicillin 200 mg/kg/day divided into 4 to 6 injections or as a continuous administration following a 30-minute IV loading dose of 2 g

When VZV encephalitis is suspected (suggestive skin lesions observed in 50% of cases, immunocompromised patients, vasculopathy detected on imaging), physicians may consider increasing the IV acyclovir dosage to 15 mg/kg/8 hrs as described below in Section 3.2.2. Dosages are detailed in Table 1.

3.1.3. Symptomatic and adjuvant treatments

Just like for any other brain damage, secondary neuronal damage must imperatively be prevented. This is particularly

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