Review Article

Childhood encephalitis: what’s new?

Abstract
Encephalitis is a severe form of a neurological disease caused by an inflammation of the brain parenchyma associated with evidences of neurologic dysfunction, which courses with non-specific CNS symptoms. The frequency of this condition is higher in children, presenting in this age group a great potential of severity, in addition to higher risks of morbidity and mortality the younger the affected child. The etiology can be infectious or autoimmune; in about half of the cases of acute encephalitis during childhood, however, a definitive cause will not be found.

Objective: To accomplish an epidemiology, diagnostic methods and treatment review about childhood encephalitis.

Methods: Studies were made in June to October 2017, and was constituted by the search of the key-words “encephalitis”, “childhood”, “autoimmune encephalitis”, “viral encephalitis”, “meningoencephalitis”, “etiology” and “epidemiology” from articles published in English and Portuguese in the years of 2004 until 2017, thus being selected 23 articles, accordingly to the relevance of the information presented.

Theory: Encephalitis is a potentially lethal neurologic syndrome, that affects children around the world, and can be caused by infectious processes, autoimmune conditions, or can still be from unidentified etiology in most of the cases. The diagnoses can be difficult for the rapid progression, the non-specific symptoms and vast possibilities of etiologic agents. It is a condition that presents itself with elevated potential of death and permanent sequelae, mainly in younger children.

Conclusion: Encephalitis is a serious disease, which can bring grand repercussions in children’s health, such as development retardation, behavioral abnormalities and direct neurologic damage. Considering this issues, it is indispensable the correct diagnostic and quick therapeutic approach from the child suspected to be in this condition.

Keywords: encephalitis, childhood, autoimmune encephalitis, viral encephalitis, meningoencephalitis, etiology and epidemiology

Abbreviations: VZV, varicella zoster; JEV, japanese encephalitis virus; TBEV, tick-borne encephalitis

Introduction
Encephalitis is a potentially fatal neurological syndrome affecting children worldwide, and is defined by the presence of cerebral inflammatory process associated with clinical evidence of neurological dysfunction. Initial presentation of childhood encephalitis may include seizures, headache, paresis, vision loss, hearing problems, and behavioral changes. This syndrome can be caused by infectious processes or autoimmune conditions, although the etiology may remain unidentified in a considerable part of the affected population. The difficulty in diagnosing this disease is due both to the rapid progression of encephalitis and to the similarity of its clinical characteristics with those of other pathologies. Another complicating factor would be the wide variety of etiologic agents that cause acute encephalitis, few of which respond significantly to the treatments used Ramanj et al. Although there is no definitive treatment in many cases of encephalitis, the identification of the etiologic agent involved is extremely important for the definition of prognosis, potential prophylaxis, family counseling and possible public health actions. According to Tunkel et al., there are some clues that may help direct the investigation, such as season, geographical location, prevalence of disease in the community, travel history, occupational exposure, contact with an insect or other animal, vaccine history, and immune status of the patient. The high morbidity and mortality rate associated with the disease results from infection caused by highly neurological virulence microorganisms, or even directly from immunomediated damage.

Considering the high potential for death and permanent sequelae, especially in younger children, the aim of this paper is to make an updated review of the available literature on childhood encephalitis, bringing data on etiology and epidemiology, clinical characteristics and diagnostic methods, showing the existing therapeutic options and prognosis after appropriate treatment.

Methodology
The present work was elaborated from a review of the available literature on the subject, using PubMed, Scielo and Medline online databases. The search included articles in English and Portuguese between 2004 and 2017. The keywords initially used were “encephalitis”, “childhood” and their English correspondents, “encefalitis” and “childhood”. Subsequently, the words “autoimmune encephalitis”, “viral encephalitis”, “meningoencephalitis”, “etiology” and “epidemiology” were included, as well as their English correspondents, “autoimmune encephalitis”, “viral encephalitis”, "...
mengoencephalitis”, “aetiology” and epidemiology. Then 23 articles were selected according to the relevance of the information presented there. The exclusion criterion used was the date of publication of the articles, excluding materials published before 2004.

**Discussion**

**Definition**

The term encephalitis refers to inflammation of the brain parenchyma, and implies the need for histopathological examination to define the diagnosis. However, what occurs in clinical practice is the deduction of pathology from symptoms of central nervous system dysfunction associated with fever and/or inflammatory signs in CSF and/or inflammatory signs in CNS imaging. According to the International Encephalitis Consortium, defining a case of encephalitis requires the patient to meet the highest criteria (presence of altered mental state-defined as alteration or decrease in level of consciousness, lethargy, or personality change- lasting), more than 24 hours), plus 2 minor criteria for possible encephalitis and 3 or more for probable or confirmed encephalitis. Among the smaller criteria we can highlight:

A. Documented fever greater than or equal to 38°C 72hours before or after symptom onset;
B. Partial or generalized seizures not attributed to previous conditions;
C. Emergence of focal neurological symptoms;
D. WBC count greater than or equal to 5/mm³;
E. Abnormalities in the brain parenchyma or neuroimaging suggestive of encephalitis that did not appear in previous or acute onset studies;
F. EEG abnormalities that are consistent with encephalopathy and are not attributed to other causes.

**Epidemiology**

The annual incidence of encephalitis is 5-10 cases per 100,000 inhabitants, occurring more frequently in children and the elderly. In industrialized countries, HSV encephalitis is the most diagnosed, with an annual incidence of 1 case per 250,000-500,000. According to Jain et al., several studies conducted in India, Kuwait and European countries reported a high prevalence of enterovirus encephalitis, reaching 22% in endemic areas. In the case of children, the incidence of encephalitis is more difficult to establish, as studies have used different criteria for case definition, different methodologies and different population groups. Still, there are reports of an incidence of approximately 10.5 cases per 100,000 children in the West. The rate of children hospitalized for encephalitis-related causes is around 3 to 13 admissions per 100,000 children per year, and the incidence rates are even higher in children under 1 year of age.

**Etiology**

The causes of encephalitis can be categorized as infectious, autoimmune (or inflammatory) or of unknown cause.

**Infectious causes**

More than 10 different infectious agents have been linked as causing encephalitis. Among these agents, viruses are the most frequently identified etiology. Bacteria, fungi and parasites can also be identified as causing encephalitis, but noticeably less frequently than viruses. In most cases, encephalitis is an uncommon manifestation of an infection, and the patient’s age, geographical location, immunization status, and vaccination status will be the most important determinants of the spectrum of infectious etiology. Globally, the 3 most common causes of infectious encephalitis in children are HSV, Varicella Zoster (VZV) and enterovirus. In immunocompetent hosts, EBV encephalitis and adeno virus occur almost exclusively in children. Immunocompromise related to HIV/AIDS or after transplantation and chemotherapy is associated with reactivation of potentially encephalopathic latent infections such as CMV, EBV, HHV-6, as well as increased susceptibility to opportunistic pathogens such as toxoplasma and cryptococci. In adults, about 70% of HSV-1 encephalitis cases already have antibodies. In children, in turn, HSV-1 encephalitis occurs during primary infection. HSV-2 encephalitis occurs in only 10% of cases of HSV encephalitis, typically occurring in immunocompromised individuals and neonates with generalized infection.

Some arboviruses are of great medical importance around the world. The Japanese Encephalitis Virus (JEV) is the leading cause of mosquito-borne encephalitis globally; Tick-borne encephalitis (TBEV) is the most common arthropod-transmitted viral infection in Europe; Nile virus (WNV) is reemerging as a major cause of encephalitis in the United States and Europe. The recognition of dengue and Chikungunya as causes of neurological complications has been increasing worldwide. Among children, La Crosse virus continues to be the leading cause of encephalitis in the United States.

**Immunomediated causes**

Autoimmune encephalitis can be recognized in up to one third of cases and can often be treated. These syndromes have a broad clinical spectrum, ranging from typical limbic encephalitis to syndromes with complex neuropsychiatric symptoms, and some clinical signs may lead to suspicion of autoimmune causes, including subacute and often fluctuating onset of symptoms such as memory and cognitive deficits, psychosis, seizures, abnormal movements and coma. Among the subtypes of immune-mediated encephalopathies are disseminated acute encephalomyelitis (ADEM), acute hemorrhagic leukoencephalopathy (AHLE), antibody-mediated encephalitis. Acute disseminated encephalomyelitis is a demyelinating inflammatory condition of the CNS, presenting a well-defined histopathology. Its symptoms include encephalopathy and multifocal neurological deficits and is the most common in children, with an average age range of 5-8 years old, with a slight predominance in males. Temporal relationship with infection or previous vaccination can often be identified. Magnetic resonance imaging plays a central role in the diagnosis, showing multiple lesions, asymmetrically distributed, involving subcortical, central and periventricular white matter, and deep gray matter.

Acute hemorrhagic leukoencephalopathy can be considered a hyperacute form of ADEM, however it is rare and there is a probable overlap with CNS vasculitis. Antibody-mediated encephalopathy is being identified more frequently. The most important subtypes are anti-NMDA-R antibody encephalitis, anti-VGKC complex encephalitis, and anti-GABA antibody encephalitis. Anti-NMDA-R antibody encephalitis has been shown to be a leading cause of encephalitis in recent prospective studies, and is the most commonly described autoimmune-associated encephalitis in children. It typically presents with psychiatric symptoms, seizures, memory loss...
and mutism. Encephalitis with anti-VGKC complex antibodies may include a broad clinical spectrum. In children, it presents with symptoms of focal temporal lobe seizures, status epilepticus, encephalopathy (behavioral change, hallucinations) and cognitive decline. Patients with anti-GABA receptor encephalitis develop rapidly progressive encephalitis with refractory seizures, status epilepticus, and/or continuous partial epilepsy. About 50% of reported cases occurred in children.

### Diagnosis

Patients with classic signs of viral encephalitis present with high fever, headache, vomiting, and alterations in the level of consciousness, which may be associated with focal neurological signs. In younger children, the definition of encephalopathy may be more difficult. Persistent irritability, lethargy, decreased interest in food are the main warning signs, and the presence of such symptoms should alert health professionals to the need for investigation. Physical examination should include assessing the level of consciousness and actively searching for subtle signs of seizures, meningism, abnormal movements, weakness, sensory loss, and cranial nerve involvement. Vital signs should be checked, the skin should be examined, and the gastrointestinal, respiratory and cardiovascular tracts should be evaluated. The presence of rash or other skin lesions, as well as lymphadenopathy or hepatomegaly may be clues to the definition of encephalitis etiology. Tremors or other abnormal movements may indicate involvement of the basal ganglia, common in WNV or toxoplasmosis infection. Upper limb weakness and fasciculation suggest arbovirus-caused cervical myelitis. Cranial nerve neuropathy associated with acute onset febrile encephalopathy with myoclonus may occur in the presence of enterovirus or listeria infection. Signs of autoantibody-mediated encephalitis include absence of fever, subacute progression, prominent psychiatric and cognitive disorders, and movement disorder.

CSF examination plays a central role in the diagnosis of encephalitis and should be collected as soon as possible unless clinically contraindicated. Cell count, bacterial and biochemical culture, PCR should be performed, and when available, other biological markers of inflammation in the CNS should be used, such as oligoclonal bands. Blood cultures should be collected prior to the empirical onset of antibiotics and HIV serology and treponemal testing should be performed. Autoantibody-mediated encephalitis can be diagnosed by detecting antineuronal antibodies in the serum or CSF, which has greater specificity. However, not all patients with autoimmune encephalitis have specific antibodies on exams, and this absence of antibodies does not exclude the autoimmune mechanism. In these cases, the suspicion of immunomediated etiology should be suspected in the presence of subacute progressive neurological syndrome, presenting the clinical characteristics already mentioned, and considering that adolescents and young adults are more likely to develop behavioral and psychiatric symptoms, while children have more commonly choreoathetosis, and/or orofacial dyskinesias.

Imaging should be performed in all patients, and MRI is the modality of choice because of its high sensitivity regarding the inflammatory changes characteristic of encephalitis. Chest x-ray should be performed to detect associated lung disease such as tuberculosis or cryptococci, for example. Electroencephalogram is very sensitive, but not specific, having great importance in patients with chronic symptoms and in those with psychiatric manifestations.

### Treatment

Empirical use of antimicrobials and supportive measures are the cornerstones of viral encephalitis therapy in children and adolescents. Initial supportive measures include cardiorespiratory stabilization, seizure control, fluid replacement, hydroelectrolytic balance, nutritional support, and prevention of nosocomial infections. The Glasgow Coma Scale, although not validated for non-trauma patients, can be of great help in monitoring the patient’s level of awareness. Signs of worsening neurological status indicate new imaging tests to assess cerebral edema, hemorrhage, or other acute changes. For infants after the neonatal period who are clinically suspected of encephalitis, immediate initiation of intravenous acyclovir therapy is recommended until viral test results are known. If HSV PCR is positive, acyclovir should be continued for 21 days. At the end of treatment, the lumbar puncture should be repeated. If it remains positive, acyclovir therapy should be continued. Empirical antibiotic therapy should be initiated in cases of suspected meningitis or sepsis. In pediatric viral encephalitis, routine use of adjunctive therapies such as glucocorticoids, plasmapheresis, intravenous immunoglobulin, interferon alfa, and therapeutic hypothermia is not recommended.

In cases of autoimmune encephalitis, other therapeutic options may be explored. In the treatment of ADEM corticosteroids are used, although there is a lack of high level evidence for this. In the case of encephalitis with anti-NMDA-R antibodies, in turn, there is moderate evidence supporting immunomodulation therapy.

### Prognosis

Several pediatric studies report a mortality rate of less than 10%, but over 50% of these patients should have significant neurological and behavioral sequelae. The most commonly reported sequelae are developmental delay, behavioral abnormality, intellectual deficit, and neurological damage (seizures, for example). Pediatric patients after encephalitis with anti-NMDA-R antibodies are more likely to have long-term disabilities, while adult patients apparently return to their normal functions. Markers of disease severity, such as coma at presentation, ICU admission, mechanical ventilation and longer hospital stays, are associated with more severe sequelae and higher mortality. Other poor prognostic factors include encephalitis in newborns and infants, HSV-1 encephalitis, HSV-2, Mycoplasma pneumoniae, ECG <6, delayed initiation of treatment, and absence of EEG improvement. Malnutrition and need for ventilatory support within the first 48 hours after admission also proved to be independent predictors of adverse outcomes.

Encephalitis patients with anti-NMDA-R antibodies are at risk of relapse, which occurs in 15-24% of cases, sometimes after many years. Studies have shown that relapses occur more frequently in patients who did not receive immunotherapy at initial presentation.

In general, the various types of encephalitis have a permanent effect on the quality of life and well-being of most survivors. It is necessary to identify the etiology and initiate therapy and support quickly and effectively in an attempt to minimize these effects.

### Final considerations

Encephalitis is an inflammation of the brain parenchyma and requires histopathological examination to determine the diagnosis. However, in clinical practice the diagnosis may be given by the presence of symptoms of central nervous system dysfunction.
associated with fever and/or inflammatory signs in the CSF and/or inflammatory signs in CNS imaging. Ideally MRI should be performed in all patients because of its high sensitivity to the inflammatory changes characteristic of encephalitis. Treatment involves the use of antimicrobials empirically and the use of supportive measures, and the use of adjunctive therapies such as glucocorticoids, plasmapheresis, intravenous immunoglobulin, interferon alfa and therapeutic hypothermia is not recommended for the pediatric age group. Encephalitis has social repercussions, as more than half of patients should have significant neurological and behavioral sequelae. Among the most common we can report developmental delay, behavioral abnormality, intellectual deficit and neurological damage. Thus, due to the permanent effect on the patients’ quality of life and well-being, the correct diagnosis and rapid therapeutic approach aiming at minimizing the possible sequelae is essential.

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Conflicts of interest
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References