Research Article

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Epidemiological Characteristics of Herpetic Meningoencephalitis in Children

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ABSTRACT

Encephalitis is an inflammatory process of the brain parenchyma that can be caused by an infection that, if it spreads to the meninges, triggers what is known as meningoencephalitis. In the pediatric population, Herpes Simplex Virus types 1 and 2 (HSV 1, HSV 2) are the main etiological agents involved due to their great ability to migrate to the nervous system, as well as the generation of immunosuppression and latency periods with subsequent reactivation. The peak of infection occurs frequently in children under 6 months of age or in those between 3 and 5 years of age, with the presence of temperature rises, altered state of consciousness, meningeal signs, and seizures as main clinical manifestations. There are diagnostic criteria that allow an approximation to be made, however it must be taken into account that in case of any medical suspicion a lumbar puncture should be carried out as a priority with gram staining, cytochemical and PCR studies, clarifying that the latter must be carried out after 72 hours after the onset of the clinical picture and emphasizing that nuclear magnetic resonance with gadolinium is the imaging study of choice due to the easy identification of early changes in the brain and meningeal parenchyma. Finally, it is important to mention that it is a condition with a high burden of morbidity and mortality, so once the diagnosis has been established and taking into account the epidemiological characteristics already mentioned.

KEYWORDS: Encephalitis; Meninges; Meningoencephalitis; Herpes simplex virus; Immunosuppression; Morbidity and mortality

INTRODUCTION

Encephalitis is an inflammatory process that affects the brain parenchyma and secondarily produces inflammation of the meninges (meningitis), which together is known as meningoencephalitis. The most common etiology is of viral origin through the Herpes Simplex Virus type 1 and type 2 [1-3], however,

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it is important to mention that it is also associated with cases of infections of other viruses belonging to the herpesviridae family, such as Varicella zoster (VZV), Epstein Barr (VEB), cytomegalovirus (CMV) and human herpes 6 (HHV 6) [4] as well as high rates of neuropsychological dysfunction, especially in the pediatric population. The Herpesviridae family is made up of a total of 3 subfamilies known as alphaherpesvirinae, betaherpesvirinae and gammaherpesvirinae [5]. The herpes simplex virus (belonging to the alphaherpesvirinae subfamily) is an enveloped double-stranded DNA virus (HSV-1 and HSV-2) that has the ability to infect the central nervous system and generate neurovirulence [6]. It is estimated that this virus can encode up to 70 genes and that it has an icosahedral capsid of 125 nm in diameter with a surface covered by a lipid bilayer that includes up to 11 glycoproteins, of which at least 10 are involved in viral replication [7]. The mechanism by which the virus infects the brain is not clear, however, it is considered that for an infection to occur there must be contamination in an exposed site (skin or mucosa) where viral replication occurs and is subsequently transported to the CNS, predominantly to neural ganglia [6]. Therefore, these viruses usually present double tropism. In addition to this, a particular characteristic of the viruses in this family is the ability to generate latency because it is usually housed in the periphery where the viral genome is stable, waiting for reactivation and subsequent transport through the neuronal synapse [5].

Regarding the pathophysiology, the infection begins with the union of the viral membrane and the membrane of the host cell with subsequent fusion of the virion to it; 4 glycoproteins (B, D, H, L and C) are involved in this process, which bind to different receptors in the host cell (heparan sulfate, nectin 1 or HVEM) allowing better anchoring and fusion of the virion. After this, the capsid is transported towards the nucleus by microtubules and through nuclear pores, where it enters to initiate the replication of early genes that inhibit the antiviral response of the cell, as well as the assembly of proteins to form the viral capsid. The dissemination of this virus is carried out through cell-cell interactions by which they not only infect other adjacent cells but also cells of the immune system such as T lymphocytes [5]; (Figure 1).

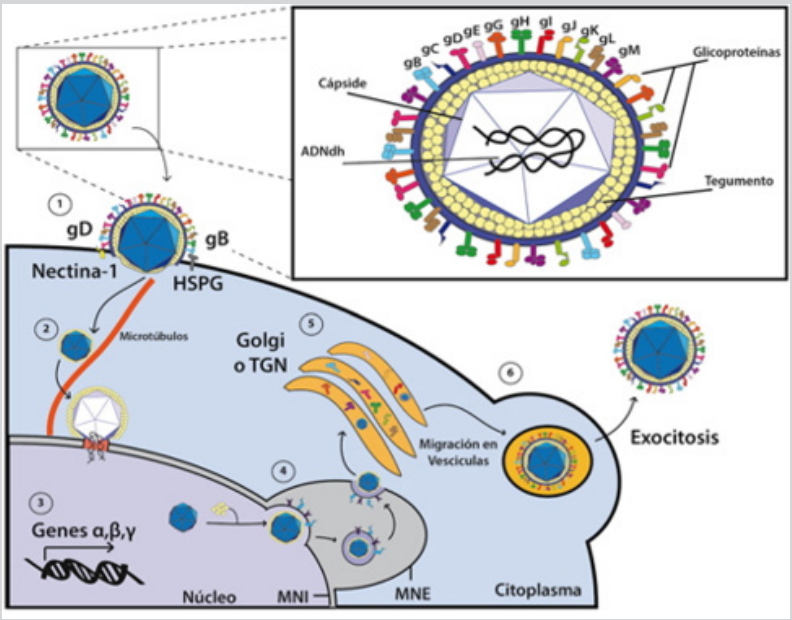

Figure 1: Pathophysiology of viral infection.

As previously mentioned, this virus can remain latent in neural ganglion cells and for infection to occur in neurons there must be contact between epithelial cells and exposed nerve terminals at the site of infection from where the virus will migrate retrograde. down the axon to the neuronal soma. Although the exact mechanisms involved in reactivation are unknown, it has been shown that they are usually associated with cell damage induced by processes that suppress latency proteins, promoting viral replication again, such as hypoxia or apoptosis, hypo/hyperthermia, radiation and fatigue [7,8].

Another of the special characteristics of the viruses in this family is the ability to effectively evade the immune system through different mechanisms. The first of these is the inhibition of the innate immune system through interferon-mediated response evasion through the VHS viral structural protein that degrades the host's mRNA, preventing the translation of antiviral elements; In addition to this, the VHS protein, the ICP0, ICP27 gene and the PKR molecule are capable of suppressing the detection of the viral double strand and the type I interferon, IFN 3 and IFN2A pathways, thus inhibiting the detection of viral DNA in the molecules. antivirals and increasing the viability of the virus [9]. The second mechanism by which the virus evades the innate immune system is the blocking of apoptosis from glycoproteins called J and D, which prevent cell death through cytotoxic granules or by Fas/FasL. Additionally, there are studies that support that HSV, especially type 1, is capable of inhibiting the presentation of CD1d on the surface of host cells in order not to be recognized by natural killer (NK) cells (Figure 2); [2, 3].

The third evasion mechanism of the defense system involves the adaptive immune system, since it has been established that viruses of the herpesviridae family are capable of evading the function of antibodies and T cells by means of glycoprotein E, which interferes with the effector capacity of IgG by binding to the crystallizable fragment avoiding the action of complement and phagocytosis via receptors. Associated with this, it has also been shown that HSV 2 is capable of inducing apoptosis in dendritic cells, preventing their role in the activation of T lymphocytes and that the HSV 1 gamma

34.5 protein prevents autophagosome maturation in infected cells, limiting its function. antiviral in addition to the antigen-presenting function [10]. Finally, the last exposed mechanism comments on the evasion of T lymphocytes (Figure 3) since the clinical manifestations of herpetic meningoencephalitis are varied, the most characteristic sign is the altered state of consciousness that may be associated with irritability and drowsiness up to comatose states. Additionally, signs or symptoms related to temperature rises, headache, alteration in cranial or motor nerves, hallucinations, aphasia, seizures, meningeal signs, among others, may be evidenced. These clinical manifestations are less specific depending on the age of the patient, taking into account that it has the particularity of being able to be associated with gastrointestinal or respiratory infections due to dual tropism [8,11]. Based on this, a series of criteria classified as major and minor have been established [2]; (Table 1).

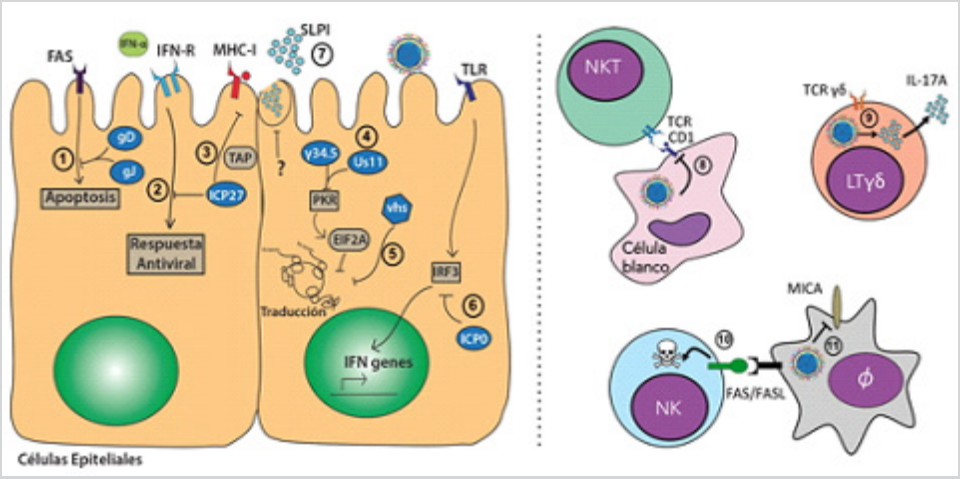

Figure 2: Evasion of the innate immune respons.

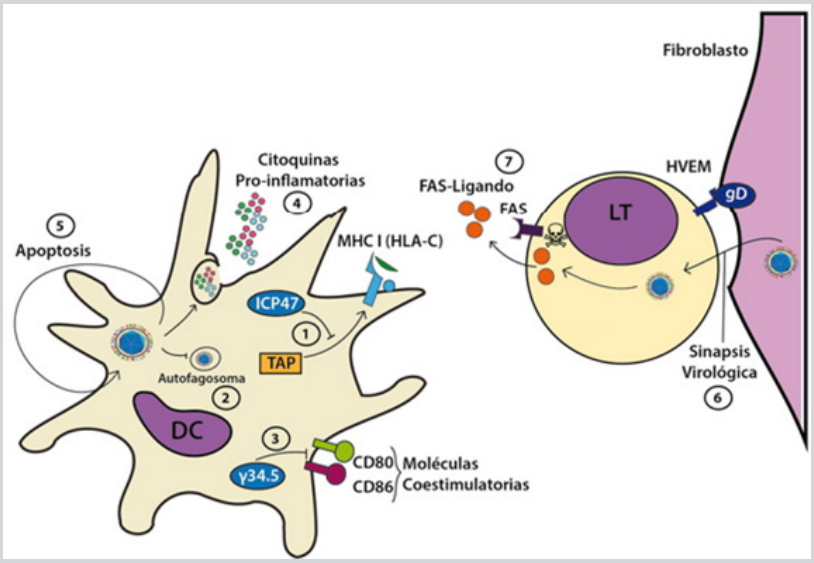

Figure 3: Evasion of the adaptive immune response.

The diagnosis of herpetic meningoencephalitis, in addition to the clinical manifestations and diagnostic criteria, requires extension studies including lumbar puncture (unless there is a contraindication for it) with microscopic study, gram stain, reaction in Polymerase Chain (PCR), bacterial, fungal and viral cultures. Regarding imaging studies, the one of choice is the nuclear Magnetic Resonance with gadolinium contrast, which shows hyperintensity of the affected area [T2] and hypointensity [T1], which characteristically in herpetic infection is usually located in the temporal lobe [2].

For the treatment of meningoencephalitis, empirical management should be initiated with intravenous acyclovir at a dose of 30 mg/kg/day, since it is evident that this action generates an impact on the prognosis of the infection; If HSV is confirmed as the etiological agent, this treatment should be carried out for 14 to 21 days. The use of other therapies such as corticosteroids influences the reduction of inflammation, thus improving the prognosis [1-3]. The prognosis of herpetic meningoencephalitis without treatment is unfavorable, it is estimated that up to 70% of patients die and survival without any sequelae is less than 2.5%, however, in those patients who have received adequate treatment with acyclovir they have a mortality of maximum 10% and up to 42% survive without sequelae [3]. Due to the high rate of morbidity and mortality associated with this pathology, the need arises to know the epidemiology and factors associated with the presentation of this disease, in order to reduce delays in treatment, generating an impact on it [9].

Table 1: Diagnostic criteria for viral meningoencephalitis.

Major Criteria	Encephalopathy: altered mental status, decreased level of consciousness, lethargy, personality change, of at least 24 hours duration, without apparent cause
Minor Criteria	Fever >38 degrees in the 72 hours before or after the onset of symptoms
	Partial or generalized seizures without epileptogenic pathology present
	CSF with >5 cells/mm^3 -> 20 cells/mm^3 in neonates ->9 cells/mm^3 up to 2 months (Pleocytosis)
	Abnormal electroencephalogram without other cause
	Alteration of the brain parenchyma in neuroimaging
	Recent onset focal signs
Possible encephalitis: 1 major criterion + 2 minor criteria	
Probable encephalitis: 3 or more minor criteria	

METHODOLOGY

This study was carried out based on a systematic review of scientific literature, which was obtained through the review of different scientific databases such as Pubmed, Up to Date, Elsevier, SciELO, Science Direct. This search was carried out based on keywords such as "Viral Meningoencephalitis", "Herpes Virus", "Aseptic Meningoencephalitis", "Viral Encephalitis", "Viral Meningitis", "Viral Meningoencephalitis in Children". Through the search, 30 articles in English and Spanish were selected, which met the required criteria, such as being carried out or updated in the last decade, being focused on the pediatric population, clearly address aspects related to the epidemiology of herpetic meningoencephalitis in children. Those who do not comply with what was previously mentioned or who do not have enough information to address the subject were excluded.

RESULTS AND DISCUSSION

The Herpes virus is the cause of at least 20% of cases of meningoencephalitis in developed countries in the general population [3]; in the United States its incidence is 20,000 cases per year [6] and in the United Kingdom it causes 1 in 250,000 cases. In children it is considered a rare entity, reaching a rate of 1 to 4 cases per 100,000 per year [1]. Gutierrez [3] indicate that this infection peaks between 5 and 30 years of age, data with which Michael et al. [8] in addition to Abel Plancoulaine et al. [10] who estimate that the disease has a peak in childhood, especially in newborns and among those between 6 months and 3 years of age. Similar to this finding, in the study "Viral meningitis in children: Epidemiology, pathogenesis, and etiology" [11] show a peak in children under one year of age and another at 5 years of age, while in the study "Herpes Simplex Virus Infection in Infants Undergoing Meningitis Evaluation." estimate that for every 100,000 live births, at least 10 of them have presented herpes virus infection [12,13].

Regarding the specific etiology of herpetic meningoencephalitis, it has been shown that in neonates it is caused by HSV 1 and 2, while in older children the presence of HSV 1 is more relevant [3, 4, 6]. This is due to the route of transmission, since in the case of neonates the condition is mainly related to maternal-foetal contact during delivery, while HSV 1 is associated with skin or mucous membrane alterations [14,15]. It is estimated that approximately 10% of herpetic meningoencephalitis cases are caused by HSV 2 [8], however neonatal infections due to HSV 1 comprise approximately 25% of cases [9], a figure that in other studies rises to 35%. [16]. Other causative agents belonging to the herpes family are varicella zoster (VZV) and human herpes virus 6 (HHV 6) whose incidence in acute disease is approximately 10% [17]. CMV and EBV have a low incidence compared to HSV [9,11,18]; (Table 2).

Table 2: Etiology of meningoencephalitis according to age group.

Epidemiological characteristic	Most frequent etiology
Newborns and Infants	HSV (1 and 2), CMV, enterovirus, parechovirus
Children	HSV, CMV, EBV, enterovirus

As for the clinical manifestations, in almost 90% of the cases temperature rises, decreased state of consciousness, meningeal signs and convulsive crises are reported [3], which is consistent with what was evidenced in the study by Kneen Michael et al. [8] where they report that fever was the most common manifestation reaching up to 80% followed by focal neurological signs. According to Aida [19] in older children, the symptoms are more specific, with torticollis, headache and photophobia as characteristic meningeal signs, however, he ensures that, despite the above being suggestive of the condition, it does not satisfactorily guides towards the etiology of the same, so in case of clinical suspicion, a series of complementary studies must be carried out, including lumbar puncture with gram stain, cytochemical and PCR since it was evidenced that up to 85% of patients present pleocytosis of lymphocyte and erythrocyte predominance. This is consistent with what was reported in the study "Herpes simplex encephalitis in Iceland 1987-2011" [20] where the presence of erythrocytes in the cerebrospinal fluid (CSF) was described in most of the patients studied; however, in some studies concludes that the absence of pleocytosis does not rule out HSV infection [21]. In addition to the above, in the cytochemical it is possible to find hypoglycorrhachia and mild hyperproteinorrachia [2,3] in up to 55% of cases [20]. where in most of the patients studied the presence of erythrocytes in the cerebrospinal fluid (CSF) was described, however, in some studies it is concluded that the absence of pleocytosis does not rule out HSV infection [21]. In addition to the above, in the cytochemical it is possible to find hypoglycorrhachia and mild hyperproteinorrachia [2,3] in up to 55% of cases [20]. where in most of the patients studied the presence of erythrocytes in the cerebrospinal fluid (CSF) was described, however, in some studies

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The PCR is the most specific test for the identification of the herpes virus in CSF, since it allows the identification of the specific infectious agent, however, this can be negative the first 3 days of the picture [2]. Other authors affirm that this is positive from 24 hours after the onset of symptoms and report a sensitivity of 98% with a specificity of 94%, however, they clarify that these depend on the moment of the test being higher at from the sixth day of the disease [3]; (Table 3). Due to what has already been mentioned, in the case of performing a lumbar puncture in the first days of the clinical picture with a negative report, several authors agree that the test should be repeated within the first 3-7 days before deciding to suspend medical management [22].

Table 3: CSF Findings in herpetic meningoencephalitis.

CSF Findings in Herpetic Meningoencephalitis	
Gram stain	Pleocytosis (<500 cells/mm^3) with a predominance of lymphocytes and erythrocytes
Cytochemical	Mild hypoglycorrhachia
	Mild hyperprotein
PCR	Identification of the Virus in CSF

Regarding imaging studies, it has been established that nuclear magnetic resonance with gadolinium is the study of choice for the detection of herpetic meningoencephalitis since this virus has the particularity of generating hypointensity on T1 and hyperintensity on T2, in addition to having the tendency of distributed towards the temporal lobe [2,4] predominantly in the inferomedial region [3]; (Figure 4). It was estimated that approximately 78% of the lesions were unilateral and 22% bilateral [20]. Some studies have shown a low prevalence of neuroimaging alterations (21%) however, this is due to the fact that the most used study in these studies was computerized axial tomography, which has a lower probability of detecting early findings. unlike resonance.

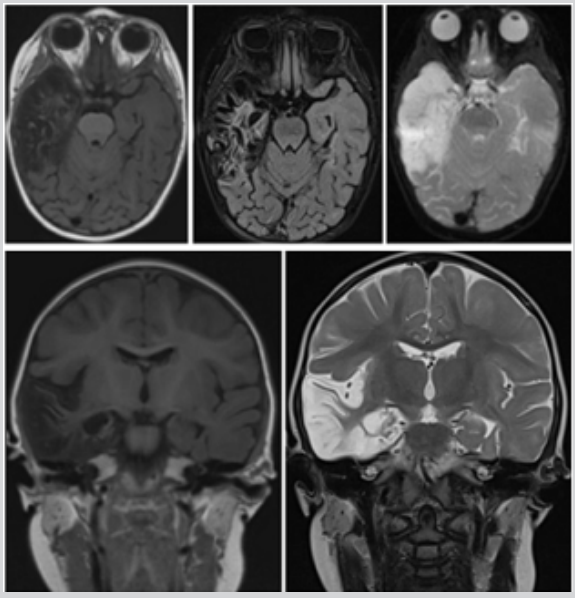

Figure 4: Nuclear magnetic resonance in herpetic meningoencephalitis, with destruction of the temporal lobe and hippocampus.

Regarding the treatment of herpetic meningoencephalitis, since it is an entity with high morbidity and mortality, in most cases, in addition to supportive management, it is decided to start empirical therapy with acyclovir at a dose of 30mg/kg/day for an approximate duration of 21 days [2,3] ; This is partly due to the fact that a large percentage of the pediatric population is considered to be immunized, which significantly conditions the fact that meningoencephalitis is caused by a viral process in which, taking into account the inclusion of vaccination against chickenpox of regularly, the VHS is the end result [24,25]. Taking into account the above, the indication is to start empirical therapy with acyclovir in a timely manner in order to positively impact the morbidity and mortality figures [26,27].

Regarding the prognosis of this disease in the presence of treatment, it is evident that approximately 80% have a complete response to treatment with a mortality rate of 3% [2] and according to Modi et al. [29] in neonates mortality was 6.9% and in children 1.2%; Additionally, the recurrence rate is approximately 5% and survival without sequelae is estimated at up to 42%. Contrary to this, it is evident that children who did not receive treatment have an estimated mortality of 70% and the survivors have at least 97.5% neurological sequelae [3]. In the study "Herpes simplex encephalitis in Iceland 1987-2011" [20] they estimate that 70% of the patients who survived were left with some neurological sequelae, including memory loss, frontal symptoms, dysphasia, seizures among others; Additionally, it is considered that those

children with higher plasmatic levels of the virus have worse results and higher mortality [30].

CONCLUSION

Herpetic meningoencephalitis is a rare neurological infection that is mainly associated with the presence of infections of viral origin, with HSV types 1 and 2 recognized as a fundamental etiological agent. The clinical manifestations are variables characterized by the presence of temperature rises and neurological signs or symptoms that determine high rates of morbidity, deterioration of the quality of life, cost overruns in health services and mortality, which can be corrected from the establishment of the diagnosis. timely, as well as the start of comprehensive medical management. Taking into account the above, it is emphasized that health personnel must maintain a high index of suspicion that is accompanied by complementary studies such as lumbar puncture with a cytochemical study or nuclear magnetic resonance with gadolinium in order to confirm the condition and reduce effectively variables related to preventable complications associated with diagnostic, therapeutic or follow-up errors. Regarding treatment, acyclovir continues to be the most appropriate medication and it is concluded that starting it empirically provides a benefit for the patient.

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