Meningoencephalitis: infectious etiology in pediatric patients at a reference hospital

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Abstract

Background: The etiologies of meningoencephalitis, meningitis, or encephalitis may be infectious or non-infectious. For the microbiological diagnosis, it is necessary to perform cultures and molecular tests. The objective of this study was to describe the infectious causes of meningoencephalitis and their clinical presentation. **Methods:** A cross-sectional study was performed at the Hospital Civil de Guadalajara Dr. Juan I. Menchaca. Patients older than 28 days of life with meningitis, encephalitis, or meningoencephalitis syndrome were included in the study. Infectious etiology was identified through cultures, Gram stains, and molecular tests of cerebrospinal fluid (CSF). The characteristics of patients with and without an etiological diagnosis were compared. **Results:** Fifty patients with meningoencephalitis ($n = 25$), meningitis ($n = 19$), or encephalitis ($n = 6$) were included in the study. The mean age was 1 year and 62% were male. An infectious etiological diagnosis was performed in 42%; 65.2% ($n = 15$) were viruses and 34.8% ($n = 8$) bacteria. In patients with etiological diagnosis, a higher number of leukocytes were found in CSF (92 leu/mm³ vs. 12 leu/mm³, $p = 0.001$); the history of gastroenteritis was more frequent (odds ratio [OR]: 3.5; 95% confidence interval (CI): 1.007-12.1; $p = 0.04$), and on examination, neck stiffness was more common (OR: 3.8; 95% CI: 1-15.2; $p = 0.04$). **Conclusions:** 42% of the patients with meningitis, encephalitis, or meningoencephalitis had an infectious etiological diagnosis; the most frequent cause was Enterovirus.

Key words: Encephalitis. Meningitis. Meningoencephalitis.

Meningoencefalitis: etiología infecciosa en pacientes pediátricos de un hospital de referencia

Resumen

Introducción: Las causas de meningoencefalitis, meningitis o encefalitis pueden ser infecciosas o no infecciosas. Para el diagnóstico microbiológico se requieren cultivos y pruebas moleculares. El objetivo del estudio fue describir las causas infecciosas de meningoencefalitis y su presentación clínica. **Métodos:** Estudio transversal realizado en el Hospital Civil de

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Guadalajara Dr. Juan I. Menchaca. Se incluyeron pacientes mayores de 28 días de vida con síndrome de meningitis, encefalitis o meningoencefalitis. Se identificó la etiología infecciosa mediante cultivos, tinciones de Gram y pruebas moleculares de líquido cefalorraquídeo. Se compararon las características de pacientes con y sin diagnóstico etiológico. **Resultados:** Se incluyeron en el estudio 50 pacientes con meningoencefalitis ($n = 25$), meningitis ($n = 19$) o encefalitis ($n = 6$). La mediana de edad fue de un año y el 62% de los pacientes fueron de sexo masculino. Se realizó diagnóstico etiológico infeccioso en el 42%: el 65.2% ($n = 15$) se debió a virus y el 34.8% ($n = 8$) a bacterias. En los pacientes con diagnóstico etiológico, se presentó un mayor número de leucocitos en líquido cefalorraquídeo (92 leu/mm^3 vs. 12 leu/mm^3 , $p = 0.001$). Fue más frecuente el antecedente de gastroenteritis (razón de momios [RM]: 3.5; intervalo de confianza al 95% [IC 95%]: 1.007-12.1; $p = 0.04$) y ante la exploración, fue más frecuente la rigidez de cuello (RM: 3.8; IC 95%: 1-15.2; $p = 0.04$). **Conclusiones:** El 42% de los pacientes con meningitis, encefalitis o meningoencefalitis tuvieron diagnóstico etiológico infeccioso. La causa más frecuente fue el enterovirus.

Palabras clave: Encefalitis. Meningitis. Meningoencefalitis.

Introduction

Meningitis is defined as the inflammation of the brain membranes. Clinically, it is manifested with irritability, neck stiffness, and Kernig's and Brudzinski's signs, while encephalitis is a consequence of the brain parenchyma involvement and is presented with alterations in consciousness, seizures, behavioral changes, aphasia, or cranial nerve palsies^{1,2}. In pediatric patients, both syndromes can occur concomitantly.

The meningoencephalitis etiology can be infectious (viruses, bacteria, parasites, and fungi) or non-infectious (demyelinating diseases, antibody-mediated encephalitis or vasculitis)¹⁻³. The concept of aseptic meningitis describes a meningeal irritation event in the presence of pleocytosis, with negative results of cultures and stains for bacteria^{3,4}.

The signs and symptoms do not allow establishing a specific etiology⁵, so epidemiological information such as the season of presentation, vaccination record, exposure to arthropods, or the consumption of particular foods may be suggestive of the causes^{3,4}. Although the cytological and chemical characteristics of the cerebrospinal fluid (CSF) can guide the diagnosis, it is necessary to perform cultures and molecular tests to confirm an infectious etiology^{3,4}.

In the pediatric population, Enteroviruses are the leading cause (85%) of infectious meningoencephalitis^{3,4}. Of the bacterial infections, 80% are due to *Neisseria meningitidis*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*; however, the occurrence for the last two has significantly decreased after the application of conjugate vaccines in the first month of life^{4,6}.

The objective of this study was to describe the infectious causes of meningoencephalitis and its clinical presentation in pediatric patients of a reference hospital.

Methods

A cross-sectional, analytical study was conducted at the Hospital Civil de Guadalajara Dr. Juan I. Menchaca (HCGJIM) of the city of Guadalajara, Jalisco, Mexico. The institution provides health services to an open population with limited economic resources. The pediatric service has 226 beds, and the emergency department has 15 beds.

The investigation was conducted from June 23, 2014, to July 3, 2015. Pediatric patients older than 28 days of age with pleocytosis and signs and symptoms suggestive of meningitis, encephalitis, or meningoencephalitis were included in the study. Patients with epilepsy or invasive intracranial devices, such as ventriculoperitoneal shunt valves or external shunts, were not included in the study. The following were considered as clinical manifestations suggestive of meningitis: irritability, neck stiffness, and Kernig's or Brudzinski's signs, while the manifestations of encephalitis were alterations in the level of consciousness (Glasgow scale of ≤ 12), seizures, behavioral changes, aphasia, cranial nerve palsy or changes in gait, strength, or sensitivity. Pleocytosis was defined as the presence of more than five leukocytes in CSF.

The variables explored were sex, age, weight, height; signs and symptoms; cytological and chemical characteristics of CSF; and history of gastroenteritis or respiratory tract infection in the 3 weeks before admission. The information of the analyzed variables was obtained from the patients' clinical records.

The CSF was obtained through a lumbar puncture with sterile technique. The samples were inoculated in enriched media (BacT/ALERT PF Pediatric FAN®) and on blood agar; microbial growth was monitored in automated BacT/ALERT® 3D system for 7 days. Any microbial growth was considered significant, except coagulase-negative *Staphylococcus*. In these cases, it

was classified as an infectious event only if there was an abnormality in the number of leukocytes and glucose level in the CSF cytochemical study. In isolated bacteria, genre and species were identified with the automated MicroScan autoSCAN-4 System®.

Simultaneously, a search for viral antigens in CSF was carried out using the CLART® ENTHERPEX⁷ test (multiple polymerase chain reaction), which identifies eight human herpes viruses and three viruses of the enterovirus family: herpes simplex 1, herpes simplex 2, herpes simplex 3, Epstein–Barr virus, cytomegalovirus, human herpes 6, human herpes 7, human herpes 8, coxsackievirus, poliovirus, and echovirus.

For CSF samples with negative cultures and negative viral antigens, molecular tests were requested for the search of *Mycobacterium tuberculosis* (Xpert MTB/Rif®) or serological tests (immunoglobulin G and immunoglobulin M [IgM]) for *Mycoplasma pneumoniae* depending on the clinical manifestations and risk factors of the patients.

The etiological diagnosis was established when positive results were obtained from cultures, Gram-stains, or molecular tests (CLART® ENTHERPEX, Xpert MTB/Rif®) in CSF.

Statistical analysis

For the qualitative variables, frequencies and percentages were estimated; for the quantitative variables, the median and the ranges were calculated. The variables studied were compared between patients with and without etiological diagnosis; as statistical testing, the χ^2 test was used for qualitative variables and the Mann–Whitney U-test for quantitative variables. The analysis was performed with the software IBM SPSS Statistics Version 20.

Results

During the study period, 50 patients were registered: 50% ($n = 25$) presented suggestive symptoms of meningoencephalitis; 38% ($n = 19$) of meningitis; and 12% ($n = 6$) of encephalitis. Of the included patients, 62% ($n = 31$) were males and 38% ($n = 19$) were females. The median age was 1 year (minimum 0.08 and maximum 15).

Antibiotics were received before obtaining CSF for culture in 18% ($n = 9$) of the patients. Three weeks before admission, 66% ($n = 33$) had a respiratory tract infection and 32% ($n = 16$) had gastroenteritis.

The signs and symptoms at the time of hospitalization were as follows: irritability, 90% ($n = 45$); hyporexia, 88%

Table 1. Isolated microorganisms in cerebrospinal fluid from patients with meningitis, encephalitis, or meningoencephalitis.

Bacteria	n	Viruses	n
<i>Streptococcus pneumoniae</i>	3	Enterovirus	6
<i>Haemophilus</i> spp.	1	Herpesvirus VI	3
<i>Streptococcus pyogenes</i>	1	Herpesvirus VII	3
<i>Brucella melitensis</i>	1	Herpes simplex 1	1
<i>Mycobacterium tuberculosis</i>	1	Herpesvirus VIII	1
<i>Mycoplasma pneumoniae</i>	1	Cytomegalovirus	1
Total	8	Total	15

($n = 44$); fever, 68% ($n = 34$); seizures, 52% ($n = 26$); hypertonia, 26% ($n = 13$); neck stiffness, 24% ($n = 12$); alteration of the state of consciousness, 22% ($n = 11$); bulging fontanelle, 12% ($n = 6$); Kernig's sign, 12% ($n = 6$); Brudzinski's sign, 10% ($n = 5$); and coma, 4% ($n = 2$).

The infectious etiological diagnosis was made in 42% ($n = 21$) of the patients. Two of them presented more than one etiological agent (*S. pneumoniae* with cytomegalovirus and *S. pneumoniae* with enterovirus). One meningeal infection produced by *M. tuberculosis* was identified with the Xpert MTB/Rif® test, and one infection by *M. pneumoniae* was recognized by the presence of IgM antibodies in the CSF.

Of the microorganisms isolated, 65.2% ($n = 15$) were viruses and 34.8% ($n = 8$) were bacteria. One of the infections was a nosocomial acquisition by a patient with acrania; the rest of them were community acquired.

No differences were observed in the frequency of infectious etiological diagnosis according to sex ($p = 0.55$), syndromic diagnosis ($p = 0.45$), history of respiratory infection ($p = 0.26$), or when comparing patients with and without a history of having received antibiotics ($p = 0.56$). In three of the patients who received antibiotics before the diagnostic tests, an infectious etiological agent was identified (herpes Type VIII, Enterovirus, and *Brucella melitensis*). Patients with a gastroenteritis history were more likely to have an infectious etiologic diagnosis (odds ratio [OR]: 3.5; 95% confidence interval [95% CI]: 1007-12.1; $p = 0.04$).

Table 1 shows the isolated microorganisms.

When comparing patients with and without an etiological diagnosis, a significant difference was observed for the number of leukocytes (92 leukocytes/mm³ vs. 12 leukocytes/mm³, $p = 0.001$) and the percentage of

Table 2. Median of the chemical and cytological indicators of cerebrospinal fluid in patients with and without bacterial meningitis.

Median of the cytological indicators	Total patients (n = 50)*	With bacterial meningitis (n = 8)*	Without bacterial meningitis (n = 42)*	p
Leukocytes (leu/mm ³)	18 (98)	92 (5757)	17 (86)	0.17
Polymorphonuclear leukocytes (%)	9.5 (71)	56.5 (58)	5 (64)	0.06
Glucose (mg/dl)	51.5 (24)	17.5 (52)	55 (21)	0.03**
Microproteins (mg/d)	51.5 (145)	196 (301)	48 (100)	0.19
Lactate dehydrogenase	24 (50)	79.5 (713)	24 (39)	0.09

*RIC, interquartile range.

**p < 0.05 Mann-Whitney U-test.

polymorphonuclear cells (50% vs. 0%, $p = 0.03$). When examining patients with and without bacterial infection, a difference was found in CSF glucose values (17.5 mg/dl vs. 55 mg/dl, $p = 0.03$) (Table 2).

When comparing symptoms in patients with and without an infectious etiological diagnosis, a difference was observed for the presence of neck stiffness (OR: 3.8; 95% CI: 1-15.2), while concerning patients with and without bacterial meningitis, a difference was found in the occurrence of Kernig's (OR: 7.1; 95% CI: 1-52.7) and Brudzinski's signs (OR: 10.7; 95% CI: 1.3-109). When estimating the sensitivity and specificity of signs and symptoms to predict infectious etiological diagnosis, it was observed that hyporexia was the most sensitive symptom and the meningeal irritation signs and neck stiffness were the most specific (Table 3).

When comparing the frequency of infectious etiological diagnosis ($p = 0.35$) or bacterial infections ($p = 0.77$) according to age, no significant statistical difference was found; however, 76% of the patients with an infectious diagnosis were older than three months; in patients with three or fewer months of life, only one event was of bacterial etiology (*Streptococcus pyogenes*).

Two of the patients presented chronic symptoms and a history of unpasteurized dairy products consumption:

1. A 9-year-old male patient with Down syndrome; the patient showed the following clinical manifestations of evolution over a month: a cough, headache, vomiting, asthenia, and adynamia. Cranial tomography revealed ventriculomegaly, so a peritoneal ventricular shunt valve was placed. The CSF cytochemical study showed 162 leukocytes/mm³, glucose 38 mg/dl, and microproteins 677 mg/dl. The Xpert MTB/Rif® test was positive for *M. tuberculosis*.

2. A 14-year-old male patient, previously healthy, had the following clinical manifestations of evolution over

three months: fever, asthenia, and adynamia. He presented left hemiplegia, aphasia, and Brudzinski's and Kernig's signs. CSF cytochemical study showed 6 leukocytes/mm³, glucose 30 mg/dl, and microproteins 207 mg/dl. Isolation of *B. melitensis* was obtained in the CSF culture.

In patients without an etiological diagnosis, the clinical manifestations at admission were irritability (89.7%), seizures (51.7%), and fever (65.5%). 37.9% of these patients were younger than 3 months; 72.4% had <30 leukocytes in the CSF, and in 79.3%, mononuclear cells were predominant. Six patients were classified as partially treated meningitis due to a history of antimicrobial use before CSF culture, and fifteen were classified as febrile seizures. Of this group, 72.4% of patients at admission presented respiratory symptoms (a cough, runny nose, or respiratory distress) and 20.7% showed gastrointestinal symptoms (diarrhea, vomit, or abdominal distension).

Discussion

The presence of fever, seizures, behavioral, and consciousness level alterations suggest the presence of infectious encephalitis. However, the clinical history of similar episodes, the absence of fever, or presenting acidosis or alkalosis suggest a non-infectious origin¹.

Curtis et al.⁵ evaluated the accuracy of different clinical signs and symptoms for the diagnosis of infectious meningitis and observed that the bulging fontanelle and neck stiffness were presented in < 20% of patients with suspected infection; however, their presence increased the risk of infection eight times (bulging fontanelle: likelihood ratio (LR): 8; 95% CI: 2.4-26, and neck stiffness: LR: 7; 95% CI: 3.2-19). At the HCGJIM, patients with suspected central nervous system (CNS)

Table 3. Sensitivity, specificity, and predictive values of the signs and symptoms to assess the infectious etiological diagnosis in patients with meningitis, encephalitis, or meningoencephalitis.

Sign or symptom	Sensitivity	Specificity	Predictive values	
			Positive	Negative
			% (95% CI)	
Irritability	90.5 (71-97.3)	10.3 (3.6-26.4)	42.2 (29-88.2)	60 (23.1-88.2)
Hyporexia	95.2 (77.3-99.1)	17.2 (7.6-34.5)	45.4 (31.7-59.9)	83.3 (43.6-96.9)
Fever	71.4 (50-86.1)	34.5 (19.9-52.6)	44.1 (28.8-60.5)	62.5 (38.6-81.2)
Seizures	52.4 (32.3-71.6)	48.3 (31.4-65.6)	42.3 (25.5-61)	58.3 (38.8-75.5)
Hypertonia	28.6 (13.8-50)	75.8 (57.9-87.8)	46.1 (23.2-70.8)	59.4 (43.5-73.6)
Neck stiffness	38.1 (20.7-59.1)	86.2 (69.4-94.5)	66.7 (39-86.2)	65.8 (49.9-78.8)
Glasgow ≤ 12	19 (7.7-40)	75.9 (57.9-87.8)	36.4 (15.2-64.6)	56.4 (40.9-70.7)
Bulging fontanelle	50 (18.8-81.2)	72.3 (43.4-90.2)	50 (18.8-81.2)	72.3 (43.4-90.2)
Kernig's sign	19 (7.7-40)	93.1 (78-98.1)	66.7 (30-90.3)	61.4 (46.6-74.3)
Brudzinski's sign	19 (7.7-40)	96.5 (82.8-99.4)	80 (37.5-96.4)	62.2 (47.6-74.9)

95% CI: 95% confidence interval.

infection, neck stiffness, and Kernig's and Brudzinski's signs were the most specific clinical features to predict an infectious etiology. However, its positive predictive value was $\leq 80\%$.

Before the use of cell cultures, only 25% of aseptic meningitis had an etiological diagnosis. Currently, with serological tests, nucleic acid amplification tests, and cultures, microbial agents can be identified up to 70%^{2,3}. In this study, in 42% of the patients, some microorganisms were identified: viruses in 65.2% ($n = 15$) and bacteria in 34.8% ($n = 8$). The most frequently identified agents were Enteroviruses.

Human herpesviruses 6 (VHH 6) and human herpesviruses 7 (VHH 7) are β -herpesviruses associated with exanthematous diseases of childhood; furthermore, they have been associated with febrile seizures⁸. Yavarian et al.⁹ identified VHH 6 in CSF of 8.8% of infants with encephalitis, independently of having presented dermatological manifestations or not. In patients at the HCGJIM, 26.1% of the encephalitis or meningitis events were attributed to VHH 6 and 7. Since serological tests were not performed, it was not possible to define whether the infections were primary or by reactivation of latent infections¹⁰.

Koskiniemi et al.¹¹ evaluated the epidemiology of encephalitis in children after the implementation of vaccination programs against measles, mumps, and rubella (MMR) viruses. In 63% of the events, a causative agent

was identified. A significant change was observed in the etiological agents; the most prevalent was the varicella virus (22%), respiratory viruses (20%), and Enteroviruses (19%). In our study, no diagnostic tests for MMR viruses were performed because the hypothesis of infection by these agents was not considered, since 96.1% of patients > 1 year of age received the triple viral (MMR) vaccine. In the country, 87% coverage is reported in the national vaccination program for the triple viral vaccine¹².

Environmental, demographic, and vaccination history factors influence the epidemiology of CNS infections¹³⁻¹⁵. Jain et al.¹⁶ identified the infectious etiology in 60.5% ($n = 632$) of pediatric patients with acute encephalitis syndrome. The most frequent causes were Japanese encephalitis virus (16.2%), dengue virus (10.8%), herpes simplex virus (9.3%), and mumps virus (8.7%). The first two agents showed predominance from July to November, and mumps virus infections occurred mainly in patients without a history of vaccination. In the western region of the same state, Beig et al.¹⁴ described that enterovirus was the main cause of encephalitis (42.1%).

In Mexico, from 2000 to 2011, the incidence of infection by dengue virus has increased from 1.72 to 14.1 events/1,00,000 inhabitants, with cases predominating in the coastal region and young people aged 10-20 years old¹⁷. Due to this increased incidence, it is

reasonable to consider the dengue virus as a probable encephalitis etiological agent. In this study, no patient was investigated for this etiology.

Ignorance in the epidemiology of vector-borne infections favors underdiagnosis. The West Nile virus has emerged as the most frequent cause of epidemic meningoencephalitis in the United States, and the infection has spread to countries in the Caribbean, Canada, and Mexico¹⁸. It is possible that, in patients with meningoencephalitis without an etiological diagnosis, the cause could be an arbovirus infection.

Chronic meningitis can manifest with non-specific symptoms such as a headache, nausea, vomiting, altered level of consciousness, or memory impairment. In these events, the presence of hypoglycorraquia is suggestive of fungal or *Mycobacterium* sp. infection¹⁹. Two patients, in this study, had chronic symptoms and a history of consumption of unpasteurized products. The isolated bacteria in these patients were *B. melitensis* and *M. tuberculosis*.

The gold standard for the diagnosis of CNS infections of bacterial origin is CSF culture, but in cases of aseptic meningoencephalitis or partially treated meningitis, the use of molecular techniques allows etiological diagnoses in up to 70% of events, favoring a rational use of antibiotics and the reduction of hospitalization days. The complexity of these tests and their cost make them unaffordable^{20,21}. However, multiple polymerase chain reaction tests have facilitated its use⁷.

The limitations of this study were the sample size and not having carried out an exhaustive search for infectious causes in patients without an etiological diagnosis. No tests were requested for arboviruses (dengue virus or West Nile virus), MMR, or respiratory viruses. The tests for *M. tuberculosis* or *M. pneumoniae* were only performed in patients with negative cultures and suggestive clinical manifestations. Moreover, 18% of patients had received antibiotics before the study, which could cause false negative results in the cultures.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of

the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Conflicts of interest

The authors declare no conflicts of interest.

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