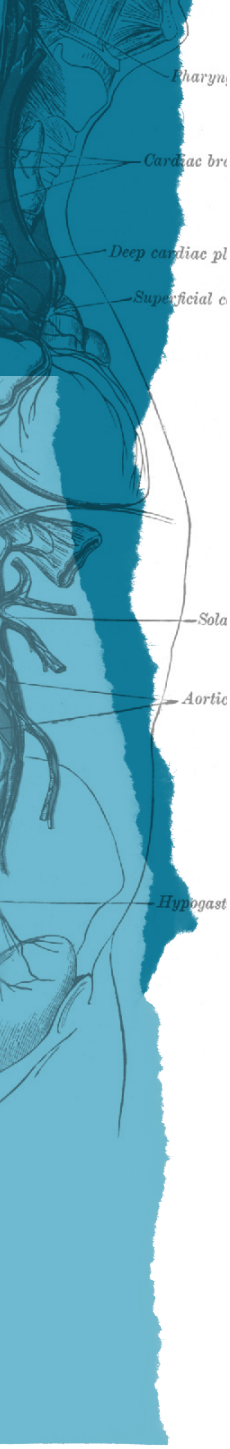

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Viral Meningitis: Clinical and Microbiological Characteristics of Patients Admitted at a Hospital University between 2017 and 2022 in Medellin (Colombia)

Meningitis viral: características clínicas y microbiológicas de pacientes ingresados en un hospital universitario entre 2017 y 2022 en Medellín (Colombia)

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ABSTRACT

Objective: This study aimed to characterize the main sociodemographic, clinical, and etiological differences between adults and children, diagnosed by commercial molecular test between 2017 and 2022 who required admission to a tertiary hospital in Colombia.

Materials and methods: A cross-sectional and retrospective study was conducted. Clinical aspects were considered, and laboratory tests included: biochemistry, cell count, and culture of cerebrospinal fluid (CSF). Absolute and relative frequencies for sociodemographic and clinical variables, as well as viral etiology, were performed. Bivariate associations were used for microbiology parameters ($p < 0.05$).

Results: A total of 82 patients were characterized, of whom 54 (65.8%) were men. The main symptoms were fever (67.1%), followed by headache (37.8%). Children were most likely to be male and have lower CSF protein levels ($p < 0.001$). In contrast, adults were more frequent to have VZV (22%) and HSV-1 (20.7%), while in children, HHV-6 (22%) and EV (13.4%) predominated. Parechovirus was the least frequent pathogen identified (1.2%).

Conclusion: Viral meningitis was more frequent in the pediatric age group and predominated in males. Pleocytosis was slightly more frequently detected in adults, and the most common identified viruses were from the herpes family. This study shows the need to identify more viral pathogens in cases of uncertain origin, considering the changing distribution and etiological frequency resulting from the increasing development of molecular tests.

Keywords: viral meningitis, etiology, epidemiology, Colombia.

RESUMEN

Objetivo: Caracterizar los principales aspectos sociodemográficos, clínicos y etiológicos entre adultos y niños diagnosticados con meningitis viral entre 2017-2022 en un hospital de alta complejidad en Colombia.

Métodos: Estudio transversal y retrospectivo. Se consideraron aspectos clínicos, pruebas de laboratorio (bioquímica, recuento celular y cultivo de líquido cefalorraquídeo) e identificación etiológica por biología molecular. Se realizaron frecuencias absolutas y relativas para el análisis descriptivo. Se usaron las pruebas de chi-cuadrado y U de Mann-Whitney para los análisis bivariados entre niños y adultos ($p < 0,05$).

Resultados: Fueron incluidos 82 pacientes. El 65,8 % correspondieron al sexo masculino. Los principales síntomas fueron fiebre (67,1 %) y dolor de cabeza (37,8 %). Los niños presentaron proteinorraquia más baja respecto a los pacientes mayores de edad ($p < 0,001$). La causa etiológica más frecuente en adultos fue varicela zóster (22 %), seguido del virus herpes simple tipo-1 (20,7 %); en los pacientes pediátricos fueron más frecuentes el virus herpes humano 6 (22 %) y los enterovirus (13,4 %).

Conclusión: La meningitis viral fue más frecuente en niños y predominantemente en hombres. La pleocitosis fue ligeramente más alta en adultos. Los virus más frecuentes fueron de la familia del herpes. Este estudio muestra la importancia de identificar la causa etiológica de la meningitis viral, debido a la distribución y frecuencia cambiante de los virus por el creciente desarrollo de las pruebas moleculares.

Palabras clave: meningitis viral, etiología, epidemiología, Colombia.

INTRODUCTION

Infectious meningitis is one of the most prevalent and life-threatening diseases affecting the central nervous system (CNS), characterized by a high mortality rate and a significant risk of long-term neurological sequelae (1). Numerous microbiological species, such as bacteria, viruses, fungi, and parasites, can cause infectious meningitis; these can affect people of different ages and vary depending on geographic location (2).

The burden of viral meningitis (VM) infection remains uncertain and poses a major public health challenge, particularly in developing countries. Reports on the incidence vary depending on the study population, and differences in case definition and diagnostic methods. Currently, the

estimated annual incidence of VM is 4.3 per 100,000 for all ages, and its mortality ranges from 4% to 13% (3). In Colombia, knowledge about the magnitude of the problem is limited due to underreporting in the national epidemiological surveillance system. However, based on data from a 2015–2017 neuroepidemiological study in Colombia using administrative records, the overall prevalence of meningitis, irrespective of etiology, was estimated at 10 cases per 100,000 population in 2017 (4).

Historically, in 2004, an epidemic of aseptic meningitis was registered in Antioquia, with a total of 263 reported cases—77% of them in Medellin. Notably, four samples of cerebrospinal fluid (CSF) sent to the National Institute of Health demonstrated infections by echovirus 30 (5). Similarly, in the department of Antioquia, between 2013 and 2014, thirteen cases of enterovirus infection in children were identified using molecular diagnostic techniques (6). In this context, enteroviruses (EV), herpesviruses (HSV), and some arboviruses have been recognized as the most important viral agents of meningitis and encephalitis (7). Enterovirus encephalitis is more prevalent in children than in adults and is often mild, although disease associated with enterovirus 71 presents has high morbidity (8). Regarding clinical presentation, in pediatric patients—particularly infants and neonates—symptoms may be subtle and nonspecific, making early diagnosis challenging. In contrast, adult patients tend to exhibit a more classical and evident clinical profile (9,10).

Furthermore, meningitis remains a major global public health challenge, and its early diagnosis is crucial to reducing morbidity and mortality. Nonetheless, in many parts of the world—particularly in resource-limited rural settings—the infrastructure and availability of conventional diagnostic methods are severely limited or nonexistent, often resulting in delays or failure to accurately identify the causative agent (11,12).

In recent years, there have been significant developments in diagnostic methods for the rapid, accurate, and early identification of the causative viruses. Among these, molecular tests based on polymerase chain reaction (PCR) have the potential to detect less frequent etiological agents of encephalitis. Consequently, efforts aimed at the early identification of the causative viruses are critical for optimal clinical management of patients and to avoid serious sequelae, such as long-term cognitive impairment, short-term memory loss, and psychiatric morbidity (13). A relevant aspect underscored in the literature is that the underutilization of polymerase chain reaction (PCR) techniques has likely contributed to the widespread failure to identify infectious etiologies.

This diagnostic gap highlights the need for greater implementation of these molecular methodologies, given their high sensitivity and specificity for detecting pathogenic nucleic acids (14).

Several studies on the clinical features of patients with bacterial meningitis have been performed. However, to our knowledge, information about the epidemiological characteristic of VM in Latin American countries is limited; in addition, some studies have shown that the viral etiology of VM differs from one geographic area to another (15,16). Globally, viral pathogens constitute the primary etiological agents of CNS infections, exceeding bacterial infections in prevalence, with a particular predilection for pediatric patients (17). Therefore, the objective of this study was to describe the main clinical features, microbial causative agents, and laboratory characteristics of viral meningitis detected by molecular testing, in the context of a tertiary referral hospital in Medellín, Colombia.

MATERIALS AND METHODS

Design and Sample

This cross-sectional study was performed between February 2017 and July 2022. This study is based on a convenience sample. The cases included patients hospitalized in the teaching Hospital San Vicente Fundación, a tertiary health institute and reference center for infectious diseases in Medellin, Colombia. There was no age restriction. Inclusion criteria were restricted to patients with cerebrospinal fluid (CSF) samples yielding positive results for viral pathogens via polymerase chain reaction (PCR) analysis. The criteria for suspected acute symptoms of meningitis infection and the inclusion of the patients followed the institutional clinical guidelines, considering findings such as headache, neck stiffness, fever, and altered consciousness. To mitigate information bias, the data collection instrument was reviewed, and standardized questionnaires were developed and shared with the research team. The consistency of the database was subsequently verified through individual assessment of atypical values. Additionally, a random audit of 20% of the records was performed to ensure data quality and reliability.

Clinical and Microbiological Information

Data were extracted from medical records. The following variables were obtained: gender, age, symptoms (existence of prodromal symptoms: fever, headache, seizures, and nausea) and death.

The molecular test used was the FilmArray® Meningitis/Encephalitis (FA-M/E) panel (BioFire Diagnostics, bioMérieux, Salt Lake City, USA) (18). This test allows the qualitative detection of 14 pathogens (bacteria, viruses, and one fungus). Among the viruses detected are cytomegalovirus (CMV), enterovirus (EV), herpes simplex (HSV) 1 and 2, human herpesvirus 6 (HHV-6), human parechovirus, and varicella-zoster virus (VZV). Finally, data were gathered on conventional microbiological procedures (chemistry, cell count, Gram stain, and conventional culture).

Statistical Analysis

Statistical analysis was performed using R (version 3.6.3, The R Foundation for Statistical Computing, Vienna, Austria) and the Jamovi spreadsheet application (Jamovi v.1.2, The Jamovi project, Sydney, Australia).

Study participants were segregated into two groups: younger (patients aged between <1 and 16 years) and patients aged 17 years or older. A descriptive analysis was performed for the individual characteristics of the participants. Descriptive data were presented as the mean and standard deviation (SD) or as the median and interquartile range (IQR), as appropriate. Characteristics between the two groups (pediatric/adults) were compared using the Mann-Whitney U-test for continuous variables and chi-square tests for categorical variables. A p-value <0.05 was considered significant.

The study was approved by the Institutional Review Board of the Hospital San Vicente Fundación according to Minutes No. 05/2021 of February 19, 2021. In addition, it took into account the ethical principles for research involving human subjects established in the Declaration of Helsinki, as well as the provisions on health research set forth in Resolution 8430 of 1993 of the Colombian Ministry of Health.

RESULTS

During the years analyzed, a total of 82 individuals were identified with viral meningitis by molecular tests. The male-to-female ratio was 1.9 with a total mean age of 25.2 ±26.5 (range: 15 days to 85 years). The average age in the pediatric group was 3.4 ± 4.5 years, in comparison to 50.6 ±17.4 years in adults. The male gender was more common in both age groups: 26 cases among children (59.1%) and 28 cases among adults (73.7%). The clinical presentation was similar in

both groups, with fever and headache being the most common symptoms, 55 (67.1%) and 31 (37.8%), respectively. Regarding the median length of hospitalization, it was clearly shorter in the pediatric group compared to the adult group, with statistically significant differences, 7 vs 16 days, respectively ($p<0.05$). Other sociodemographic and clinical characteristics are summarized in Table 1.

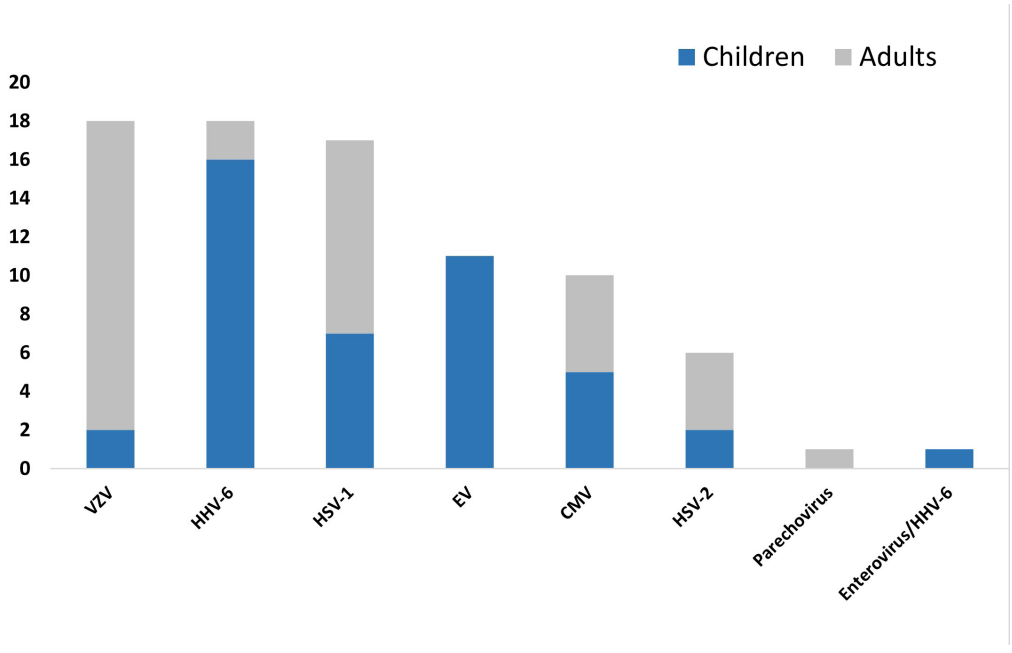
Table 1. Sociodemographic and clinical data of patients with viral meningitis diagnosed by molecular test at Hospital Universitario San Vicente Fundación, Medellin, Colombia, 2017-2022

Feature		Total (n=82)	Children (n= 44)	Adults (n=38)	P value*
Gender (%)	Female	28 (34.2)	18 (41.0)	10 (26.3)	0.164
	Male	54 (65.8)	26 (59.0)	28 (73.7)	
Age, years, Me (IQR) ‡		14 (1 – 45.7)	1 (0.5 – 5)	28.5 (38 - 66.3)	< 0.001
Symptoms and signs (%)	Fever	55 (67.1)	37 (83.0)	18 (47.4)	0.004
	Headche	31 (37.8)	13 (29.5)	18 (47.4)	0.096
	Nausea or vomiting	15 (18.3)	12 (27.3)	3 (7.9)	0.023
	Seizures	13 (15.9)	9 (20.4)	4 (10.5)	0.219
	Neck rigidity	9 (11.0)	8 (18.2)	1 (2.6)	0.024
Clinical conditions (%)	HIV positive	15 (18.3)	0 (0.0)	15 (39.5)	-
	Empiric antibiotic therapy	39 (47.6)	27 (61.4)	12 (31.6)	0.007
Length of stay, days (IQR) ‡		12 (6 - 22.0)	7 (5 -17.6)	16 (9.8 - 23)	0.006
Outcome (%)	Death	11 (13.4)	3 (6.8)	8 (21.1)	0.059

Me: median
IQR: Interquartile ranges
HIV: Human immunodeficiency Virus
*Chis-square tests
‡ Mann-Whitney U test

Source: own elaboration.

Regarding the causative agents, VZV along with HHV-6 were the most commonly diagnosed, with 18 cases each (22%), followed by HSV-1 with 17 detections (20.7%). Meanwhile, other etiological agents were reported with lower frequencies, including EV with 11(13.4%), CMV with 10 (12.2%), HSV-2 with 6 (7.3%), and parechovirus with 1 case (1.2%). A single codetection (EV and HHV-6) was found. The details of viral infections by age group are shown in the following figure.



VZV: Varicella-zoster virus
HHV- 6: Human herpesvirus 6
HSV- 1: Herpes simplex virus 1
EV: Enterovirus
CMV: Cytomegalovirus
HSV- 2: Herpes simplex virus 2

Note. Etiological distribution according to age group of patients with viral meningitis diagnosed by molecular testing, Hospital Universitario San Vicente Fundación, Medellin, Colombia, 2017-2022.
Source: own elaboration.

Figure. Etiologic profile of viral meningitis by age group

Table 2 presents the laboratory findings, including leukocyte count, protein, and glucose levels in cerebrospinal fluid (CSF). A statistically significant difference was observed in protein concentrations between pediatric and adult patients (p=0.0025), with lower values recorded in the

pediatric group. In addition, four positive bacterial cultures were isolated: *Klebsiella pneumoniae* (2 cases), *Serratia marcescens* (1 case), and *Enterococcus faecium* (1 case), indicating the presence of viral and bacterial coinfection.

Table 2. Cerebrospinal fluid microbiological indicators of patients with viral meningitis diagnosed by molecular testing at Hospital Universitario San Vicente Fundación, Medellin, Colombia, 2017-2022

	Total (n = 82)	Children (n= 44)	Adults (n= 38)	*p value*[a]
CSF parametersb				
CSF WBC count (cells/µl)	13 (1 - 110)	9 (1 - 156.8)	16 (0.8 - 95.8)	0.872
CSF mononuclear count (cells/µl),	5 (0 - 40.0)	3 (0 - 31.8)	5 (0 - 40)	0.718
CSF polymorphonuclear count (cells/µl)	6 (0 - 46.8)	5 (0 - 45.3)	9 (0 - 32.6)	0.610
CSF protein (mg/dL)	69.6 (36 -132)	44.5 (34.0 - 98.0)	112.2 (55.1 - 172-2)	0.002
CSF glucose (mg/dL)	51.0 (41 - 70)	50.5 (41.5 - 68.5)	58.0 (42.3 - 71.3)	0.764
Positive culture (%)	4 (5.1)	2 (2.5)	2 (2.5)	-
a: Mann-Whitney U test b: Median (IQR) CSF: Cerebrospinal Fluid WBC: white blood cells IQR: Interquartile ranges				

Source: own elaboration.

DISCUSSION

Viral infections of the CNS encompass both acute and chronic conditions caused by a range of different pathogens. In general terms, viral meningitis is more common than bacterial meningitis, particularly in pediatric populations and in countries with access to vaccination programs.

This condition can have a complex and variable pathogenesis that is influenced by the host, viral etiology, and environmental factors (3). This study highlights the epidemiological and microbial aspects of viral meningitis in the context of the clinical practice, in a tertiary hospital in Medellín, Colombia. In the present study, among adults, varicella-zoster virus was the most frequently identified agent, whereas in children, human herpesvirus 6 was more commonly detected. Children were more likely to be male and to present with lower cerebrospinal fluid (CSF) protein levels ($p<0.05$).

Regarding gender analysis, this study demonstrated a clear predominance of viral CNS infections among males compared to females. This finding is in agreement with previous reports stating that male adults differ significantly from female adults in clinical presentation, etiologies, and outcomes (19), men and women can differ in susceptibility to various infections; for example, males are more susceptible to meningitis, pneumonia, rabies, syphilis, tetanus, and some types of cancers than females (19,20).

Concerning age, viral meningitis is considered one of the most common clinical conditions affecting different population groups. In the present study, younger patients were the most affected group, which is consistent with the literature, where viral meningitis occurs most commonly in young children and the incidence decreases with age (21). It is important to highlight that 27 patients were less than one year old, which represents around one-third of the study sample. This finding is consistent with previous reports showing that infants <1 year of age are the most affected age group due to their immature immune system (22).

Generally, although the etiology of meningitis can vary, the symptoms are usually similar (23). As expected, in the present study, most of the patients presented fever. In this regard, Fica and colleagues documented that the main clinical manifestations were fever, headache, impairment of consciousness and, less frequently, seizures (24). In the current study, clinical manifestations such as nausea, seizures, and neck stiffness were less frequent. On the other hand, according to the length of hospital stay, it was shorter in children was shorter than in adults, which implies that the clinical course in younger ages is more benign, with the symptoms being resolved more quickly than in adults.

Regarding etiology, herpesviruses were found to be more frequent, moreover, they were detected in a wide range of ages. Concerning VZV, since the development of PCR for diagnosis, the number of diagnosed cases has increased as a cause of meningoencephalitis (25)mild cases of herpes simplex virus (HSV, and it is considered the third most common causative agent of viral meningitis after EV and HSV-2 (26). In the present study, 18 cases of VZV were detected. The greater proportion of positive for VZV-positive subjects was found among individuals aged 28 to 85 years old, with only two in younger patients. VZV reactivation appears most frequently in older adults presenting with meningoencephalitis, among patients aged ~50–60 years, with an upward course in the decades >60 years (27). In contrast, the median age in patients with VZV-related meningitis in the present study was 42 years, this finding can be linked to young immunocompromised patients. Reactivation of VZV infection in the CNS is more common in patients with HIV in comparison with other immunodeficient patients and immunocompetent individuals (28). In this report, of the 18 patients with VZV, seven were positive HIV-positive.

On the other hand, positive HHV-6 results were identified in 16 young patients, none of whom were known to be HIV positive, and in 2 adults, both of whom were HIV seropositive. Interestingly, PCR testing is becoming more widely used in the diagnosis of suspected meningoencephalitis and its HHV-6 positivity in the CSF is increasingly documented (29,30). The proportion of cases in the present study (22.0%) agrees with prior reports from other parts of the world that comprising between 10.7% and 31.3% of all positive CSF PCR panel results among patients with suspected meningoencephalitis (29,30). The role of HHV-6 as an etiologic agent in CNS infections in immunocompetent patients is still controversial, however, it has been associated with meningitis/encephalitis as a primary infection or a consequence of reactivation of latent infection, as is the case with other DNA viruses (31). The detection of this virus requires a cautious interpretation, since its presence does not necessarily mean active infection.

The third most frequent microorganisms detected during this study was HSV-1 in these cases there was a distribution in both age groups, with genders equally affected, this finding has been previously reported (32). This virus is common, with seropositivity among older adults estimated to be 60–90% around the world; it is also responsible for ~90 % of HSV encephalitis in adults and children (33). Previously in Colombia, the frequency of herpetic infections in school-age children from the Department of Antioquia was determined by establishing a seroprevalence of 78% for

HSV-1 (34) . Latency and reactivation are characteristics of viruses from the herpes family, including HSV-2 and CMV, and they can affect both genders and all age groups, including immunosuppressed patients (35). Furthermore, differentiating between VZV and HSV in CNS infections in the absence of a dermatological rash represents a true challenge (36). Primary genital infections caused by HSV-2 are accompanied by meningitis more than one-third of women and 11% of men (23), however, numerous cases of either HSV-1 or HSV-2 meningitis are reported without any recent occurrence of genital lesions (37).

In the present study, EV were identified exclusively in the pediatric population. Specifically. Nearly half of these patients were infants aged 1 year or younger. This align with previous reports indicating that the majority of aseptic meningitis cases caused by EV occur mainly in children under one year old (38). Also, there was greater number of males with EV slightly above females (7/11), it is probably related to the predisposition of the EV in affecting the male gender, as has been demonstrated in other studies (39). EV is rarely fatal, but may still be complicated by significant short-term morbidity and prolonged clinical recovery (6). Finally, other viral agents, including parechovirus were detected, but at a lower frequency.

Regarding the diagnosing process of this type of meningitis, it begins with the identification of a CSF pleocytosis, where the WBC count typically ranges between 80 and 100 cells/µl, with a large proportion of lymphocytes (>80%). Specifically, glucose can be usually normal to slightly depressed, and protein levels usually remain normal to mildly elevated (40). Moreover, the comparison of medians in the CFS parameters between adults and children showed that there are slightly greater numbers of WBC, as well as a higher glycorrhachia, in adults. However, protein concentration showed that children present a protein concentration in the CSF that is lower in comparison to adults with a difference that is statistically significant; this is consistent with other studies (14), according to the fact that the inflammatory response is less on a CSF level in children.

It is important to note that some bacteria, such as mycoplasma, spirochetes, mycobacteria, and Brucella, and various fungi, can occasionally present as acute aseptic meningitis (37)respectively. Indeed, the number of cases of viral meningitis that occurs annually exceeds the total number of meningitis cases caused by all other etiologies combined. Focal CNS infections, on the other hand, such as occur in the spinal cord with viral myelitis, are much less common and may be confused with non-infectious disorders that cause acute flaccid paralysis (AFP. In the present study,

a young female patient had a coinfection with meningeal tuberculosis; therefore, complementary tests and clinical factors should be considered.

There are limitations to this study. Primarily, it was conducted as a single-center, but provides a sound perspective on the viral etiology in meningitis; this information will be useful as a baseline to update the epidemiology of this disease to other contexts. On the other hand, this study is limited by its retrospective design at a single hospital setting and the lack of a control group; thus, signs and symptoms, laboratory results and medical decisions could have missed additional relevant data. Likewise, as is documented previously (14), tools to diagnose VM may be underutilized due to the generally benign course of illness, and even though approximately most cases were included with PCR test during the period of study, other suspected patients did not undergo tests and they could be missed. Furthermore, other viruses not included in the master list of PCR testing (described in the methodology), may result in underestimating other etiological causes. Likewise, since the region is also endemic for arboviruses like dengue and zika, the screening for these possible meningitis causes would need a broader study range.

One of the main contributions of this study is that it provides local epidemiological data from a referral hospital setting, allowing for the identification of the most frequent viral etiologies of meningitis. This knowledge supports the avoidance of unnecessary antibiotic use and helps reduce prolonged hospital stays. Etiological distribution varied by age group: for example, VZV was more common in adults, whereas HHV-6 predominated in pediatric patients. The timely identification of these agents allows for the initiation of targeted antiviral therapy, such as acyclovir, thereby reducing the risk of complications. Moreover, the findings offer academic and public health value by supporting the prioritization of molecular diagnostic tools (e.g., PCR) in regional hospitals, which may improve early diagnosis and facilitate outbreak detection—as previously occurred in Antioquia in 2004 with enterovirus, as referenced in this study.

CONCLUSION

In summary, viral meningitis infection is a disease of growing public health importance, the current retrospective study provides comprehensive information concerning VM distribution in a referral center. Although, the clinical presentation and prodromes are similar in both age groups, there was an etiologic diversity of VM. HHV-6 and EV are the most frequent pathogens in children,

while VZV and HSV-1 predominate in adults. Therefore, knowing the most common causative agents responsible for aseptic meningitis will help in better understanding the disease. These results highlight that further research is needed to identify other possible additional viral pathogens in the current diagnostic methods since viral agents are considered the major cause for meningitis worldwide.

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Conflicts of Interest: None stated by the authors.

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