GSC Advanced Research and Reviews

eISSN: 2582-4597 CODEN (USA): GARRC2

Cross Ref DOI: 10.30574/gscarr

Journal homepage: https://gsconlinepress.com/journals/gscarr/

(RESEARCH ARTICLE)

Viral infections of the central nervous system

Zineb Nassiri [1, 2, *], Salma Amrani Idrissi [1, 2], Asmaa Lamrani Hanchi [1, 2] and Nabila Soraa [1, 2]

[1] *Department Microbiology, Mohamed VI University Hospital, Marrakesh, Morocco.*
[2] *Faculty of medicine and pharmacy, Cadi Ayyad University Marrakesh, Morocco.*

GSC Advanced Research and Reviews, 2023, 14(03), 209–218

Publication history: Received on 07 February 2023; revised on 13 March 2023; accepted on 16 March 2023

Article DOI: https://doi.org/10.30574/gscarr.2023.14.3.0085

Abstract

Background: Viral infections of the central nervous system are an important cause of morbidity and mortality.

Aim: This study was designed to identify the viruses responsible for viral involvement of the CNS and to determine their frequency, circulation pattern, and seasonality.

Methods: Detection, by multiplex PCR using FilmArray® Meningitis/Encephalitis panel, of viruses in the cerebrospinal fluid of all patients admitted for suspected viral infection of central nervous system and requiring hospitalization in the various departments of the Mohamed VI University Hospital of Marrakesh.

Results: Viral infection was diagnosed in 74 of 984 patients (7.5%). The viruses responsible were identified as enterovirus in 22 cases (26.82%), Cytomegalovirus in 21 cases (25.6%), Herpes simplex virus-1 and Varicella-Zoster virus in 12 cases each (14.63%). Other agents were also reported with lower frequencies namely human herpes virus 6 and herpes simplex virus-2. Although the overall rate of CNS viral infection was significantly higher between the summer and spring seasons, the seasonality of the different viral pathogens was variable.

Conclusion: The FilmArray® test can be an aid in the diagnosis of meningitis/meningoencephalitis, especially of viral etiology. Its rational use can improve the management of patients with potentially severe infections without additional cost.

Keywords: Central nervous system infection; Virus; meningitis; Meningoencephalitis; PCR; Enterovirus

1. Introduction

The central nervous system (CNS) plays a fundamental role in the functioning of the body and its adaptation to the environment.

Central nervous system infections are currently a real diagnostic and therapeutic challenge due to mortality, sequelae and significant socio-economic costs.

Viral infections following virus replication in the CNS can cause meningitis, encephalitis and myelitis.

Encephalitis, in particular, is a serious illness often accompanied by long-term or life-long sequelae and a high fatality rate. [1].

* Corresponding author: Zineb Nassiri

The incidence of CNS viral infections is estimated to be 20-30/100,000 per year, about three times higher than bacterial infections whose prevalence has decreased through vaccination in many countries. [2].

Many viruses can be responsible for CNS damage, neurotropic viruses, which can cross the blood-brain barrier, which are directly responsible for neuroinvasive lesions.

The most frequently detected etiological pathogens in the world are viruses belonging to the families Herpesviridae [Herpes simplex virus (HSV), varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV)] and Picornaviridae (enterovirus (EV), parechovirus). A wide range of less common viruses (such as mumps viruses, and measles), or arthropod-transmitted viruses (arbovirus) have been recognized as additional etiologies of acute CNS infections [3].

The diagnosis in this case is essentially based on the identification of the virus responsible in the cerebrospinal fluid (CSF). Over the past two decades, techniques based on nucleic acid amplification and hybridization have revolutionized the diagnosis of CNS infections and improved the detection rate of viral agents, thus reducing the unnecessary use of antibiotics and the length of hospitalization. [4].

This study was conducted with the aim of identifying, from the updated data, the viruses responsible for CNS viral infection as well as determining their frequency, circulation pattern and seasonality.

2. Material and methods

2.1. Type and framework of the study

This is a retrospective study with descriptive aim, carried out within the Department of Microbiology of the Arrazi Hospital of the Mohamed VI University Hospital Center (UHC), including all patients treated for a suspicion of meningitis or meningo-Encephalitis of viral origin and requiring hospitalization in the various departments of the Mohamed VI UHC of Marrakesh.

2.2. Study duration

This work was completed over a 5-year period from January 2018 to December 2022.

2.3. Inclusion criteria

This study included all patients hospitalized at the various departments of the Mohamed VI UHC, who had received Meningitis/ Encephalitis (M/E) multiplex PCR during the study period.

2.4. Exclusion criteria

Have been excluded: patients who did not benefit from PCR (M/E), patients treated in outpatient without medical records, non-viral CNS infections (bacterial, tubercular, parasitic, fungal and aseptic inflammatory origin) and control PCRs.

2.5. Data collection

Data collection was based on the microbiology service database.

2.6. Data analysis

The Microsoft Excel 2016 software was used for the statistical analysis of the data. These have been converted to a percentage, average or median.

Multiplex PCR using FilmArray® Meningitis/Encephalitis (M/E) panel of Biofire: Allows simultaneous and rapid one-hour search for 15 different pathogens involved in meningitis and encephalitis on the same CSF sample, 7 viruses (CMV, EV, HSV-1, HSV-2, Human herpes virus 6 (HHV-6), Human parechovirus, VZV and 6 bacteria [(Escherichia coliK1, Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis, Streptococcus agalactiae, Streptococcus pneumoniae and 2 yeasts (Cryptococcus neoformans/gattii(CN)]. Each FilmArray cassette is single-use and includes all the lyophilized reagents required for nucleic acid extraction, amplification and detection.

This study focused solely on the viral etiology of CNS infections in symptomatic patients.

3. Results

Over a 5-year period, 8292 CSF samples were received at the microbiology laboratory, of which 984 were analyzed by PCR Filmarray® Meningitis/Encephalitis, a prevalence of 12% of CRL that received syndromic PCR.

Of the 984 CSF samples analyzed, the FilmArray® M/E panel detected at least one neuro-meningeal tropism virus in 74 patients and the coexistence of two or more pathogens was found in 10 patients with a co-infection rate of 14.66% (Table 1)

Table 1 Co-infection of agents causing CNS viral disease.

Types of co-infection	**Number**
Viral co-infection	
CMV+HHV-6	2
CMV+HSV-2	2
CMV+ VZV	1
HHV-6+VZV	1
EV+HHV-6+HSV-1	1
Bacterial co-infection	
HHV-6+ Neisseria meningitidis	1
HHV-6+ Pneumococcus	1
CMV+ Haemophilus influenzae	1
Fungal co-infection	
CMV+ Cryptococcus neoformans	1

The total confirmed cases were almost similar throughout the study period. However, an increase in cases was observed in 2021, with 26 cases of confirmed CNS viral infections (31.7%).

Patients in this study were 10 days to 99 years old, with a median age of 20.8 years. 47.3% were children and 52.7% were adults.

Of the total number of patients, 38 were male (51.35%) and 36 were female (48.65%), with a H/F sex ratio of 1.06.

Concerning the distribution of patients by hospital departments, 40.54% of patients were hospitalized at the infectious diseases department, 25.67% at the pediatric emergency department, 16.21% at the A pediatric department, 4.05% in the pediatric intensive care unit and neurology departments, 2.7% in emergency and life-saving departments, 1.35% at the neonatal intensive care units, of neurochirugia department and the B pediatric department.

The PCR was performed under clinical suspicion of meningitis (51.39%) meningoencephalitis (45.84%) and myelitis (2.77%). The clinical symptomatology was in the context of an immunodepressive terrain represented mainly by HIV infection in 28% of patients.

CSF cytology was normal in 37.13% of patients and high in 54.05% of whom 67.5% was lymphocytic predominant.

Of the 984 CSF samples tested throughout the study period, 74 (7.5%) were positive for at least one agent of viral infection of CNS. (Table 2/Figure 1) summarizes the distribution of different viruses by year of detection. Among the positive CSF, Enterovirus was the most frequently detected virus, representing 26.82% (22/82) of cases, followed by Cytomegalovirus (21/82, 25.6%), and HSV-1 and VZV 12/80, 14.63%). Other agents were also reported with lower frequencies, HHV-6 (10/82, 12.2%) and HSV-2 (5/82, 6.1%) (Table 2).

Table 2 Distribution of viruses detected over the years from 2018 to 2022 (n= 82).

	All years	2018	2019	2020	2021	2022
	N° (%)	N° (%)	N° (%)	N° (%)	N° (%)	N° (%)
Enterovirus	22 (100)	5 (22.7)	3 (13.7)	3 (13.7)	10 (45.4)	1 (4.5)
CMV	21 (100)	4 (19)	3 (14.3)	3 (14.3)	7 (3.4)	4 (19)
HSV1	12 (100)	3 (25)	2 (16.6)	2 (16.6)	2 (16.6)	3 (25)
HV2	5 (100)	1 (20)	1 (20)	0 (0)	3 (60)	0 (0)
VZV	12 (100)	2 (16.7)	1 (8.3)	2 (16.7)	3 (25)	4 (33.3)
HHV6	10 (100)	2 (20)	3 (30)	3 (30)	1 (10)	1 (10)

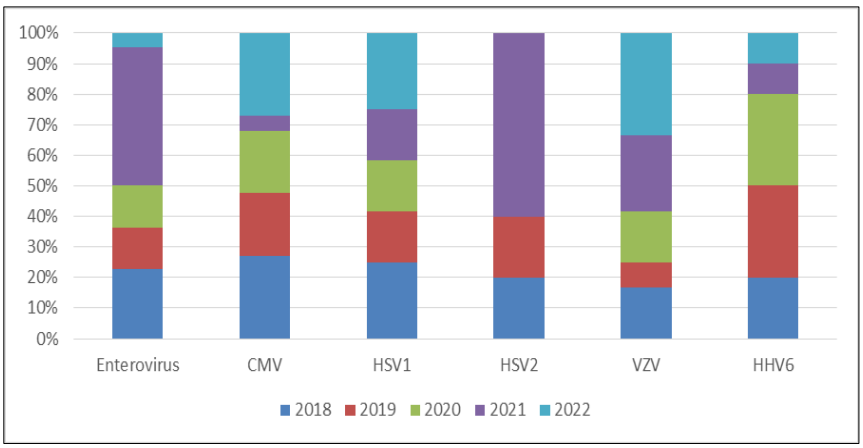

Figure 1 Distribution of viruses detected over the years from 2018 to 2022.

EV was found only in children, CMV mainly in young adults while the other viruses detected were present in almost all age groups at varying percentages (Figure 2).

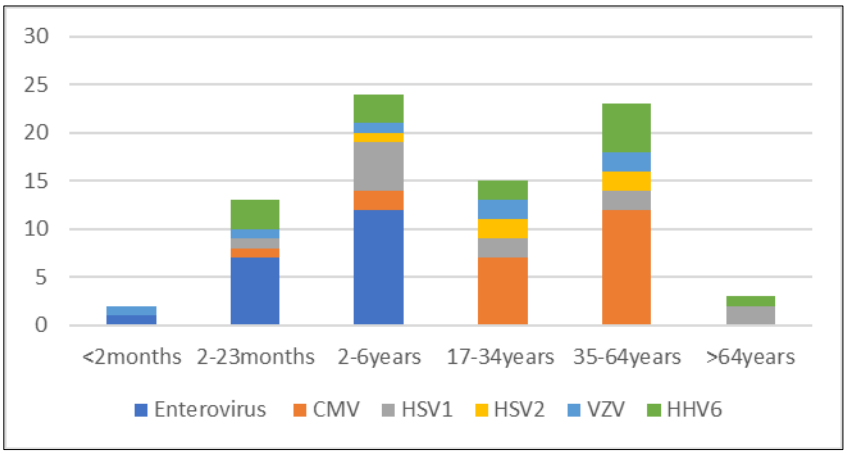

Figure 2 Distribution of viral pathogens by age group

Seasonal viral distribution: Morocco is distinguished by four types of climate: humid, sub-humid, semi-arid and arid. The climate observations, concerning Morocco, carried out over the last decades attest to the progression of the semi-arid climate towards the north of the country. These data indicate that during the first 3 years a significant circulation of viruses responsible for CNS infection was identified during the summer seasons (June-September) with a peak in late

fall as shown in Figure 3. In 2021- 2022, a predominance of CNS viral infections was recorded mainly in late winter-spring.

Over the entire study period and in general, EV has been circulating throughout the year except in February (Figure 4), however, data from the 5 years identified significant peaks during the summer season (June-September). The highest detection rate was observed between March and June 2021, with a detection rate of up to 45.5% of all EV-positive CSF (Figure 3).

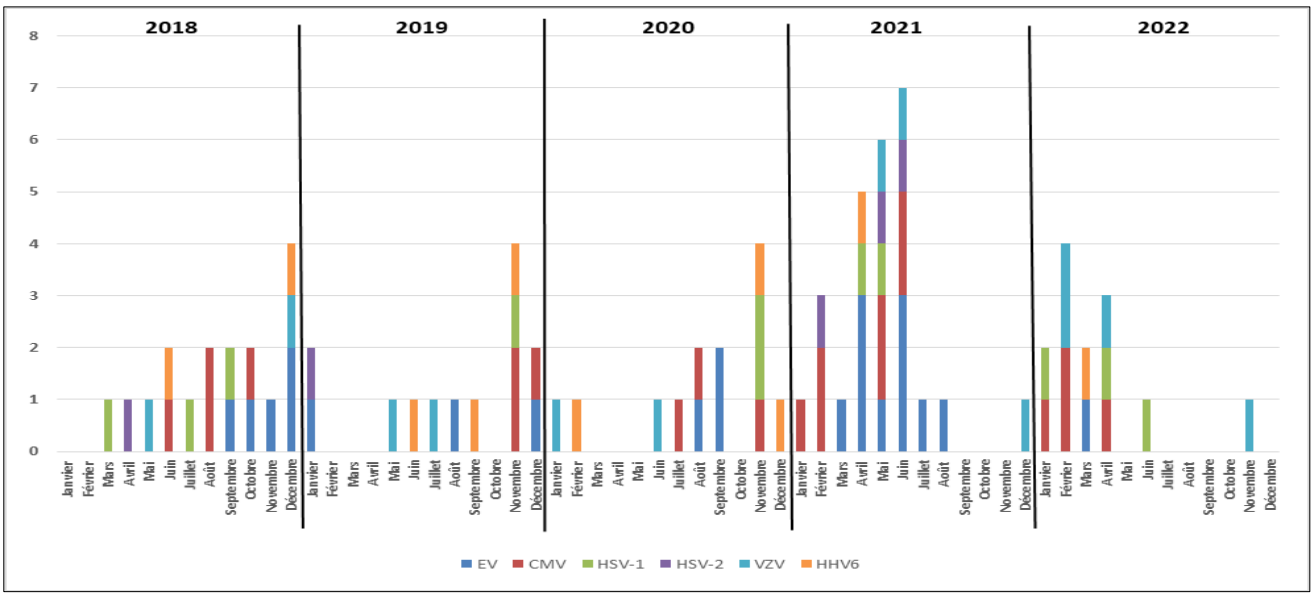

Figure 3 Distribution of viruses detected by Filmarry® M/E by month of the 5 years (2018-2022)

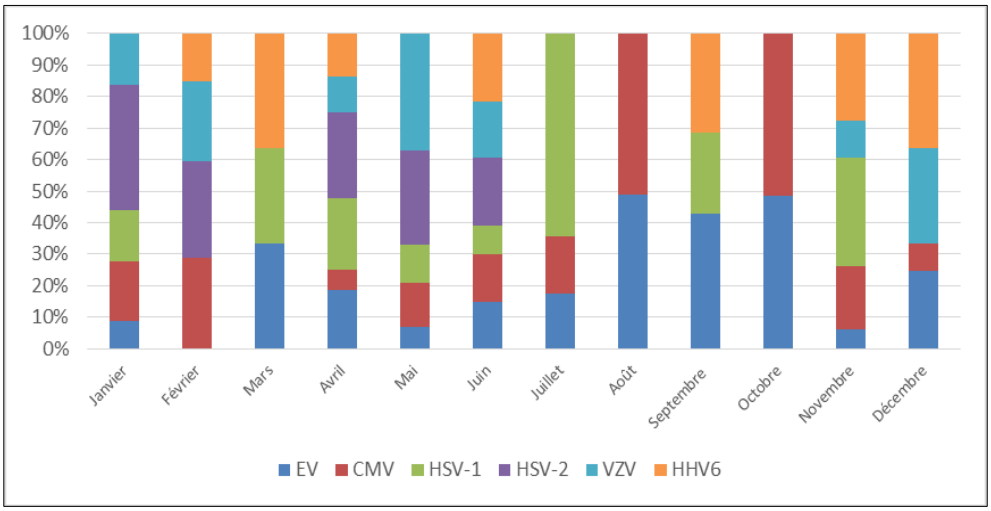

Figure 4 Distribution of viruses detected by month for all years combined.

CMV was the second leading cause and the first cause in immunocompromised (HIV) CNS viral infections (Figure 5/Table 3). It tended to move in a pattern that varied from year to year, but was not detected in March and September. The highest detection rate was observed between January and June 2021, with a detection rate of up to 31.8% of all CSF positive for CMV.

Table 3 Distribution of viruses detected by Filmarry® M/E by year in HIV-positive patients (n=23).

Years	CMV	Enterovirus	HSV1	HSV2	VZV	HHV6
2018	3	0	0	1	1	1
2019	2	0	0	0	1	0
2020	2	1	0	0	0	0
2021	4	0	0	3	2	0
2022	2	0	0	0	0	0
Total	13	1	0	4	4	1

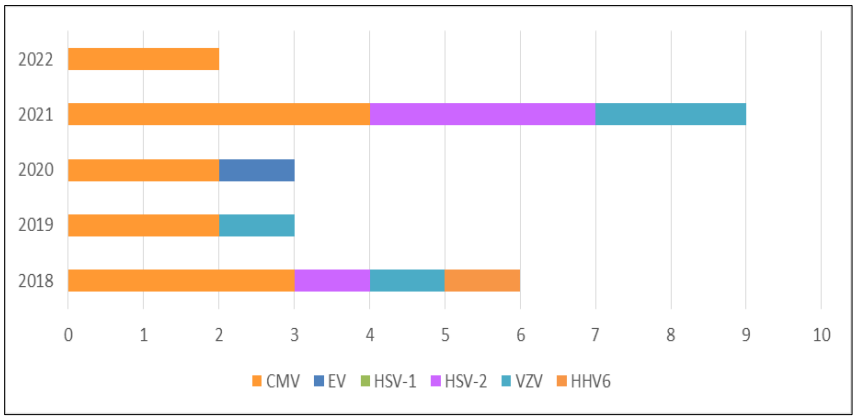

Figure 5 Distribution of viruses detected by Filmarry® M/E by year in HIV positive patients.

Although the overall rate of CNS viral infection was significantly higher between the summer and spring seasons, the seasonality of different viral pathogens varied, as illustrated in Figure 3.

4. Discussion

Some neurotropic viruses can be responsible for CNS infection through various mechanisms, including direct replication in the CNS, resulting in meningitis, meningoencephalitis, or immune-related processes, such as acute disseminated encephalomyelitis. Viral pathogenicity and virulence strongly determine the expression of CNS infection, and host-related risk factors such as immunosuppression often increase the risk of infection [5,22].

This study reports an overall positivity rate of 7.5% for viral agents by the multiplex PCR technique using FilmArray® M/E panel. Similar studies in India and the US reported an approximate positivity rate [13,15]. While others [10,11,12,14,17] found higher rates of up to 44%.

In terms of age and sex analysis, a mean age of 20.8 years and a male predominance were reported which is consistent with several studies [6,8,10,11], a study in Columbia (2018 agrees with the results of this study with a mean age of 20 years and a male predominance [9].

The present study indicated a slight predominance of the clinical meningitis form to meningoencephalitis as a reason for hospitalization, which represented 51.39% and 45.84% respectively, while myelitis represented only 2.77%. These results are consistent with several studies [6,17,19,20], while others have shown the predominance of the meningoencephalitis form, as in the Brazilian study by Mendoza et al., where meningoencephalitis was the most frequent reason for hospitalization in 51.5% of cases, followed by meningitis in 36% of cases and then myelitis in 4.5% of cases [7].

Neuro-meningeal symptomatology occurred in an immunosuppressive (HIV) setting in 28% of cases, similar results were reported by Mawuntu et al in Indonesia (2018) [16].

Etiological agents vary considerably from one region of the world to another, or even from one continent to another. Several factors such as age, geographic location, socio-economic status, climate, and host immune competence affect the epidemiology of CNS viral infections [29].

The distribution of pathogens in this study showed the prevalence of EV (26.82%). Other authors have also reported that enteroviruses are the most common cause of CNS infection [6,20,21].

They are responsible for most viral meningitis, accounting for about one billion infections each year worldwide [30].

The EV cases found in this study were all in children, consistent with previous studies also showing a high rate of enterovirus CNS infection in children [23, 24]. However, other authors believe that CNS enterovirus infections are underestimated in adults [25].

CMV infection was found in 21 CSF samples, 62% of patients with CMV infection in CSF were HIV positive. CMV acts as an opportunistic agent, causing acute and chronic CNS infections in immunodeficient patients [7]. Some studies suggest that CMV infection of the CNS is probably underestimated in immunocompetent patients [26].

Since CMV may exist in a quiescent state in leukocytes, detection of the CMV genome could occur without active infection.

HSV is considered the second most common cause of viral meningitis after enterovirus in developed countries. [27,30]

HSV-1 was detected in 14.63% of the 74 positive CSF samples. This finding is consistent with previous studies that show that HSV-1 is the most common causative agent especially in encephalitis and is the most detected virus in the CNS in elderly patients (>64 years). [28]

VZV was detected in CSF in patients of all ages in children and adults, of whom 33% (4 patients) were immunocompromised. Other authors have also reported that VZV infects the CNS of patients with retroviral HIV infection with a higher risk of developing disseminated forms [7,27].

Reactivation of herpes simplex virus, type 1 and 2, varicella zoster virus, and cytomegalovirus is common in the context of human immunodeficiency virus (HIV) infection.

Infection of the CNS with more than one virus is rare in the literature, Co-infections have been previously reported in 1-7% of positive samples [7,15,18]. In this study, co-infections were detected in 10 patients. 6 patients were infected with two viruses and 1 patient with 3 viruses (EV, HSV1 and HHV6).

The triple virus co-infection was observed in Triple virus co-infection was observed in an apparently immunocompetent 2-year-old child with meningitis. In this case, it is possible that the disruption of the blood-brain barrier by the enterovirus may have facilitated the introduction of other viruses into the CNS.

The possibility of false positives can be discussed since this multiplex PCR does not distinguish between the active and latent forms of herpesviridae. The use of other quantification techniques may be required depending on the clinical context.

In terms of seasonality, and in general, our data indicate that CNS viral infection circulates throughout the year, but with higher rates during the summer seasons and a decrease during the cold seasons. Our results are consistent with literature data in some countries [23,30,32,33] which reported that the seasonal dynamics of neurotropic viruses are higher during the summer and early fall.

On the other hand, a recent study conducted in Iran (2019) reported higher circulation rates during the cold months (fall to spring) [31].

As mentioned previously, enterovirus was the most frequently detected virus, and reached significant peaks during the summer seasons (June-September). According to reports of several previous studies EV circulates throughout the year but tends to peak in summer [30,35, 36].

The mechanisms that explain this observation are not well known, but some theories have been proposed. Green et al. suggest that during the summer and fall, there is potentially increased fecal-oral transmission of enteroviruses promoted by warm weather and scanty clothing, especially in children [35].

Limitations of the Study

This is a retrospective study and we were not able to review the charts of patients with suspected CNS, which would have allowed us to obtain more information and perform a more thorough analysis.

5. Conclusion

CNS viral infections represent a significant public health burden due to the high morbidity and mortality, the difficulties in diagnosis and the lack of specific treatment in most cases. The application of molecular methods allows the rapid detection of pathogens in the acute phase of the disease. A useful strategy for the laboratory diagnosis of CNS infections in humans is to search for a wide panel of potential causative agents at one time using molecular techniques. The FilmArray® test can be a tool to assist in the diagnosis of meningitis/meningoencephalitis. As well, its rational use can improve the management of patients with potentially severe infections at no additional cost.

Compliance with ethical standards

Acknowledgments

I would like to thank everyone who contributed to the success of this work especially Professor Soraa.

Disclosure of conflict of interest

Authors declare no conflict of interest.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

References

[1] Anna Papa, Tzimoula Kotrotsiou , Elpida Papadopoulou and al Challenges in laboratory diagnosis of acute viral central nervous system infections in the era of emerging infectious diseases: the syndromic approach. Expert Rev Anti Infect Ther. 2016 Sep;14(9):829-36.

[2] Angelina Kakooza-Mwesige, Desire Tshala-Katumbay, Sharon L. Juliano. Viral infections of the central nervous system in Africa. Brain Res Bull. 2019 Feb;145:2-17

[3] Granerod J, Cunningham R, Zuckerman M, et al. Causality in acute encephalitis: defining aetiologies. Epidemiol Infect 2010; 138:783-800.

[4] Debiasi RL, Tyler KL. Molecular methods for diagnosis of viral encephalitis. Clin Microbiol Rev 2004; 17:903-925, table of contents.

[5] Tobias Dahm, Henriette Rudolph, Christian Schwerk, et al. Neuroinvasion and Inflammation in Viral Central Nervous System Infections 2016 ;2016:8562805.

[6] Anna Papa, Elpida Papadopoulou. Acute viral infections of the central nervous system, 2014-2016, Greece ; 2018 90(4):644-647

[7] Laura Patricia Mendoza , Roberta Vieira de Morais Bronzoni, Osvaldo Massaiti Takayanagui, Victor Hugo Aquino, Luiz Tadeu Moraes Figueiredo. Viral infections of the central nervous system in Brazil. J Infect 2007 Jun;54(6):589-96.

[8] Naeima Houseein, Amenh B. Yousif. An Epidemiological Profile of Meningitis and Encephalitis in Adults Admitted to Benghazi Medical Centre in 2018. Asian Journal of Medical Principles and Clinical Practice2(3): 1-7, 2019

[9] Sara Radmard, Savina Reid, Prajwal Ciryam, Alexandra Boubour, Nhan Ho, Jason E. Zucker, Dean Sayre, William Greendyke, Benjamin Miko, Marcus R. Pereira, Susan Whittier, Daniel A. Green, Kiran T. Thakur. Clinical

Utilization of the FilmArray Meningitis/Encephalitis (ME) Multiplex Polymerase Chain Reaction (PCR) Assay. Front Neurol. 2019 Mar 26;10:281.

[10] Sze Hwei Lee, Shey-Ying Chen, Jung-Yien Chien, Tai-Fen Lee, Jong-Min Chen, Po-Ren Hsueh. Usefulness of the FilmArray meningitis/encephalitis (M/E) panel for the diagnosis of infectious meningitis and encephalitis in Taiwan. 2019 Oct;52(5):760-768.

[11] Cailleaux M, Pilmis B, Mizrahi A, Lourtet-Hascoet J, Van J-CN, Alix L, et al. Impact of a multiplex PCR assay (FilmArray®) on the management of patients with suspected central nervous system infections.Eur J Clin Microbiol Infect Dis.1 févr 2020;39(2):293 7

[12] Kahraman H, Tünger A, Şenol Ş, Gazi H, Avcı M, Örmen B, et al. Investigation of bacterial and viral etiology in community acquired central nervous system infections with molecular methods. Mikrobiyol Bul. juill 2017;51(3):277 85.

[13] Bansidhar Tarai Poonam Das. FilmArray® meningitis/encephalitis (ME) panel, a rapid molecular platform for diagnosis of CNS infections in a tertiary care hospital in North India: one-and-half-year review. Neurological Sciences volume 40, pages81–88 (2019).

[14] Olof Säll, Sara Thulin Hedberg, Marita Neander, Sabina Tiwari, Lester Dornon, Rabin Bom, Nina Lagerqvist, Martin Sundqvist, Paula Mölling. Etiology of Central Nervous System Infections in a Rural Area of Nepal Using Molecular Approaches. 2019 Jul;101(1):253-259.

[15] Leber AL, Everhart K, Balada-Llasat J-M, Cullison J, Daly J, Holt S, et al. Multicenter Evaluation of BioFire FilmArray Meningitis/Encephalitis Panel for Detection of Bacteria, Viruses, and Yeast in Cerebrospinal Fluid Specimens.J Clin Microbiol. sept 2016;54(9):2251 61.

[16] Arthur H. P. Mawuntu , Janno B. B. Bernadus, Rama Dhenni, Ageng Wiyatno , Riane Anggreani, Feliana and al. Detection of central nervous system viral infections in adults in Manado, North Sulawesi, Indonesia. 2018 Nov 16;13(11):e0207440.

[17] F de Ory, A Avellón, J E Echevarría, M P Sánchez-Seco, G Trallero, M Cabrerizo, I Casas, F Pozo, G Fedele, D Vicente, M J Pena, A Moreno, J Niubo, N Rabella, G Rubio, M Pérez-Ruiz and al. Viral Infections of the Central Nervous System in Spain: A Prospective Study,J Med Virol 2013 Mar;85(3):554-62.

[18] Boudet A, Pantel A, Carles M-J, Boclé H, Charachon S, Enault C, et al. A review of a 13-month period of FilmArray Meningitis/Encephalitis panel implementation as a firstline diagnosis tool at a university hospital. 24 oct 2019;14(10):e0223887.

[19] Dharmendra Pandey, Rohidas Laxman Mahale. Clinico-epidemiological profile of meningitis patients diagnosed at a tertiary care hospital in Mumbai. 2018; 5(10): 109-113.

[20] Fatma Ben Abid, Mohammed Abukhattab, Hafedh Ghazouani, Obada Khalil, Ahmed Gohar, Hussam Al Soub, Muna Al Maslamani, Abdullatif Al Khal, Eman Al Masalamani, Said Al Dhahry, Samar Hashim, Faraj Howadi, Adeel A. Butt. Epidemiology and Clinical Outcomes of Viral Central Nervous System Infections. Int J Infect 2018 Aug;73:85-90

[21] Cinnia Huang, Dale Morse, Brett Slater, Madhu Anand, Ellis Tobin,3 Perry Smith, Michelle Dupuis, Rene Hull, Rocco Ferrera, Blair Rosen, and Leo Grady. Multiple-Year Experience in the Diagnosis of Viral Central Nervous System Infections with a Panel of Polymerase Chain Reaction Assays for Detection of 11 Viruses. Clin Infect 2004 Sep 1;39(5):630-5

[22] P Brandon Bookstaver, Phillip L Mohorn, Ansal Shah, Lauren D Tesh, April M Quidley, Ravish Kothari, Christopher M Bland, Sharon Weissman. Management of Viral Central Nervous System Infections: A Primer for Clinicians. 2017 May 1;9:1179573517703342.

[23] Bassant Meligya, Dalia Kadryb, Iman H. Draz, Huda Marzouka, Nevine R. El Baroudya, Amira Sayed El RifayE pidemiological Profile of Acute Viral Encephalitis in a Sample of Egyptian Children.2018 Feb 14;6(2):423-429.

[24] Maryam Khalili, Hamid Rahimi Hajiabadi, Mojtaba Akbari, Bahram Nasr Esfahani, Rana Saleh, Sharareh Moghim. Viral aetiology of acute central nervous system infections in children, Iran Maryam Khalili, Hamid Rahimi Hajiabadi, Mojtaba Akbari, Bahram Nasr Esfahani, Rana Saleh, Sharareh Moghim. J Med Microbiol. 2022 Oct;71(10)

[25] Peigue-Lafeuille H, Archimbaud C, De Champs C, Croquez N, Laurichesse H, Clavelou P, et al. Enteroviral meningitis in adults, underestimated illness: description of 30 observations from 1999 to 2000, and evolution of clinical practices during 2001. Pathol Biol (Paris) 2002;50:516e24.

[26] Studahl M, Ricksten A, Sandberg T, Elowson S, Herner S, Sall C, et al. Cytomegalovirus infection of the CNS in non-compromised patients. Acta Neurol Scand 1994;89(6):451

[27] Kewpoowat Q , Salazar L, Aguilera E, Wootton SH, Hasbun R. Herpes simplex and varicella zoster CNS infections: clinical presentations, treatments and outcomes. Infection. 2016;44:337–345.

[28] Saverio G. Parisi a,b, Monica Basso, Claudia Del Vecchio, Samantha Andreis, Elisa Franchin, Federico Dal Bello and al.Viral infections of the central nervous system in elderly patients: a retrospective study Int J Infect Dis 2016 Mar;44:8-10.

[29] Sen PK, Dhariwal AC, Jaiswal RK, Lal S, Raina VK, Rastogi A. Epidemiology of acute encephalitis syndrome in india: changing paradigm and implication for control. J Commun Dis. 2014;46:4– 11.

[30] Shilu Mathew, Hebah A. Al Khatib, Khalid Al Ansari, Joanne Nader, Gheyath K. Nasrallah and al. Epidemiology Profile of Viral Meningitis Infections Among Patients in Qatar (2015–2018). Frontiers in Medicine, 16 Jun 2021, 8:663694

[31] Zeinab Berangi, Manoochehr Karami, Younes Mohammadi, Milad Nazarzadeh, Seyed Mohsen Zahraei, Hamidreza Javidrad , Saber Heidari. Epidemiological profile of meningitis in Iran before pentavalent vaccine introduction. BMC Pediatr. 2019 Oct 22;19(1):370

[32] Ayman Yosry, Taha Gad, Waleed Fathalah, Marwa Khairy, Hanan Abd El Hafez and Rabab Fouad .Epidemiological profile of patients suspected with meningitis: A cross sectional study among 1712 Egyptian patients. International Journal of Microbiology and Immunology Research,2014; Vol. 2(4), pp. 054-062

[33] Jose´ R. Romero, MD and Jason G. Newland, MDand Encephalitis: Traditional and Emerging Viral Agents. Jose´ R. Romero, MD and Jason G. Newland, MD Viral Meningitis and Encephalitis: Traditional and Emerging Viral. Semin Pediatr Infect Dis 2003 Apr;14(2):72-82.

[34] Sauran Yerdessov, Assel Zhunussova, Aliya Imanova, Arnur Gusmanov, Yesbolat Sakko, Gulnur Zhakhina, Kamilla Mussina, Dmitriy Syssoyev and al. Epidemiological characteristics and climatic variability of viral meningitis in Kazakhstan, 2014–2019 Front Public Health. 2023 Jan 4;10:1041135

[35] Greene SK, Schmidt MA, Stobierski MG, Wilson ML. Spatio-temporal pattern of viral meningitis in Michigan, 1993-2001. J Geogr Syst. (2005) 7:85–99.

[36] Philip Rice. Viral meningitis and encephalitis. 2013 Sep;25(3):363-80.