CLINICAL AND SUB-CLINICAL CHARACTERISTICS OF MENINGITIS CAUSED BY VARICELLA ZOSTER VIRUS

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Encephalitis - meningitis today is still a serious public health problem with a high mortality rate.

Objectives: To describe the clinical and subclinical characteristics of encephalitis-meningitis caused by Varicella zoster virus (VZV) in people from 15 years old.

Material and methods: A retrospective descriptive research on 40 patients with encephalitis-meningitis diagnosed based on positive VZV PCR results in cerebrospinal fluid treated at the National Hospital of Tropical Diseases and Bach Mai Hospital from January 2020 to June 2023.

Results: Common clinical manifestations of VZV meningitis are headache (90.6%), fever (59.4%), and nausea (43.8%). Common manifestations of encephalitis are behavioral and language disorders (75%), and fever (50%). In the cerebrospinal fluid, the median number of white blood cells in the two meningitis and encephalitis groups were 235.5 (100 - 440) cells/mL and 157 (46 - 497) cells/mL, respectively, of which white blood cells were lymphocytes predominate, protein of the two meningitis and encephalitis groups are 1.0 (0.5 - 1.6) G/L and 2.1 (0.9 - 5.7) G/L, respectively. We can find out brain damage on CT or MRI in the temporal lobe, frontal lobe, and insula lobe. In addition, demyelinating lesions occur in 25%.

Keywords: *Meningoencephalitis, Varicella zoster, Herpes zoster.*

INTRODUCTION

Encephalitis-meningitis today is still a serious health problem in the community with a high mortality rate[1,2], and leaving many serious sequelae, placing a burden on families and society. Varicella zoster virus (VZV) is considered one of the three most common viral causes of meningoencephalitis with rates ranging from 5 to 29%.[1,3,4] Meningoencephalitis caused by VZV has been recorded due to the reactivation of VZV contracted during adolescence. Thanks to advances in diagnosis using molecular biological techniques in recent years, current research around the world is focusing on learning about diseases caused by VZV, especially central nervous system infections such as encephalitis, and meningitis. Research results show that VZV causes a variety of diseases: meningitis, encephalitis, cerebrovascular damage, etc[1]. In particular, encephalitis caused by VZV often has a high mortality rate if not detected and treated. timely treatment[5].

In Vietnam, previously due to limitations of microbiological techniques, the disease caused by VZV was not fully evaluated. In recent years, the development of molecular biology methods such as gene sequence amplification (PCR) testing and multiplex gene amplification (Filmarray) has contributed to clarifying the viral causes of encephalitis. - Meninges[6]. Therefore, we conducted this study with the purpose of "Evaluating clinical and paraclinical characteristics of meningoencephalitis caused by VZV". Research results can help clarify the causes of central nervous system infections in Vietnam. The results of this study will help managers

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Date of submission: *October 16, 2023*

Date of reviewed completion: *October 28, 2023*

Accepted date for publication: *December 15, 2023*

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and clinicians come up with more effective measures to prevent central nervous system infections.

SUBJECTS AND METHODS

Subject: Includes 40 patients were diagnosed encephalitis or meningitis caused by VZV based on clinical and sub-clinical characteristics, and positive cerebrospinal fluid multiplex PCR results for VZV.

- Diagnostic criteria for VZV encephalitis: Based on the definition of acute encephalitis,1 patient with a positive VZV PCR test in cerebrospinal fluid and at least one of the following symptoms (according to the International Encephalitis Association 2013)[7].

+ Mental disturbances lasting > 24 hours.

+ Fever/history of fever ≥ 38°C within 72 hours before and/or after illness.

+ Whole body convulsions or local convulsions (excluding febrile convulsions).

+ There are focal neurological signs.

+ Cerebrospinal fluid shows lymphocytosis (> 5 white blood cells/µl).

+ CT-scan or MRI: There are lesions suspicious for acute encephalitis.

+ Abnormalities on the EEG consistent with encephalitis

- Diagnostic criteria for VZV meningitis: Symptoms and/or signs of meningitis without evidence of brain parenchymal involvement,[2] and a positive VZV CSF PCR test result.

- Exclusion criteria.

+ Medical records are incomplete.

+ Patients with encephalitis - meningitis who are co-infected with any other bacteria or fungi.

Methods: A retrospective descriptive study

- Time and location in research: The study was conducted at Bach Mai Hospital from January 2020 to June 2023.

- Sample selection method: All patients meeting research criteria admitted to the hospital during the study period were included for analysis.

- Research variables: In this study, we evaluate the following indicators

+ Clinical epidemiological index: age (years), gender (male, female), geography, medical history.

+ Clinical research index:

• Systemic manifestations include: fever, skin rash due to shingles

• Meningeal signs and symptoms: headache, nausea/vomiting, stiff neck, kerning.

• Signs of brain damage include: consciousness (based on the Glasgow scale), seizures, signs of focal paralysis, and urinary and bowel disorders.

+ Subclinical index:

• Blood formula, blood chemistry, creatinine, electrolytes, CRP, procalcitonin, AST, ALT, glucose, INR.

• Cerebrospinal fluid test: evaluate color, and pressure, and count the number and composition of cells, biochemical tests include protein, glucose, and chlorine.

• Computed tomography (CT) and brain MRI: evaluate the location of the injury. MRI of the brain with a 3.0 Tesla machine, CT scan of the brain with a PRESTO machine from Hitachi.

• Testing for Varicella zoster virus in cerebrospinal fluid using Filmarray technique (multi-primer gene sequence amplification technique), performed on Filmarray/Biomerieux kit Meningitis/Encephalis Panel v1.4 and Seegene system.

Analyzing data: Data entry and processing using SPSS 20.0 software. Research results are presented as percentage, mean, median, and standard deviation. Use the Shapiro-Wilk test to evaluate the normal distribution.

Research ethics: The information collected is only used for research purposes and does not disclose personal information or medical conditions of research participants.

RESULTS

During the study period, there were 40 patients with encephalitis-meningitis who met the criteria to be selected for analysis, of which 18 patients were diagnosed with meningitis (45%), and 22 patients were diagnosed with encephalitis (55%).

Table 1. General characteristics of the research group

Characteristics	Meningitis (n=18) (n,%)	Encephalitis (n=22)(n,%)
Age (years)	41.9 ± 18.5	56.4 ± 16.4
≤ 20	3 (16.7)	2 (9.1)
20 - 40	7 (38.9)	2 (9.1)
40 - 60	4 (22.2)	5 (22.7)
> 60	4 (22.2)	13 (59.1)
Sex		
Male	8 (44.4)	15 (68.2)
Female	10 (55.6)	7 (31.8)
Geography		
Urbun	10 (55.6)	8 (36.4)
Rural	8 (44.4)	14 (63.6)
History of chronic disease		
Have ever had shingles	1 (5.6)	2 (9.1)
Chronic cardiovascular disease	5 (27.8)	7 (31.8)
Diabetes	0 (0.0)	6 (27.3)
Long-term corticosteroids use	1 (5.6)	3 (13.6)
HIV infection	0 (0.0)	4 (18.2)
Cancer	2 (11.1)	1 (4.5)
Renal failure	0 (0.0)	1 (4.5)

The average age of meningitis and encephalitis patients was 41.9 ± 18.5 and 56.4 ± 16.4 years, respectively. While meningitis is relatively evenly distributed in all age groups, encephalitis is more common in people aged > 60 years old (59.1%). Both groups with encephalitis and meningitis had chronic diseases such as cardiovascular disease and diseases related to immunodeficiency such as diabetes (15%), long-term corticosteroid use (10%), and HIV (10 %), cancer (7.5%) and this rate is higher in the group of encephalitis patients.

Table 2. Clinical features

Characteristics	Meningitis (n=18) (n,%)	Encephalitis (n=22)(n,%)
Fever		
< 37.5°C	7 (38.9)	10 (45.5)
37.5 - 38°C	6 (33.3)	6 (27.3)
38.1 - 39°C	4 (22.2)	5 (22.7)
> 39°C	1 (5.6)	1 (4.5)

Characteristics	Meningitis (n=18) (n,%)	Encephalitis (n=22)(n,%)
Headache	18 (100.0)	14 (63.6)
Vomiting or nausea	8 (44.4)	10 (45.5)
Rash on the skin	5 (27.8)	16 (72.7)
Behavioral disorders	0 (0.0)	6 (27.3)
Language disorders	0 (0.0)	6 (27.3)
Whole body convulsions	0 (0.0)	3 (13.6)
Focal neurological signs		
Cranial nerve paralysis	0 (0.0)	11 (50.0)
Urinary and bowel disorders	0 (0.0)	1 (4.5)
Disorders of consciousness (GCS ≤ 12)	0 (0.0)	8 (36.4)
Stiff neck	10 (55.6)	16 (72.7)
Kernig (+)	10 (55.6)	17 (77.3)
Increased intracranial pressure signs	7 (38.9)	3 (13.6)

In encephalitis-meningitis caused by VZV, mild fever from 37.5 - 38°C (from 27.3 - 33.3%) or no fever (from 38.9 - 45.5%) is common. Common manifestations of meningitis are headache (100%), stiff neck (55.6%), kerning (+) (55.6%), and vomiting or nausea (44.4%). Common signs of encephalitis are kerning (+) (77.3%), stiff neck (72.7%), headache (63%), and cranial nerve paralysis (50%). Rash on the skin were detected in 27.8% of meningitis patients and 72.7% of VZV encephalitis patients.

Table 3. Characteristics of blood formula and biochemical tests

Characteristics	Meningitis (n=18) (n,%)	Encephalitis (n=22)(n,%)
RBC (T/L)	4.8 ± 0.7	4.5 ± 0.7
Hemoglobin (G/L)	135.1 ± 14.2	130.5 ± 18.7
WBC (G/L)	8.7 ± 4.5	10.0 ± 3.5
< 4 G/L	2 (11.1)	0 (0.0)
4 - 10 G/L	11 (61.1)	12 (60.0)
> 10 G/L	5 (27.8)	8 (40.0)
Neutrophils	65.5 ± 13.0	71.3 ± 14.9
> 65%	11 (61.1)	16 (80.0)
≤ 65%	7 (38.9)	4 (20.0)
Platelet (G/L)	259.7 ± 57.1	274.6 ± 67.8
CRP (mG/L)	0.08 (0.04 - 0.97)	1.5 (0.4 - 6.5)
PCT (nG/L)	0.07 (0.05 - 0.08)	0.27 (0.26 - 0.33)
Creatinin (µmol/L)	73.5 (55.0 - 88.0)	68.0 (58.0 - 81.0)
AST (U/L)	21.0 (17.3 - 30.0)	28.0 (20.0 - 48.0)
ALT (U/L)	19.0 (11.0 - 28.0)	21.0 (16.0 - 29.5)
INR	1.02 ± 0.16	1.04 ± 0.1

Characteristics	Meningitis (n=18) (n,%)	Encephalitis (n=22)(n,%)
Natri (mmol/L)	137.6 ± 3.2	134.4 ± 5.3
Kali (mmol/L)	3.7 ± 0.3	3.6 ± 0.5

In meningitis and encephalitis caused by VZV, the number of white blood cells does not increase > 10 G/L, accounting for 27.8% and 40.0%, respectively, in which the proportion of neutrophils mainly increases > 65% (61.1% and 80% respectively). In addition, the indexes of red blood cells, hemoglobin, platelets, AST, ALT, kidney function (Creatinine), INR, and electrolytes are usually within normal limits

Table 4. Characteristics of cerebrospinal fluid

Characteristics	Meningitis (n=18) (n,%)	Encephalitis (n=22)(n,%)
Pressure		
Normal	12 (66.7)	17 (77.3)
Increasing	6 (33.3)	5 (22.7)
Color		
Clear	15 (83.3)	16 (72.7)
Opaque	3 (16.7)	2 (9.1)
Yellowish	0 (0.0)	2 (9.1)
Pink	0 (0.0)	2 (9.1)
Number of cells	415 (200 - 684)	100 (60 - 241)
≤ 5 Cells/mL	0 (0.0)	2 (9.1)
5 - 250 Cells/mL	5 (27.8)	15 (68.2)
> 250 Cells/mL	11 (61.1)	5 (22.7)
> 1000 tế bào/mL	2 (11.1)	0 (0.0)
Components of cells		
NEU %	37.0 ± 26.2	39.3 ± 26.8
LYM %	61.5 ± 25.4	56.9 ± 25.3
MONO %	5.3 ± 3.7	11.2 ± 9.5
Protein (G/L)	1.12 ± 0.60	1.15 (0.53 - 2.65)
≤ 0,45 G/L	3 (16.6)	2 (9.1)
0,45 - 1 G/L	5 (27.8)	8 (36.3)
> 1 G/L	10 (55.6)	12 (54.6)
Glucose (mmol/L)	3.1 ± 0.9	4.6 ± 2.7
< 2.8 mmol/L	6 (33.3)	5 (22.7)
2.8 - 4.0 mmol/L	11 (61.1)	7 (31.8)
> 4.0 mmol/L	1 (5.6)	10 (45.5)
Clo (mmol/L)	118.8 ± 4.2	115.4 ± 8.6
< 120 mmol/L	15 (68.2)	15 (61.1)
≥ 120 mmol/l	7 (31.8)	7 (38.9)

In VZV encephalitis and meningitis, cerebrospinal fluid is usually clear (72.7 - 83.3%) but may be cloudy (9.1 - 16.7%), yellow (9.1%), or bloody (9.1%). The number of cells that do not increase is seen in encephalitis, accounting for 9.1%, and an increase of > 1000 cells/mL, seen in meningitis, accounts for 11.1%. Cerebrospinal fluid protein does not increase from 9.1 - 16.7%, and increases > 1.0 G/L accounts for 54.6 - 55.6%.

Table 5. Characteristics of CT and cranial magnetic resonance imaging

Location of damage	CT-scanner (n = 16), (n,%)	MRI (n = 10), (n,%)
Temporal, frontal lobe, and Putamen	1 (6.25)	1 (10.0)
Temporal, and Occipital lobe	1 (6.25)	0 (0.0)
Insular cortex, and Cauliflower	0 (0.0)	1 (10.0)
Temporal, Frontal lobe, and Medulla	0 (0.0)	1 (10.0)
Demyelination of cerebral white matte	1 (6.25)	5 (50.0)
Sinusitis, sinus fluid collection, or/and sinus mucosa thickening	5 (31.25)	5 (50.0)
No damage detected	14 (87.5)	3 (30.0)

Lesions on imaging (MRI and CT brain) are often located in many locations in the brain, including lesions in the temporal lobe, frontal lobe, insula, putamen, and pons. In addition, there was 25% white matter demyelination. MRI results detected lesions (70%).

DISCUSSIONS

Epidemiological characteristics

In meningitis caused by VZV, the disease occurs sporadically in all age groups from 20 years old to over 60 years old. In contrast, encephalitis occurs mostly in people > 60 years old (59.1%). The medical literature and many reports also recorded results like ours, VZV reactivation is believed to often occur in elderly patients, related to the decline of cell-mediated immunity, especially related to T lymphocyte function[5,8,9]. Furthermore, we see that while meningitis occurs more often in women than in men (55.6% vs. 44.4%), encephalitis is more common in men (68.2%). Obtaining a history of childhood chickenpox or shingles is very important in determining the cause, but we were only able to do so in 7.5% of patients, possibly because the patient did not clearly remember the history. get chickenpox yourself.

Clinical features

Clinical manifestations of brain and meningeal lesions are similar to those of other viral encephalitis and meningitis, similar to many previous reports[5,8-11]. Characteristic skin lesions due to Zona are often recorded[1]. However in our study we encountered 27.8% of meningitis patients and 72.7% of encephalitis patients who have not got any shingles. These are signs that help diagnose the clinical cause. While encephalitis caused by other viruses such as Japanese encephalitis and Herpes encephalitis often have high fever,[1] in this study most patients with meningitis and encephalitis caused by VZV did not have fever (38.9 - 45.5%) or only mild fever (27.3 - 33.3%). Furthermore, we also noted that a high proportion (50%) of patients with VZV encephalitis had focal nerve paralysis. This is explained by the pathogenesis related to vascular damage in VZV pathology[1].

Subclinical characteristics

In this study, in peripheral blood, we encountered 27.8% of meningitis patients and 40% of encephalitis patients with peripheral blood leukocytosis > 10 G/L. In particular, from 61.1% (meningitis) to 80% (encephalitis) of patients had an increase in the percentage of neutrophils > 65% even though other inflammatory indicators such as CRP and Pro-calcitonin did not increase or very slight increase. An increase in the number of white blood cells and the ratio of neutrophils in peripheral blood is observed in

many patients with encephalitis - meningitis caused by viruses of the Herpes group[1,12]. Therefore, an increase in the number of white blood cells and the ratio of neutrophil count is also a sign of suspected Herpes infection. Regarding cerebrospinal fluid, although 72.7% of encephalitis and 83.3% of meningitis have clear cerebrospinal fluid, 16.7 - 27.3% of patients have abnormal color: cloudy (9,1 - 16.7%), yellow (0 - 9.1%), and bloody (0 - 9.1%). This has not been reported in the literature or previous reports[1]. Non-increased cerebrospinal fluid cell count has been recorded in many reports,1,9 in our study accounting for 9.1%. However, we observed that 11.1% of meningitis patients had abnormally high cerebrospinal fluid cell counts > 1000 cells/mL. This has been rarely reported in viral meningitis previously and may be related to immune-mediated defense mechanisms. Meningoencephalitis caused by VZV is said to have cerebrospinal fluid protein ranging from normal to slightly increased[1], however many recent reports and our study noted that cerebrospinal fluid protein increase > 1G/L predominates. (54.6 - 55.6% of patients).

Characteristics of brain imaging

Of the 22 patients diagnosed with encephalitis in our study, 10 patients underwent computed tomography, 4 patients underwent MRI, and 6 patients received both computed tomography and MRI of the brain. Brain lobe damage includes temporal lobe (15%), frontal lobe (10%), occipital lobe (5%), insula (5%), and pons (5%). Demyelinating lesions are considered characteristic of the vascular pathologic consequences of VZV[1], in our study only 25% were observed, however, this result is similar to many other reports, where the majority as a result, no damage was observed on the scan[5,8,9,11,13]. We also noticed that although the patient was diagnosed with encephalitis, only 12,000 lesions were observed on the computed tomography scan. 5% of lesions (compared to 70% detected on MRI), especially 1 patient had normal computed tomography results but later had lesions detected on brain MRI. Similar results have been mentioned in the literature and previous reports[1,13]. Cranial MRI helps avoid misses and detect lesions in encephalitis earlier than computed tomography.

When compared with the criteria in the 2013 "International Encephalitis Consensus",[7] we see the emphasis on the main criterion: mental disturbance lasting > 24 hours in the diagnosis of encephalitis. However, in our study, there were 14 patients (63.6%) with brain parenchymal damage due to VZV proved by imaging or focal neurological manifestations without symptoms. perceptual disorder. Unlike Herpes simplex 1 encephalitis - another common cause also belonging to the Herpes group, which often damages the brain lobes causing cognitive disorders[12], VZV causes encephalitis, damaging mainly the axons of neurons is a consequence of vascular disease caused by VZV[1]. Therefore, clinically it is rare to see patients showing signs of mental disorders. This is also an interesting feature in the context of VZV encephalitis, and is an additional difference to the criteria in the "2013 International Acute Encephalitis Consensus".

CONCLUSIONS

- VZV meningitis occurs sporadically in all ages, the majority occurring in women (55.6%), while encephalitis is common in men (68.2%), age group > 60 years old (59 .1%), and diseases related to immunodeficiency.

- Clinical manifestations of VZV encephalitis-meningitis are similar to other viral encephalitis - meningitis, skin lesions due to Shingles often appear at a rate of 27.8 - 72.7%.

- There is an increase in leukocytes in 27.8 - 40% of patients with VZV encephalitis-meningitis, mainly polymorph nuclear leukocytosis (from 61.1 - 80%).

- In encephalitis-meningitis caused by VZV, clear cerebrospinal fluid predominates. However, 16.7 - 27.3% of patients have abnormal cerebrospinal fluid color (cloudy, yellowish, bloody), especially 11.1% of meningitis patients had cell counts > 1000 cells/mL. Cerebrospinal fluid protein > 1G/L predominates in 54.6 - 55.6% of patients.

- On CT and MRI scans of the brain, brain damage was seen in many locations including the temporal lobe (15%), frontal lobe (10%), occipital lobe (5%),

insula (5%), and pons. (5%). Demyelinating lesions 25%. Brain MRI is more effective than computed tomography in detecting lesions.

REFERENCES

1. J. David Beckham và Kenneth L. Tyler (2020). Encephalitis, chapter 89, Mandell, Douglas, and Bennett's principles and practice of infectious diseases, Editor John E. bennett, 9 edition, Publishing house Elsevier, Philadelphia: 1226- 1247.

2. Rodrigo Hasbun, Diederik van de Beek, Matthijs C. Brouwer, Allan R. Tunkel (2020). Acute Meningitis, chapter 87, Mandell, Douglas, and Bennett's principles and practice of infectious diseases, Editor John E. bennett, 9 edition, Elsevier Philadelphia: 1183-1219.

3. Gaudin M, Theïs C, Mrozek N, et al. Varicella zoster virus and meningitis in immunocompetent patients: Specificity and questions. Clinical Infection in Practice. 2022;13:100125. doi:10.1016/j.clinpr.2021.100125.

4. Koskiniemi M, Rantalaiho T, Piiparinen H, et al. Infections of the central nervous system of suspected viral origin: a collaborative study from Finland. J Neurovirol. 2001;7(5):400-408. doi:10.1080/135502801753170255.

5. Becerra JCL, Sieber R, Martinetti G, Costa ST, Meylan P, Bernasconi E. Infection of the central nervous system caused by varicella zoster virus reactivation: a retrospective case series study. International Journal of Infectious Diseases. 2013;17(7):e529-e534. doi:10.1016/j.ijid.2013.01.031.

6. Alvarez JC, Alvarez J, Tinoco J, et al. Varicella-Zoster Virus Meningitis and Encephalitis: An Understated Cause of Central Nervous System Infections. Cureus. 2020;12(11):e11583. doi:10.7759/cureus.11583.

7. Venkatesan A, Tunkel AR, Bloch KC, et al. Case Definitions, Diagnostic Algorithms, and Priorities in Encephalitis: Consensus Statement of the International Encephalitis Consortium. Clinical Infectious Diseases. 2013;57(8):1114-1128. doi:10.1093/cid/cit458.

8. Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: towards a global perspective. BMJ Open. 2014;4(6):e004833. doi:10.1136/bmjopen-2014-004833.

9. Broucker TD, Mailles A, Chabrier S, Morand P, Stahl JP, Group OB of the SC and I. Acute varicella zoster encephalitis without evidence of primary vasculopathy in a case-series of 20 patients. Clinical Microbiology and Infection. 2012;18(8):808-819. doi:10.1111/j.1469-0691.2011.03705.x

10. Tabaja H, Sharara SL, Abi Aad Y, et al. Varicella zoster virus infection of the central nervous system in a tertiary care center in Lebanon. Médecine et Maladies Infectieuses. 2020;50(3):280-287. doi:10.1016/j.medmal.2019.08.005.

11. Herlin LK, Hansen KS, Bodilsen J, et al. Varicella Zoster Virus Encephalitis in Denmark From 2015 to 2019—A Nationwide Prospective Cohort Study. Clinical Infectious Diseases. 2021;72(7):1192-1199. doi:10.1093/cid/ciaa185.

12. Bui Vu Huy, Vu Minh Dien. Research on clinical characteristics and prognostic factors of Herpes simplex encephalitis. Journal of Medical Research. 2011;74(3):147-155.

13. Mirouse A, Sonneville R, Razazi K, et al. Neurologic outcome of VZV encephalitis one year after ICU admission: a multicenter cohort study. Ann Intensive Care. 2022; 12:32. doi:10.1186/s13613-022-01002-y.