

Varicella zoster virus central nervous system infection – a retrospective study from a tertiary center in Greece

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Abstract

Introduction Central nervous system (CNS) infection due to the varicella zoster virus (VZV) can complicate the primary infection or the reactivation, leading to significant mortality and morbidity. This study aimed to describe the clinical, laboratory, and radiological characteristics of patients with confirmed VZV CNS infection in a tertiary hospital in Greece.

Methods Data about patients hospitalized from January 2018 to September 2023 with CNS infection by VZV, confirmed by a syndromic polymerase chain reaction in the cerebrospinal fluid (CSF), were retrospectively collected and evaluated.

Results In total, 14 patients were recorded. The median age was 49 years, and 35.7% were male. Headache was present in 71.4%, a rash in 57.1%, and fevers, nausea or vomiting, and disorientation in 35.7%. The CSF showed lymphocytic pleocytosis in all patients. Brain magnetic resonance imaging was performed in 53.8%. Empirical antivirals were given in 69.2%, and intravenous acyclovir was given to all patients after identification of VZV in the CSF. Only 7.1% (1 patient) required intensive care unit admission, and 7.1% (1 patient) died. Patients presenting without a rash may be slightly younger, have a slightly lower Charlson comorbidity index, be more likely to present with photophobia or phonophobia, and have lower serum CRP.

Conclusions Patients presenting with VZV CNS infection have lymphocytic pleocytosis in the CSF and usually have a favorable outcome with antiviral treatment. Those presenting without a rash may have a different overall clinical phenotype from those with a rash; however, this must be evaluated in larger studies in the future.

Keywords Varicella zoster virus, meningitis, encephalitis, central nervous system infection, acyclovir.

Introduction

Varicella zoster virus (VZV), also known as human herpesvirus-3 (HHV-3), is the cause of chickenpox (varicella) in the case of primary infection or shingles (herpes zoster), in the case of

reactivation, with the latter typically presenting with pain and rash with a dermatomal distribution; however, in some cases, pain in a dermatomal distribution without a rash may occur (zoster sine herpete). Chickenpox is the primary infection caused by VZV and primarily affects children in temperate climates, causing a typical febrile illness and a rash characterized by pruritic papulovesicular lesions. It has a worldwide distribution and is highly contagious, spreading from one infected person to another through close contact. A vaccine against chickenpox can significantly reduce the likelihood of contracting the disease. Herpes zoster mostly occurs in adults after reactivation of VZV in the dorsal root ganglia, where it may remain dormant for years after primary infection. Its incidence varies and is approximately up to 9 cases per 1,000 people. Though it is less contagious than chickenpox, direct contact with vesicular fluid may transmit the virus. Zoster sine

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herpete is a variation of herpes zoster where VZV causes typical pain with dermatomal distribution without the development of a rash, thus making clinical diagnosis difficult.¹

Central nervous system infection due to VZV can complicate either the primary infection or reactivation, leading to increased mortality and morbidity.^{2,3} These manifestations are particularly significant in the context of the constantly growing older and immunocompromised populations.⁴ Furthermore, atypical clinical presentations, such as central nervous system (CNS) infection without skin manifestations, can pose significant clinical challenges for timely diagnosis.^{5,6}

Despite being one of the most common infectious causes of encephalitis and aseptic meningitis, VZV infection may be underreported in the literature.⁷ Moreover, treatment recommendations are not based on randomized controlled trials but rather on small-scale studies, highlighting the need for further research on the subject.¹

The objective of this study was to provide a comprehensive description of the clinical, laboratory, and radiological characteristics, as well as the outcomes, of patients with confirmed VZV central nervous system infection in a tertiary hospital in Crete, Greece.

Methods

This is a retrospective cohort study of patients hospitalized in the University Hospital of Heraklion, Crete, Greece. Patients of any age with a positive polymerase chain reaction (PCR) for VZV nucleic acid in the cerebrospinal fluid (CSF) along with pleocytosis (more than five enucleated cells/mm³) in the CSF, negative CSF cultures for bacteria and compatible clinical presentation (at least one of the following: headache, fever, altered mental status, behavioral changes, nuchal rigidity, nausea or vomiting, seizures or focal neurological symptoms) were considered to have CNS infection due to VZV and were included in the analysis.⁸ Patients who were not hospitalized at the University Hospital of Heraklion were excluded. Data on positive PCR were retrieved from the Laboratory of Clinical Virology of the University Hospital of

Heraklion from January 1st 2018, to September 30th 2023. The molecular identification of VZV was performed using the FilmArray Meningitis/Encephalitis (ME) Panel (BioFire Diagnostics, USA). Clinical and laboratory data were retrieved from the hospital's electronic medical record. Demographical characteristics, initial clinical presentation, physical examination, and laboratory data were obtained. Only the laboratory values were retrieved and evaluated when no clinical data were available. The study was conducted following the Declaration of Helsinki and approved by the Institutional Review Board of the University Hospital of Heraklion (protocol code 08/24-03-2021).

Descriptive statistics were performed with GraphPad Prism 6.0 (GraphPad Software, Inc., USA). Qualitative data are presented as counts and percentages. Data are presented as numbers (%) for categorical variables and medians [interquartile range (IQR)].

Results

Characteristics of patients with CNS infection by VZV

During the study, 31 patients with a CNS infection due to the VZV were diagnosed. Only 14 were hospitalized at the University Hospital of Heraklion, Crete, Greece; the rest were hospitalized in other hospitals. Thus, the 14 patients for whom data were available were included in the analysis. The median age was 49 years (range: 1-88 years), and 35.7% (five patients) were male. The most common comorbidities were hypertension in 21.4% (three patients), active cancer (solid or hematological) in 21.4% (three patients), cerebrovascular disease in 21.4% (three patients), previous history of cancer (solid or hematological) in 14.3% (two patients), chronic pulmonary disease in 14.3% (two patients), dementia in 14.3% (two patients), diabetes mellitus in 7.1% (one patient), dyslipidemia in 7.1% (one patient), chronic kidney disease in 7.1% (one patient), heart failure in 7.1% (one patient), and rheumatological disease in 7.1% (one patient). All 14 VZV-positive patients were negative for other pathogens of the multiplex PCR. The rest of the

pathogens were tested by the FilmArray ME panel.

Clinical characteristics of patients with CNS infection by VZV

Headache was present in 71.4% (10 patients), a rash in 57.1% (eight patients), fever in 35.7% (five patients), nausea or vomiting in 35.7% (five patients), disorientation in 35.7% (five patients), nuchal rigidity in 28.6% (four patients), focal neurological signs in 28.6% (four patients), photophobia in 28.6% (four patients), phonophobia in 14.3% (two patients), behavioral changes in 14.3% (two patients), and seizures in 7.1% (one patient). The Glasgow Coma Scale (GCS) was 15 out of 15 in all patients except for one, where it was 14 out of 15. Regarding the rash, the most common type was a typical zoster rash, with blisters along the area of a dermatome. In 7.1% (one patient), Ramsay-Hunt syndrome was diagnosed with a rash involving the ear, while in 7.1% (one patient), facial zoster was diagnosed involving the dermatome of the fifth cranial nerve. No patient presented with chickenpox. The epidemiological and clinical characteristics of the patients are shown in Table 1 and Table 2.

Laboratory characteristics of patients with CNS infection by VZV

The CSF was more commonly retrieved in the emergency department in 35.7% (five patients), the internal medicine department in 28.6% (four patients), the neurology department in 21.4% (three patients), the dermatology department in 7.1% (one patient), and the pediatric intensive care unit (ICU) in 7.1% (one patient). The CSF glucose to serum glucose was lower than 50% in 50% of the patients (seven patients). The CSF protein was increased (higher than 60 mg/dL) in 85.7% (12 patients). All 14 patients had an increased white cell number in the CSF, and lymphocyte predominance was present in all patients. The characteristics of the CSF and the rest of the laboratory exams are shown in Table 3. In 50% (seven patients), C-reactive protein (CRP) was increased (higher than 0.5 mg/dL).

PCR for VZV was positive in the CSF of all patients. However, in most cases, the result was

not quantitative. Quantitative PCR was performed in four patients; median copies were 7100/mL. VZV antibodies were examined only in eight patients, with IgM antibodies being positive only in one patient and IgG antibodies being negative only in one patient.

Treatment of patients with CNS infection by VZV

Empirical antivirals were given in 69.2% (nine out of 13 patients with available data), and antivirals were given to all after identification of VZV genetic material with PCR. Acyclovir was the antiviral used in all cases. In 66.7% (eight out of 12), an intravenous-to-oral transition was performed with a change from acyclovir to valacyclovir. The median duration of intravenous therapy was ten days (range: 2-14), and the median duration of treatment, regardless of route of administration, was 14 days (range: 5-24). In 50% (six out of 12 with available data), antibiotics for bacterial infection were given empirically for the CNS infection; however, in all cases, they were stopped after the negative CSF culture and the positive PCR for VZV. In 25% (three patients), antibiotics were administered for another concomitant presumed source of bacterial infection. One patient (7.1%) required ICU admission, and one patient (7.1%) died.

Brain imaging of patients with CNS infection by VZV

Brain magnetic resonance imaging (MRI) was performed in 53.8% (seven out of 13 patients with available data). In five of those, abnormal findings were found. These findings were leukoencephalopathy in 60% (three patients), trigeminal nerve inflammation in 20% (one patient), and mild meningeal inflammation in 20% (one patient).

Comparison of patients presenting with and without a rash

Tables 2 and 3 compare patients presenting with CNS infection by VZV with and without a rash. Patients who presented with zoster rash differed from those who did not, being slightly older, having a slightly higher Charlson

Table 1. Characteristics of individual patients with varicella zoster virus central nervous system infection

Patient number	Age (years) and gender	Medical history	Charlson comorbidity index	Duration of symptoms until presentation (days)	Symptoms	Empirical antivirals for CNS infection	Duration of treatment in total (and IV)	Outcome
1	23F	None	0	NR	NR	NR	NR	Survived
2	1F	Leukemia	2	1	AMS. Fever, rash	Yes	NA (4)	Died
3	83F	Malignancy (non-active), hypothyroidism	4	5	Rash, FNS, fever, headache	No	14 (14)	Survived
4	47M	MS, HTN	1	4	Headache, nausea, AMS, rash	Yes	14 (2)	Survived
5	31F	None	0	5	Fever, photophobia, neck stiffness, headache	Yes	14 (9)	Survived
6	40F	Malignancy (active)	0	4	Headache, neck stiffness, photophobia, phonophobia, nausea, fever	No	14 (10)	Survived
7	44F	None	0	15	Rash, headache	Yes	14 (9)	Survived
8	58M	CVD, malignancy (active)	9	0	Headache, AMS, FNS, behavioral changes, seizures	No	NR	Survived
9	86M	CVD, AF, dementia, COPD, malignancy (non-active)	8	3	Rash, AMS, nausea	Yes	5 (9)	Survived
10	88M	DM, COPD, CVD, HF, AF, HTN, CKD	10	2	Headache, AMS, rash	Yes	14 (14)	Survived
11	76F	Dementia	4	10	Rash, FNS, behavioral changes	No	24 (14)	Survived
12	69F	CTD, HTN, dyslipidemia	3	4	Headache, nausea, neck stiffness, fever, rash	Yes	21 (14)	Survived
13	44F	Hypothyroidism, depression	0	10	FNS, photophobia, AMS, neck stiffness, headache	Yes	14 (14)	Survived
14	51M	None	2	1	Headache, photophobia, phonophobia	Yes	14 (10)	Survived

AF – atrial fibrillation; AMS – altered mental status; CKD – chronic kidney disease; CNS – central nervous system; COPD – chronic obstructive pulmonary disease; CTD – connective tissue disorder; CVD – cerebrovascular disease; DM – diabetes mellitus; F – female; FNS – focal neurological symptoms; HF – heart failure; HTN – hypertension; IV – intravenously; M – male; MS – multiple sclerosis; NA – not applicable; NR – not reported.

Table 2. Clinical and epidemiological characteristics of patients with varicella zoster virus central nervous system infection in total and in regards to whether they had a rash.

Characteristic	All patients (n=14)	Patients with a rash (n=8)	Patients without a rash (n=6)
Male gender, n (%)	5 (35.7)	3 (37.5)	2 (33.3)
Age, years, median (IQR)	49 (37.8-77.8)	72.5 (44.8-85.3)	42 (29.5-52.8)
Charlson comorbidity index, median (IQR)	2 (0-5)	3.5 (1.3-7)	0 (0-3.8)
Hypertension, n (%)	3 (21.4)	3 (37.5)	0 (0)
Active cancer, n (%)	3 (21.4)	1 (12.5)	2 (33.3)
CVD, n (%)	3 (21.4)	2 (25)	1 (16.7)
Previous cancer, n (%)	2 (14.3)	2 (25)	0 (0)
Dementia, n (%)	2 (14.3)	2 (25)	0 (0)
COPD, n (%)	2 (14.3)	2 (25)	0 (0)
Diabetes mellitus, n (%)	1 (7.1)	1 (12.5)	0 (0)
CKD, n (%)	1 (7.1)	1 (12.5)	0 (0)
Dyslipidemia, n (%)	1 (7.1)	1 (12.5)	0 (0)
Rheumatologic disease, n (%)	1 (7.1)	1 (12.5)	0 (0)
Heart failure, n (%)	1 (7.1)	1 (12.5)	0 (0)
Clinical characteristics			
Duration of symptoms (days), median (IQR)	4 (1.5-7.5)	4 (2.3-8.8)	4 (0.5-7.5)
Headache, n (%)	10 (71)	5 (62.5)	5 (83.3)
Rash, n (%)	8 (57.1)	8 (100)	0 (0)
Nausea/vomiting, n (%)	5 (35.7)	3 (37.5)	2 (33.3)
Disorientation, n (%)	5 (35.7)	4 (50)	1 (13.3)
Fever, n (%)	5 (35.7)	3 (37.5)	2 (33.3)
Focal neurologic signs, n (%)	4 (28.6)	2 (25)	2 (33.3)
Photophobia, n (%)	4 (28.6)	0 (0)	4 (66.7)
Phonophobia, n (%)	2 (14.3)	0 (0)	2 (33.3)
Behavioral changes, n (%)	2 (14.3)	0 (0)	2 (33.3)
Seizures, n (%)	1 (7.1)	0 (0)	1 (16.7)
Empirical antivirals for CNS infection, n (%)	9 (69.2)	6 (75)	3 (60)
Antivirals after diagnosis, n (%)	13 (100)	8 (100)	5 (100)
Intravenous to oral antiviral switch, n (%)	8 (66.7)	5 (62.5)	3 (75)
Duration of intravenous treatment, days, med (IQR)	10 (7-14)	11.5 (5.3-14)	10 (7-12)
Duration of treatment, days, median (IQR)	14 (14-14)	14 (14-21)	14 (14-14)
ICU admission, n (%)	1 (7.1)	1 (12.5)	0 (0)
Duration of hospitalization, days, median (IQ	9.5 (7.5-14.5)	11 (5-16)	9.5 (7.5-12.5)
Mortality, n (%)	1 (7.1)	1 (12.5)	0 (0)

CKD – chronic kidney disease; COPD – chronic obstructive pulmonary disease; CVD – cerebrovascular disease; ICU – intensive care unit; IQR – interquartile range; NA – not applicable.

Table 3. Laboratory characteristics of patients with varicella zoster virus central nervous system infection in total and in regards to whether they had a rash.

Characteristic	All patients (n=14)	Patients with a rash (n=8)	Patients without a rash (n=6)
CSF glucose, mg/dL, median (IQR)	57.5 (50.5-67.8)	57 (49.5-79)	59 (48.5-64)
Serum glucose, mg/dL, median (IQR)	115 (98.5-127.8)	120.5 (103.8-139.8)	104.5 (92.3-117)
CSF to serum glucose ratio, median (IQR)	50.8 (46.8-55.1)	48.9 (44.7-53.9)	54.1 (46.7-62.4)
CSF protein, mg/dL, median (IQR)	118 (89.8-207.3)	97.3 (65-165.8)	161 (109.4-245)
CSF WBCs, /mm ³ , median (IQR)	164 (35.8-435.8)	98.5 (26-331)	416 (119.8-588)
CSF lymphocytes among white cells, %, median (IQR)	88 (72-92)	87 (67.5-91)	88 (71.3-93)
WBCs in blood, /mm ³ , median (IQR)	8,250 (5,175-10,100)	8,250 (5,150-13,100)	8,050 (5,100-10,100)
Neutrophils in blood, /mm ³ , median (IQR)	4,750 (3,325-6,725)	4,550 (2,975-5,175)	5,550 (3,450-8,075)
Lymphocytes in blood, /mm ³ , median (IQR)	1,550 (650-2,325)	1,600 (425-2,475)	1,300 (775-1,925)
Platelets, /mm ³ , median (IQR)	193,000(175,800-257,800)	183,500 (171,300-233,500)	248,500 (189,000-372,300)
CRP upon admission, mg/dL, median (IQR)	0.59 (0.1-2.3)	1.4 (0.3-5.6)	0.1 (0.5-0.8)
Creatinine upon admission, mg/dL, median (IQR)	0.81 (0.69-1)	0.9 (0.7-1.4)	0.8 (0.7-0.9)
Urea upon admission, mg/dL, median (IQR)	26.5 (18.8-44.8)	34.5 (19.5-62.8)	23 (18.8-31.8)
Sodium upon admission, mEq/L, median (IQR)	138 (134.8-140)	137.5 (134.3-140.5)	138 (134.8-140)
MRI done, n (%)	7 (53.8)	4 (57.1)	3 (50)
Abnormal findings in MRI, n (%)	5 (71.4)	3 (75)	2 (66.7)

CSF – cerebrospinal fluid; IQR – interquartile range; MRI – magnetic resonance imaging; NA – not applicable; WBC – white blood cells.

comorbidity index, not having photophobia or phonophobia, and higher serum CRP.

Discussion

In the present study, 14 patients with CNS infection due to VZV during six years are presented. The most common clinical presentation included headache and rash. Patients who presented with zoster rash differed slightly from those who did not, being slightly older, having a slightly higher Charlson comorbidity index, not having photophobia or phonophobia, and having higher serum CRP. All patients were treated with intravenous acyclovir,

and mortality was low, with only one patient dying overall.

VZV, an alphaherpesvirus (also known as human herpesvirus-3, HHV-3) with neurotropic attributes that can remain dormant in the autonomic nervous system ganglia, is an essential cause of viral meningitis and encephalitis. Disseminated VZV infection can affect a wide range of patients across the age and immunosuppression spectrum,⁹ such as patients with hematological malignancy,¹⁰ allogeneous stem cell transplant,¹¹ solid organ transplantation,¹² and patients undergoing immunosuppressive treatment for other reasons such as those treated

with fingolimod, anti-TNF factors, corticosteroids, tacrolimus or cyclophosphamide.^{13,14} Notably, VZV central nervous system infection was recognized as an important diagnostic consideration for patients with HIV infection as early as the early 1990s.¹⁵ That is still true in the antiretroviral era, with a multicenter study by Reimer-McAtee et al. demonstrating an increased risk of being diagnosed with VZV-related central nervous system infection in patients living with HIV who presented with encephalitis.¹⁶

On the other hand, there is mounting evidence that VZV-related central nervous system infection can manifest in patients without any cause of immunosuppression.⁵ In a retrospective analysis of aseptic meningitis in 177 otherwise healthy patients, 14.1% were diagnosed with VZV. Of note, those with VZV were older than those diagnosed with enterovirus-related aseptic meningitis (which was the leading cause of identifiable viruses, with 38.4%).¹⁷ On a smaller scale, Gaudin et al. reported five cases of confirmed PCR VZV central nervous system infection in young patients. Of note, only three presented with a rash, and all had favorable outcomes.¹⁸

Recent analyses also report various degrees of immunosuppression among their study populations. In a retrospective analysis of 16 patients by Alvarez et al., five out of 16 patients with VZV central nervous system infection were immunocompromised.¹⁹ In another analysis by Pahud et al. of 26 patients, 20 were immunocompromised,²⁰ whereas in an analysis by Tabaja et al., only three out of 20 patients had any degree of immunosuppression (i.e., active malignancy, chemotherapy or biological agents)²¹ and in an analysis by Becerra et al. two out of 11 were immunocompromised.²² Lenfant et al. reported 42% immunosuppression in their analysis.²³

Therefore, our data are comparable with these analyses since, in the present study, only 28.6% of patients were immunocompromised, with three having an active malignancy and one having a rheumatologic condition under long-term corticosteroid treatment. Interestingly, none of our patients had a diagnosis of HIV infection.

Varicella zoster virus reactivation, resulting in central nervous system disease, seems to affect people of all ages. However, older patients are at a higher risk. Petitgas et al. analyzed patients enrolled in the ENCEIF cohort, a French cohort of older patients with encephalitis, and the incidence of VZV-related encephalitis increased with age, with 30% of cases in those over 80 years old, 15% of cases in the 65-79 years of age group and 7% in those younger than 65 years of age.²⁴ These findings are consistent with the findings of Arruti et al., where 23 cases of confirmed VZV presented in a population over 65 years of age. In that analysis, VZV encephalitis was the most common cause of viral encephalitis, ahead of HSV. Arruti et al. also reported increased mortality with increasing age or time elapsed from the onset of symptoms to treatment initiation and a high percentage of neurologic sequelae at discharge (40%).²⁵ Also consistent are the findings of Herlin et al., who described 92 patients in Denmark where the median age was 75, there was a high percentage of immunocompromised patients. Unfavorable outcomes were 69% at discharge, whereas three-month mortality was up to 11%.²⁶ Our study differs in that the median age was below 55 (even when excluding the youngest, an infant with acute leukemia, from the analysis); however, the representation of older people was strong, with five out of 14 patients over 65 years.

The presence of VZV central nervous disease in the absence of dermatological findings is increasingly recognized. In a retrospective analysis of 11 people living with HIV and VZV CNS infection, only four presented with skin findings.¹⁵ This also seems to be the case in immunocompetent populations, as shown in previously mentioned analyses.² This analysis, however, is consistent with the traditional clinical course of VZV reactivation, with eight out of 14 patients presenting with vesicular lesions. Of note was that the rash preceded the neurological image in only five patients.

The absence of inflammatory syndrome is an important finding that is also being observed. In the present study, two patients (excluding a case of acute leukemia) presented with WBC over 10,000/mm³ and none above 15,000. Of note,

only four had CRP levels higher than 1 mg/dL, and only five presented with fever before hospitalization. These findings are consistent with the literature. In the analysis by Becerra et al., over half of the population presented with absent inflammatory syndrome, and in the analysis by Tabaja et al., 79% had a WBC count of less than 11,000/mm³.^{21,22} Herlin et al. and Han et al. also reported median values of WBCs below 10,000/mm³.^{17,26} Lenfant et al. report a broader range of inflammatory markers as expressed by CRP; however, in their between-groups comparison (favorable versus unfavorable outcomes), there was no statistical significance.²³ This is consistent with the findings of Yuan et al.²⁷

In the present study, a subanalysis was performed among patients who presented with zoster rash and those who presented without such a rash. Patients who had a rash differed slightly from those who did not, being slightly older, having a slightly higher Charlson comorbidity index, not having photophobia or phonophobia, and having higher serum CRP. However, the small number of patients presented herein may have affected the power of the analysis. Thus, larger studies are needed to evaluate whether these differences were due to chance. Independently of whether presentation without a rash constitutes a different disease phenotype, the absence of the rash could be misleading, making clinicians think that VZV infection is unlikely, thus making them less likely to empirically treat with antivirals for VZV CNS infection.²⁰ This could lead to significant delays in appropriate treatment, possibly affecting the disease outcome.²⁰

The management of central nervous system infections is based on administering intravenous acyclovir; however, guidelines suggest that it is not based on large-scale trials. Guidelines from the Infectious Diseases Society of America (IDSA) refer only to encephalitis, with the recommendation of acyclovir having a rating of B-III (moderate evidence, based on expert opinions/clinical experience/descriptive studies). Based on that guideline, the preferred regimen is acyclovir, with ganciclovir being an alternative. No recommendation is made for the use of

corticosteroids.²⁸ Valacyclovir, an oral agent with good bioavailability, is also used in some cases and has been successfully used in the treatment of VZV encephalitis.²¹ In the present study, all 14 patients were initially treated with intravenous acyclovir. Eight of them received oral valacyclovir later on. Recovery from infection was noted for 13 out of 14 patients. The only patient who died probably succumbed to the primary cause that was associated with his immunosuppression (acute leukemia in an infant that required intensive care).

Cognitive impairment after VZV infection is a significant complication after the resolution of the infection. Grahn et al. demonstrated this in a case-control study of 14 patients who experienced VZV central nervous system infection as compared to healthy individuals, finding that the study population had significant long-term cognitive impairment.²⁹ In a series of 23 patients with VZV meningitis, Liu et al. also demonstrated cognitive decline, and the Montreal Cognitive Assessment (MoCA) scores of these patients were significantly lower than those of the control group. Additionally, cellular metabolism, as demonstrated by MRI in that series, was impaired in the hippocampal regions bilaterally.³⁰ Moreover, the overall functional status can be affected after VZV central nervous system infection is resolved. In a retrospective multicenter analysis of 72 patients, Lenfant et al. showed that although aseptic meningitis had a better prognosis, increased protein levels in the cerebrospinal fluid were associated with a steeper decline in neurological functionality estimates (as expressed via the modified Rankin scale). In that same analysis, 60% of the patients had unfavorable outcomes, and of those who completed follow-up, 12.9% died.²³

This study has some notable limitations. First, it is a single-center study with quite a small number of patients. Thus, the results should be read with caution since they represent the patterns of a specific geographical area. The small number of patients precluded the conduction of statistical analysis. Moreover, data about patients hospitalized in other hospitals whose cerebrospinal fluid samples were positive during the study period were not included in the present

study. Third, some information about the included patients may have been missed. Additionally, diagnosing VZV CNS infection was based on PCR, identifying VZV's genetic material. However, in most cases, the technique used was qualitative; thus, the data about the DNA quantity is unavailable for all patients. Finally, repeat serology was not performed, even though it is not the suggested method for diagnosing zoster or VZV CNS infection.

Conclusions

Patients presenting with VZV CNS infection in the present study had lymphocytic pleocytosis in the CSF and usually had a favorable outcome with antiviral treatment. The clinical presentation may not include the development of a typical zoster rash in almost half the cases. These patients may be slightly younger, have slightly lower Charlson comorbidity index, be more likely to present with photophobia or phonophobia, and have lower serum CRP. Those presenting without a rash may have a different overall clinical phenotype from those with a rash; however, this must be evaluated in larger studies in the future.

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Ethics statement: The study was conducted following the Declaration of Helsinki and approved by the Institutional Review Board of the University Hospital of Heraklion (protocol code 08/24-03-2021).

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