Original Article

Varicella Zoster Virus Infection of the Central Nervous System – 10 Year Experience from a Tertiary Hospital in South India

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Abstract

Introduction: Varicella zoster virus is an exclusively human neurotrophic virus. The primary infection with the virus causes varicella. The virus remains latent in nervous tissue and upon secondary activation causes a variety of syndromes involving the central nervous system (CNS) including meningoencephalitis and cerebellitis. **Materials and Methods:** In this study, we looked at the epidemiology, clinical and laboratory features, and outcomes of patients who were admitted with varicella zoster of the CNS from 2005 to 2014. **Results:** There were 17 patients. Fever was present in 13 patients, seizures in 9 patients and headache and vomiting in 4 patients each. A generalized varicella rash was present in 8 out of 17 patients. A single dermatomal herpes zoster was present in seven patients. Two patients had no rash. Varicella zoster polymerase chain reaction (PCR) in cerebrospinal fluid (CSF) was done in 5 patients of which 4 were positive and 1 was negative. Nine patients had diabetes with an average glycated hemoglobin of 8.6%. Total number of deaths was five. **Conclusions:** Patients with diabetes who develop varicella or herpes zoster may be at risk for CNS complications. The diagnosis of varicella encephalitis has to rest on a combination of clinical findings and CSF PCR, as neither the rash nor the PCR is sensitive enough to diagnose all the cases with varicella encephalitis.

Keywords: Varicella, varicella meningoencephalitis, varicella zoster virus

Introduction

Varicella zoster virus (VZV) is an exclusively human, neurotropic, alpha herpes virus causing infections worldwide. Primary infection with the virus causes varicella after which the virus remains dormant in the ganglia of the cranial nerves, dorsal roots, and the autonomic neurons for a long time. A decline in the cell-mediated immunity results in virus reactivation causing a spectrum of neurological syndromes such as herpes zoster, vasculopathy, myelopathy, retinal necrosis, cerebellitis, and zoster sine herpete.[1] Primary varicella infection predominantly affects children <10 years of age. Adults account up to 7%.[2] Varicella meningoencephalitis has an incidence of 1–2 episodes/10,000 varicella cases with the highest incidence among adults and infants.[3] The main aim of this article is to describe the clinical, laboratory and radiological features, and factors influencing the outcome in patients with VZV central nervous system (CNS) infection.

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Subjects and Methods

In this retrospective case series, we included patients discharged with a diagnosis of varicella zoster CNS infection (meningitis or encephalitis or both) during the period 2005–2014 in Christian Medical College in Vellore, South India which is a Tertiary Teaching Hospital with an average of 2500 inpatients and 8000 outpatients/day. The predominant catchment area for the hospital includes the districts of Vellore and Tiruvannamalai in Tamil Nadu state and Chittoor district of the Andhra Pradesh state. The study was approved by the Institutional Review Board and the Ethics Committee. The data were collected from the electronic database and the inpatient

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medical records of the hospital. The criteria for inclusion in the series are a patient aged more than 18 years with a diagnosis of varicella CNS infection made based on the clinical features of a CNS infection and the presence of a rash or a positive VZV polymerase chain reaction (PCR) in the cerebrospinal fluid (CSF).

Results

Demography

There were a total of 17 patients. The average age of the patients was 50 years (range 19–86 years). There were 11 males and 6 females. The average duration of illness was 5.5 days (range: 1–20 days).

Clinical features

Fever was present in 13 patients, seizures in 9 patients and headache and vomiting in 4 patients each. A generalized varicella rash was present in 8 out of 17 patients. Herpes zoster rash restricted to one dermatome was present in seven patients. Four of these involved the trigeminal nerve, one involved the C5 dermatome, one involved the D4 dermatome and one involved the D6 dermatome. Two patients had no rash. The single patient with HIV infection had presented with a dermatomal zoster rash generalized tonic–clonic seizures and unresponsiveness for 48 h. He responded well to acyclovir and had an uneventful recovery. He had no other opportunistic infections. CD4 count was unavailable for this patient. Nine patients had diabetes with average glycated hemoglobin (HbA1C) of 8.6%. Leukocytosis (total white blood cell [WBC] count >10,000 cells/mm^3) was present in ten patients (mean: 12,976 cells/mm^3). Six patients had renal failure (serum creatinine >1.4 mg/dl). The mean CSF WBC count was 93 cells/mm^3 (range 0–510 cells). All of them had lymphocytic predominance. PCR for VZV was done in 5 patients of which 4 were positive and 1 was negative.

Imaging

Six patients had magnetic resonance imaging (MRI) of the brain of which four had abnormal findings. The MRI brain and spinal cord of a patient who had presented with ascending weakness and seizure with a herpes zoster rash showed bilateral cortical-subcortical swelling involving the insular cortex, left medial temporal, cingulate, and inferior frontal gyri with areas of restricted diffusion and vasogenic edema with a suspicious focus of bleed in the left insular cortex. There was significant thoracic cord swelling with areas of hemorrhage [Figure 1]. Another patient had cortical and subcortical patchy areas of T2-weighted and FLAIR hyperintensities in the right frontal and parietal lobes with hemorrhagic transformation. There was a loss of flow void on T2-weighted images in the right internal carotid artery suggestive of thrombosis [Figure 2]. The other two patients had nonspecific abnormal findings on the MRI.

Treatment and outcome

All the patients received intravenous acyclovir. Two patients were discharged against medical advice. Four patients were

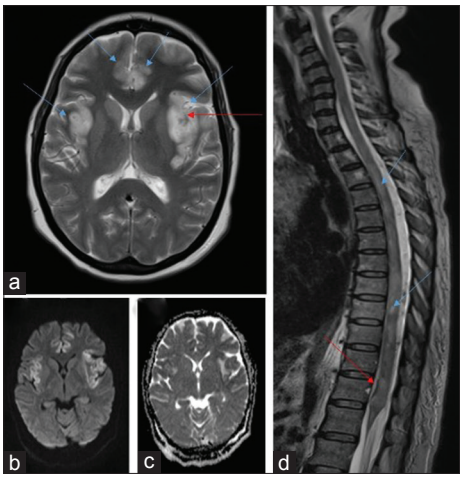

Figure 1: (a) T2-weighted axial image of the brain shows swelling and hyperintensity of the insular cortex and cingulate gyri (blue arrows) with a focus of hemorrhage within (red arrow). (b and c) diffusion weighted images and apparent diffusion coefficient maps show evidence of diffusion restriction in the insular cortex and cingulate gyri, (d) T2-weighted sagittal image of the spine shows diffuse swelling with patchy areas of hyperintensity (blue arrows) and small foci of hypointensity (red arrow) suggestive of hemorrhage in the cord

mechanically ventilated of which three of them expired. Total number of deaths was five. The first patient was in the postpartum period. She had a breast abscess complicated by septic shock with multi-organ dysfunction which ultimately led to her death. The second patient died of aspiration pneumonia. The third patient had encephalitis with associated myelitis and required mechanical ventilation. She died of worsening encephalitis and respiratory failure. The fourth patient was an 86-year-old man who developed health-care-associated pneumonia. He was managed conservatively without invasive ventilation and succumbed to his illness. The fifth patient developed left-sided hemiparesis and had a thrombus in the right internal carotid artery. She also had a catheter-related bacteremia with septic shock and multiorgan dysfunction.

Discussion

Varicella encephalitis is a dreaded complication of varicella infection affecting people of all age groups. Of the seventeen patients, only one was immunocompromised (6%). This finding is comparable to results from other studies –18% in Switzerland,[4] 12% in the United States,[5] and 10% in Israel.[6] The single patient with immunocompromised state had HIV infection.

A significant finding of our study is that 9 of the 17 patients had diabetes mellitus [Table 1]. The majority of these patients had uncontrolled diabetes with an average HbA1C of 8.6%. Four of these nine patients either died or were discharged against medical advice. This finding deserves special attention. Okamoto *et al*. have shown that patients with diabetes have significantly lower cell-mediated immunity to VZV than those without diabetes.[7] While previous studies have shown

Table 1: Individual clinical and laboratory features of the 17 patients with varicella zoster virus infection of the central nervous system

Number	Sex	Age	Duration of illness in days	Clinical features	Rash	Risk factors	HbA1c (g %)	CSF WBC count (cells/mm^3)	CSF VZV PCR	Treatment received	Mechanical ventilation	Outcome
1	Male	65	2	Fever, headache, vomiting, seizures	None	Diabetes	8.2	510	Positive	Acyclovir	No	Improved
2	Male	48	5	Fever, altered mentation	Varicella	Diabetes	7.2	Not done	Not done	Acyclovir	No	Improved
3	Female	71	2	Fever, headache	Zoster rash - trigeminal nerve	Diabetes	8.1	60	Not done	Acyclovir	No	DAMA*
4	Male	27	4	Fever, seizures	Varicella	-	-	2	Not done	Acyclovir	No	Improved
5	Female	65	1	Headache, vomiting	Varicella	-	-	50	Not done	Acyclovir	No	Improved
6	Male	22	3	Fever, altered mentation	Zoster rash - trigeminal nerve	Diabetes	7.0	170	Not done	Acyclovir	No	Improved
7	Female	34	20	Fever, seizures	Varicella	-	-	3	Not done	Acyclovir	Yes	Died
8	Male	76	Not known	Fever, altered mentation	Varicella	Diabetes	12.0	0	Not done	Acyclovir	No	Died
9	Male	46	10	Vomiting, altered mentation	Zoster rash - C4 dermatome	-	-	38	Not done	Acyclovir	No	Improved
10	Female	68	2	Seizures, ascending weakness	Zoster rash - D6 dermatome	-	-	95	Not done	Acyclovir	Yes	Died
11	Male	86	Not known	Fever, seizures	None	Diabetes	5.9	290	Positive	Acyclovir	No	Improved
12	Male	19	7	Fever, altered mentation	Zoster rash - trigeminal nerve	-	-	46	Positive	Acyclovir	No	Died
13	Male	30	6	Fever, seizures	Varicella	-		50	Not done	Acyclovir	No	Improved
14	Female	30	7	Fever, vomiting	Varicella	Diabetes	13.6	18	Positive	Acyclovir	Yes	Improved
15	Female	43	7	Fever, headache	Zoster rash - trigeminal nerve	Diabetes	NA	85	Negative	Acyclovir	Yes	Died
16	Male	55	4	Seizures	Varicella	Diabetes	NA	55	Not done	Acyclovir	No	DAMA
17	Male	55	3	Fever, seizures	Zoster rash - C5 dermatome	HIV infection	-	10	Not done	Acyclovir	No	Improved

*DAMA = Discharged against medical advice, NA = Not available, HbA1c = Glycated hemoglobin, WBC = White blood cell, CSF = Cerebrospinal fluid, VZV = Varicella-zoster virus, PCR = Polymerase chain reaction

that diabetes is a risk factor for herpes zoster,[8,9] the same has not been shown for varicella encephalitis. Our finding is particularly relevant for developing countries where varicella vaccination is not part of the national immunization programs, but the prevalence of diabetes is alarmingly on the rise. It is possible that in these countries the number of cases with varicella encephalitis may rise in the future. Vaccination may be the solution to this problem. Ampofo *et al*. followed up 461 healthy adults after varicella vaccination and showed that varicella vaccine was effective in protecting adults from serious VZV disease in the long-term.[10] Hata *et al*. have shown that varicella vaccine (Oka) is effective in inducing cell-mediated immunity is elderly subjects with or without diabetes.[11] Given these findings, patients with diabetes and varicella or herpes zoster should be treated aggressively. Varicella vaccination should also be considered for all diabetics who have not had varicella in the past.

Two patients had no clinical evidence of a vesicular rash, but the diagnosis was made based on PCR implying a possibility of varicella encephalitis even in the absence of a rash. Becerra *et al*. also reported that only 5 out of 11 patients (45%) had a vesicular rash in patients with varicella meningoencephalitis.[4] In another study, from California, only 11 out of 26 patients (42%) who tested positive for VZV PCR had a rash.[5] In a study from the UK, seven out of eight patients (88%) with CNS varicella infection had a rash. This suggests that varicella should be suspected in any patient with encephalitis and it may be prudent to check for VZV PCR in CSF even in the absence of a rash. The common practice of stopping acyclovir if HSV PCR is negative should be abandoned.[4]

One of our patients had a negative VZV PCR. This female patient aged 45 years presented with fever, headache, and seizures and had a vesicular rash involving the trigeminal

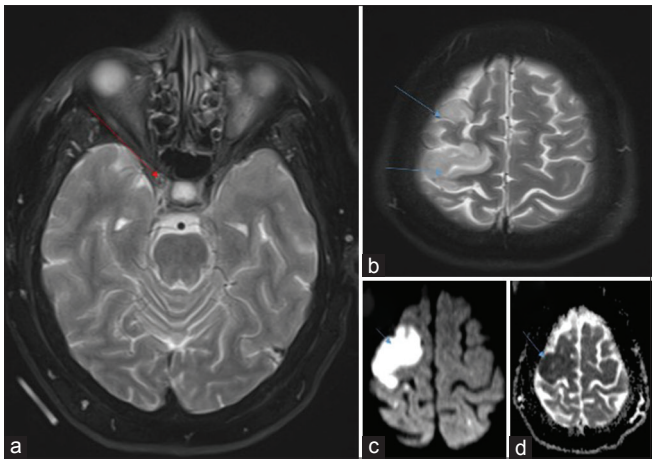

Figure 2: (a) T2 weighted axial image of the brain shows loss of flow void in the cavernous segment of right internal carotid artery (red arrow), suggestive of thrombosis, (b) T2 weighted axial image of the brain shows gyral swelling and hyperintensity in the right high frontal lobe (blue arrows), (c and d) diffusion weighted images and apparent diffusion coefficient maps show corresponding diffusion restriction, suggestive of acute infarcts (blue arrows)

nerve. She required mechanical ventilation and in the course of the illness developed occlusion of the right internal carotid artery with hemiparesis. CSF PCR for VZV, though highly specific, has a sensitivity of only 60%. In such cases, anti-VZV IgM antibody may be useful in making a diagnosis.[12]

Three patients did not have CSF pleocytosis. Becerra *et al*. noted that in their series, only 50% of patients with encephalitis had CSF pleocytosis. Higher CSF pleocytosis is seen more in the meningitic spectrum of CNS VZV disease. VZV CNS infection in HIV infection also has a higher likelihood of presenting without CSF pleocytosis. Brown *et al*. reported that only 6 out of 15 patients with VZV-associated neurological disease and HIV infection had CSF pleocytosis.[13] The diagnosis in such patients has to be made clinically and based on VZV PCR.

Conclusions

VZV is one of the common etiological agents causing encephalitis, and the incidence seems to be increasing. In patients with concomitant diabetes mellitus and primary varicella infection or herpes zoster, there appears to be an increased risk for CNS disease. This has to be substantiated by a prospective study with a control arm. In the meantime, vaccination should be considered for diabetics without immunity to VZV, and those diabetics with varicella or herpes zoster should be aggressively treated with acyclovir. Diagnosis of varicella encephalitis has to rest on a combination of clinical findings and CSF PCR, as neither the rash nor the PCR is sensitive enough to diagnose all the cases with varicella encephalitis.

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Conflicts of interest

There are no conflicts of interest.

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