Short Report

Alpha herpes virus infections in a group of patients clinically suspected of central nervous system infections in Sri Lanka. A brief laboratory report

WKH Dheerasekara[1], WPDS Attanayake[1], MS Raziya[1], BDS Jayawardhana[1], RGLS Rajamanthri[1], MARV Muthugala[1]

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Abstract

Alpha herpes viruses cause central nervous system (CNS) infections during primary infection or following reactivation. Laboratory data on CSF samples received by the Virology Laboratory, Teaching Hospital, Kandy from March, 2017 to March, 2019 from patients clinically suspected of having infections of the central nervous system (CNS) were retrospectively analyzed to determine positivity rate of human herpes simplex virus (HSV) and varicella zoster virus (VZV) infections. Data from 352 patients was analyzed. Eight patients (2.3%) were positive for VZV and three patients (0.8%) were positive for HSV. None of the 8 patients who were HVZ DNA positive had a history of chickenpox. Two of these 8 patients did not have the typical chickenpox rash during their illness. HVZ IgG data was not available to determine whether their illness was primary or secondary.

Keywords: HSV, VZV, CNS infections, Sri Lanka, Alpha herpes virus

Introduction

Alpha herpes viruses are a subfamily of *herpesviridae* that include three human pathogens, Herpes Simplex type 1 (HSV-1), Herpes Simples type 2 (HSV-2) and Varicella Zoster Virus (VZV). These viruses primarily cause infection of muco-epithelial cells and establish latency in the peripheral nervous system. Alpha herpes viruses cause central nervous system (CNS) infections during primary infection or following reactivation from the latent state.[1-5] Patients with CNS infections develop a wide range of clinical features including headache, fever, seizures, altered behavior and altered level of consciousness though these may not be present in all patients. Clinical

[1] *Department of Virology, National Hospital, Kandy, Sri Lanka*

Address for correspondence: Dr Rohitha Muthugala, Department of Virology, National Hospital, Kandy, Sri Lanka
Telephone: + 0094779229529 Email: rohithavm@yahoo.com

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manifestations may be atypical, and diagnosis can be challenging. Laboratory diagnosis is therefore needed to ensure optimal treatment.[6] Aciclovir is the choice of treatment and has proven to be highly effective when commenced early for treatment for CNS infections caused by HSV or VZV.[7]

The *International Herpes Management Forum* (IHMF) has recommended polymerase chain reaction (PCR) of the cerebrospinal fluid (CSF) as the diagnostic method of choice for alpha herpes virus CNS infections.[8] Negative results should be interpreted taking into account the patient's clinical presentation and the timing of CSF sampling.

All patients with alpha herpes virus CNS infections should receive intravenous aciclovir 10 mg/kg every 8 h for 21 days.[5,6] After completion of therapy, PCR of the CSF can confirm the elimination of replicating virus in the patient.

There are a limited number of studies on alpha herpes virus CNS infections in Sri Lanka. Therefore, laboratory data were retrospectively analyzed to determine positivity rate of human HSV and VZV infections among clinically suspected patients with central nervous system infections.

Methods

Laboratory data on 352 patients with suspected CNS infections (encephalitis, meningitis or myelitis) were analyzed. Results of CSF samples received by the Virology Laboratory, National Hospital Kandy from government hospitals in the Central, North Central, and Eastern Provinces of Sri Lanka from March 2017 to March 2019 were included in the study.

Nucleic acids were extracted from fresh CSF samples using the QIAamp DNA Mini Kit, (QIAGEN, Germany) according to the manufacturer instructions. Detection of each type of alpha herpes virus DNA was carried out using a validated commercial real time multiplex PCR kit (RealStar® *alpha* Herpesvirus PCR Kit 1.0, altona Diagnostics, Germany; PCR machine: Rotor – Gene Q, QIAGEN, Germany). Data on the laboratory request form was analyzed.

Results

There were 180 (51.1%) males and 172 (48.9%) females of ages ranging from two days to eighty five years (Table 1). There were 142 (40.3%) in the paediatric age group (< 14 years) and 210 (59.7%) in the adult group (>14 years).

Of the 352 patients, 8 (2.3%) were positive for VZV and 3 (0.8%) for HSV. Of the VZV positive patients, 6 (75%) had the typical chicken pox rash while 2 patients (25%) did not develop a rash throughout the illness. None of the VZV positive patients had a history of varicella infection in the past. Five patients had VZV encephalitis, one patient had VZV meningitis, one patient had VZV myelitis and one patient had VZV hemorrhagic cerebellitis. There were two fatalities and 6 patients recovered completely following treatment.

Of the three positives for HSV, two had HSV-1and one had HSV-2 infection. One of the HSV-1 positive patients had encephalitis while the other patient had neonatal HSV-1. The patient with a positive HSV-2 result presented with meningitis. The patient with neonatal infection had developed recurrent HSV CNS infections.

Table 1: Summary of CSF analysis of alpha herpes virus DNA positive patients

Patient	Age	Clinical presentation	CSF cell count				CSF Protein	CSF Sugar	CSF PCR results
			Total WBC /mm^3	L %	PMN %	RBC/mm^3			
1	03 years	Encephalitis	11	90	10	3760	Normal	Normal	VZV
2	76 years	Myelitis	523	99	01	19	Elevated	Normal	VZV
3	48 years	Meningitis	505	92	08	NA	Elevated	NA	VZV
4	72 years	Encephalitis	ND						VZV
	14 years	Encephalitis	<05	100	00	NA	Normal	Normal	VZV
6	05 years	Hemorrhagic cerebellitis	467	98	02	57	Elevated	Normal	VZV
7	03 years	Encephalitis	45	78	22	12	Elevated	Normal	VZV
8	11 years	Encephalitis	NA						VZV
9	05 days	Sepsis	05	100	00	2430	Elevated	Normal	HSV 1
10	02 years	Encephalitis	345	97	03	67	Normal	Normal	HSV 1
11	60 years	Meningitis	67	87	13	02	Slightly elevated	Reduced	HSV 2

NA-not available for data analysis
ND- not done (sample was insufficient, only CSF PCR based on clinical picture)

Discussion

Alpha herpes virus CNS infection is considered the most common treatable CNS virus infection in some parts of the world.[8] However, in the present study, it constituted only 3.1% (11/352). A recent study in Sri Lanka[9] reported a VZV CNS infection prevalence of 9% while a cross sectional study conducted at two tertiary care hospitals in Sri Lanka reported 3% VZV positivity among 99 tested patients.[10] All the VZV CNS positive cases were clinically identified as primary infections. However, 2 of the 8 patients did not have the typical skin manifestation of chickenpox and did not give a history of chickenpox. Since anti VZV IgG testing was not done on these 2 patients, it was not possible to ascertain whether their VZV infection was a primary infection or reactivation of a latent infection. Absence of the typical skin rash should therefore not exclude the possibility of VZV CNS infection.[1,3,4]

There were two fatalities despite early and adequate treatment with intravenous aciclovir and both patients were considered as immunosuppressed. One patient was on long term steroid therapy for connective tissue disorder and the other patient had uncontrolled diabetes mellitus.

Conclusion

In Sri Lanka, almost all patients clinically diagnosed as encephalitis receive empirical aciclovir with antibiotics. Routine practice is to continue aciclovir for 14 days depending on the clinical response. Providing a diagnostic service for human alpha herpes virus infections would be useful in optimizing treatment in patients with VZV and HSV CNS infections.

Conflicts of interests

There are no conflicts of interests

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