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 Dheerasekara¹, WPDS Attanayake¹, MS Raziya¹, BDS Jayawardhana¹, RGLS Rajamanthri¹, MARV Muthugala¹

Sri Lankan Journal of Infectious Diseases 2020 Vol.10 (1):72-75
DOI: http://dx.doi.org/10.4038/sljid.v10i1.8277

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
manifestations may be atypical, and diagnosis can be challenging. Laboratory diagnosis is therefore needed to ensure optimal treatment. 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.

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. 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. 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-1 and 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 |
|---------|-------|--------------------------------|------------------|-------------|-----------|-----------------|
| 1       | 03 years | Encephalitis                  | 11 WBC/mm³, 90 L%, 10 PMN % | Normal      | Normal    | VZV             |
| 2       | 76 years | Meningitis                    | 523 WBC/mm³, 99 L%, 01 PMN % | Elevated    | Normal    | VZV             |
| 3       | 48 years | Meningitis                    | 505 WBC/mm³, 92 L%, 08 PMN % | Elevated    | NA        | VZV             |
| 4       | 72 years | Encephalitis                  |                 |             |           | VZV             |
|         | 14 years | Encephalitis                  | <05 WBC/mm³, 100 L%, 00 PMN % | Normal      | Normal    | VZV             |
| 6       | 05 years | Hemorrhagic cerebellitis      | 467 WBC/mm³, 98 L%, 02 PMN % | Elevated    | Normal    | VZV             |
| 7       | 03 years | Encephalitis                  | 45 WBC/mm³, 78 L%, 22 PMN % | Elevated    | Normal    | VZV             |
| 8       | 11 years | Encephalitis                  |                 |             |           | VZV             |
| 9       | 05 days  | Sepsis                        | 05 WBC/mm³, 100 L%, 00 PMN % | Elevated    | Normal    | HSV 1           |
| 10      | 02 years | Encephalitis                  | 345 WBC/mm³, 97 L%, 03 PMN % | Normal      | Normal    | HSV 1           |
| 11      | 60 years | Meningitis                    | 67 WBC/mm³, 87 L%, 13 PMN % | 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. However, in the present study, it constituted only 3.1% (11/352). A recent study in Sri Lanka 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. 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.

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

References

1) Arruti M, Pineiro LD, Salicio Y, et al. Incidence of varicella zoster virus infections of the central nervous system in the elderly: a large tertiary hospital-based series (2007-2014). J Neurovirol 2017; 23(3):451-459 doi: http://doi.org/10.1007/s13365-017-0519-y

2) Häusler M, Schaade L, Kemeny S, et al. Encephalitis related to primary varicella zoster virus infection in immunocompetent children. J NeuroSci 2002; 195(2):111-6 doi: https://doi.org/10.1016/s0022-510x(02)00017-5

3) Koskiniemi M, Piiparinen H, Rantalaiho T, et al. Acute central nervous system complication in varicella zoster virus infections. J Clin Virol 2002; 25(3):293-301 doi: 10.1016/s1386-6532(02)00020-3

4) Steiner I, Kennedy PG, Pachner AR. The neurotropic herpes viruses: herpes simplex and varicella-zoster. Lancet Neurol 2007; 6(11):1015–1028. doi: https://doi.org/10.1016/S1474-4422(07)70267-3

5) Whitley RJ. Herpes simplex encephalitis: adolescents and adults. Antiviral Res 2006; 71(2–3):141–8. doi: https://doi.org/10.1016/j.antiviral.2006.04.002

6) Sauerbrey A, Wutzler P. Laboratory diagnosis of central nervous system infections caused by herpesviruses. J Clin Virol. 2002; 25:S45–S51 doi: https://doi.org/10.1016/s1386-6532(02)00033-1

7) Scott H. James, David W. Kimberlin, and Richard J. Whitley. Antiviral therapy for herpesvirus central nervous system infections: Neonatal herpes simplex virus infection, herpes simplex encephalitis, and congenital cytomegalovirus infection. Antiviral Res. 2009; 83(3): 207-213. doi: https://doi.org/10.1016/j.antiviral.2009.04.010

8) Kenneth L Tyler. Herpes simplex virus infections of the central nervous system: encephalitis and meningitis, including Mollaret’s. Journal of the IIMF 2004; 11:57A-64A. PMID: 15319091

9) Gunathilaka, D, Ramesh, R, Wickramasinghe, N, et al. Varicella zoster virus as a cause of infectious encephalitis in a cohort of Sri Lankan patients. CMJ 2016; 61(4):196 doi: https://doi.org/10.4038/cmj.v61i4.8392

10) Janarthani Lohitharajah, Neelika Malavige, Carukshi Arambepola et al. Viral aetiologies of acute encephalitis in a hospital-based South Asian population. BMC Infectious Diseases 2017; 17:303 doi: https://doi.org/10.1186/s12879-017-2403-z