The clinical profiles and outcomes of patients with herpesviruses in cerebrospinal fluid: 2019 - 2022

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Background. Herpesviruses are ubiquitous and commonly cause neurological syndromes. A paucity of data exists describing the clinical profiles and outcomes of these viruses in cerebrospinal fluid (CSF).
Objectives. To describe the clinical profile and outcomes of patients with a positive CSF viral panel testing for six herpesviruses (herpes simplex virus 1 and 2 (HSV1; HSV2), varicella zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV) and human herpesvirus 6 (HHV6)).
Methods. A retrospective descriptive study included all hospitalised patients aged 13 years and older in whom a herpesvirus was detected by a herpesvirus panel performed on CSF. A folder review was performed to acquire demographic, clinical and laboratory information.
Results. We identified 204 CSF herpesviruses in 184 patients. Most were people living with HIV (*n*=137/184, 74.5%). EBV was the most frequently identified herpesvirus (*n*=152/204, 74.5%). The herpesvirus was considered the cause of the clinical neurological syndrome in 20 patients (20/184, 10.9%), of whom most had VZV (7/20, 35%). Patients with VZV presented with encephalopathy (4/11, 36.4%), meningoencephalitis (3/11, 27.3%) and stroke (3/11, 27.3%). Encephalopathy, seizures and lower-limb weakness (*n*=5/19, 26.3%) were more common in patients with CMV. Those with HSV1 presented with seizures (*n*=2/5, 40%) and those with HSV2 with encephalopathy (*n*=3/6, 50%) and meningoencephalitis (*n*=2/6, 33.3%). EBV was the most common herpesvirus in patients with tuberculosis (TB) (45/49, 91.8%). Antiviral therapy was prescribed in 19/184 (10.3%) patients. The in-hospital mortality rate of all patients was 21.7%.
Conclusion. EBV was the most common herpesvirus detected on CSF. Most patients with TB and HIV had EBV detected in their CSF, which may represent reactivation in these patients. This study highlighted the undertreatment of CMV and overtreatment of EBV. Greater awareness regarding the clinical indications for antiviral therapy in this setting is needed.

Keywords: herpesvirus, cerebrospinal fluid, HIV, CSF, CSF viral panel

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Herpesviruses, which include herpes simplex virus 1 and 2 (HSV1; HSV2), cytomegalovirus (CMV), Epstein-Barr Virus (EBV), varicella zoster virus (VZV) and human herpesvirus 6 (HHV6), have the capacity to cause a vast array of clinical neurological syndromes in both immunosuppressed and immunocompetent people.[1]

Of these, HSV is a common cause of viral encephalitis in the developed world[2] with an effective antiviral treatment option, namely intravenous (IV) acyclovir.[3] HSV2 is one of the most common causes of aseptic meningitis in adults, second to enteroviruses.[4] Developed countries report a yearly incidence of 1 - 4 million cases of HSV encephalitis.[5] CMV causes encephalitis, ventriculitis and myelitis as primary infection or reactivation and is predominantly a disease associated with advanced HIV infection.[6]

EBV, like the other herpesviruses, is a ubiquitous virus commonly acquired early in life.[7] The virus is dormant in B-lymphocytes and reactivation occurs commonly in immunocompromised people, rarely causing a subacute encephalitis.[7] The presence of EBV in cerebrospinal fluid (CSF) does not imply true neurological infection,[7] but a high EBV viral load may aid in diagnosing primary central nervous system (CNS) lymphoma in patients at risk.[8] EBV contributes to the oncogenesis of various malignancies such as nasopharyngeal carcinoma and lymphoma and has also recently been implicated in multiple sclerosis.[9] Reactivation of VZV may be an early manifestation of HIV[10] and has been associated with morbidity in people living with HIV (PLWH) due to increased risk of stroke[11] and seizures in this patient population.[12] The neurological manifestations of VZV can include encephalitis, meningitis, myelopathy, cranial neuropathy or vasculopathy.[13,14] VZV has been linked to an increased risk of stroke due to vasculopathy in both adults and children.[15] HHV6 is capable of chromosomal integration and reactivation but its presence in CSF is rarely associated with disease in immunocompetent adults. If it does reactivate, limbic encephalitis is the most common presentation.[7] HHV6 positivity in CSF in adulthood is as a result of reactivation or chromosomally

integrated HHV6 in most patients, as most people are exposed prior to adulthood.[16] HHV6 encephalitis is more common in patients who are immunocompromised following haematopoietic stem cell transplantation (HSCT) or solid-organ transplant.[17]

Examination of CSF for herpesviruses remains a crucial component in identifying viruses in patients with a suspected CNS viral infection.[18] The application of polymerase chain reaction (PCR) on CSF has allowed clinicians to appreciate the diverse clinical neurological presentations of these viruses.[1] There is a paucity of data on the clinical description of patients with a herpesvirus detected in CSF, especially within the African context. We thus aimed to describe the patient characteristics, clinical features and outcomes of this population.

Methods

Study design and setting

This is a retrospective descriptive study of all hospitalised patients aged 13 years and older in whom a herpesvirus was detected on a herpesvirus panel performed on CSF between January 2019 and December 2022. The study was conducted at Tygerberg Hospital (TBH), a 1 380-bed tertiary academic hospital in Western Cape Province, South Africa. It is the largest hospital in Western Cape Province and the second largest hospital in South Africa, serving as a referral centre for multiple primary and secondary facilities that support a population of more than 3.4 million.[19]

Data collection and processing

Patients were identified using an electronic laboratory database of positive CSF herpes viral panel findings, tested using the Seeplex® Meningitis ACE Detection Kit (Seegene Inc., South Korea).[20] We report the positive findings of the Seeplex Meningitis-V1 kit component, which detects six viruses (HSV1, HSV2, VZV, EBV, CMV and HHV6).

Demographic and clinical data were extracted from Enterprise Content Management, an electronic health record system. Laboratory results were extracted from the National Health Laboratory Service (NHLS) system using a standardised form. Radiological imaging was obtained from the Picture Archiving and Communication System (PACS). The following data were collected: demographic information, comorbid illnesses, clinical features and the neurological diagnoses as documented by the treating clinician. Patients were allocated to clinical neurological syndromes based on the medical notes of the treating physician/team. The clinical neurological syndromes were classified into six categories: encephalopathy, meningitis, meningoencephalitis, stroke, seizure and/or lower-limb weakness. Where patients had clinical features of more than one neurological syndrome, both were captured. The term encephalopathy was used interchangeably in cases where 'encephalitis' or 'encephalopathy' were documented. Where terms such as encephalopathy, seizures, meningitis, encephalitis, meningoencephalitis and/or lower-limb weakness were not used, the researcher used discretion in categorising the patient based on clinical description used by the treating physician (e.g. depressed level of consciousness = encephalopathy, neck stiffness = meningitis, strange behaviour or altered sensorium = encephalitis).

We captured results of the following investigations: HIV status and, where positive, the CD4 count and HIV viral load. We documented the C-reactive protein (CRP), creatinine, CSF and the head and/or spinal computed tomography/magnetic resonance imaging findings. We also reviewed whether the treating clinician/team attributed the herpesvirus as the most likely cause of the clinical presentation/neurological syndrome and whether the herpesvirus was treated. Outcome, defined as in-hospital mortality or survival to discharge, was captured. Patients were excluded from analysis if clinical records were incomplete (no documentation of symptoms and signs, or where laboratory results were unavailable).

Data analysis

Statistical analysis was performed using SPSS v29 (IBM, USA). All descriptive numerical data with a normal distribution were described using means and standard deviation, whereas non-normal data were described using median and interquartile ranges (IQRs). Chi-square or Fisher's exact test was used to identify statistical significance for all categorical outcomes. When comparing the means of continuous data, the Mann-Whitney U test was used when the data did not have a normal distribution. Statistical significance was set at $p<0.05$.

Ethical approval

Ethical approval for the study was granted by the Health Research Ethics Committee of Stellenbosch University (ref: S23/07/168).

Results

During the 4-year study period, a total of 851 specimens were sent for CSF herpesvirus testing. Of these, 188 patients tested positive for at least one herpesvirus, resulting in a prevalence of 22.1% among the tested patients. After excluding four participants due to incomplete clinical records, 184 patients were included for final analysis. Most patients were female (*n*=100, 54.3%; Table 1) The median (IQR) age was 38 (30 - 46) years. One herpesvirus was identified in 164 patients (89.1%), and 20 patients (10.9%) had two herpesviruses identified in CSF. No participants had more than two herpesviruses.

Herpesviruses

The most frequent CSF herpesviruses were EBV (*n*=152, 74.5%), followed by CMV (*n*=19, 9.3%), VZV (*n*=11, 5.4%), HHV6 (*n*=11, 5.4%), HSV2 (*n*=6, 2.9%) and HSV1 (*n*=5, 2.5%; Table 2). EBV was the most frequent virus in PLWH and HIV-negative patients.

Other herpesviruses and PLWH

HIV was the most common comorbidity (*n*=136, 73.91%; Table 1). Among PLWH, the median (IQR) CD4 count was 81 (32 - 197.5) cells/μL and the median viral load was 22 174 (224 - 221 289) copies/mL. Most PLWH were not on antiretroviral treatment (ART) (*n*=91, 66.9%). The prevalence of HIV among patients with HSV2, CMV, VZV and EBV detected in CSF was high (Table 2). PLWH with CMV, VZV and HSV2 had a median (IQR) viral load of 228 444 (7 162 - 531 724) copies/mL, were mostly not on ART (73%), and had a median CD4 count of 46 (IQR 12 - 81) cells/mm^3. Except for one patient with diabetes, most patients with VZV were PLWH (*n*=9/11, 81.8%). All patients with HSV1 were PLWH.

Herpesviruses and other neurological infections

Forty-nine (26.6%) patients had active and/or disseminated tuberculosis (TB) where presumed neurological TB was identified as the cause of the clinical syndrome, and anti-TB therapy was initiated in these cases (Table 1). In these patients, the CSF GeneXpert was only positive in one patient. The majority of patients with TB had EBV detected in their CSF (*n*=45, 91.8%). Of the other infective neurological processes, the following were also considered the cause of the neurological syndrome: neurosyphilis (*n*=20, 10.9%), bacterial meningitis (*n*=13, 7.1%) and cryptococcal meningitis (*n*=8, 4.3%).

Clinical neurological syndromes

Patients with VZV presented with encephalopathy (*n*=4/11, 36.3%), meningoencephalitis (*n*=3/11, 27.3%) and stroke (*n*=3/11, 27.3%)

Table 1. Demographic profile, laboratory characteristics and outcomes of patients with a positive CSF herpesvirus test (*N*=184)

Demographic and clinical profile	*N*=184
Age, years	38 (30 - 46)
Sex (female)	100 (54.3)
Comorbidities and co-infections	
Hypertension	26 (14.1)
Diabetes	5 (2.7)
Autoimmune	7 (3.8)
TB	49 (26.6)
Malignancy	5 (2.7)
HIV	137 (74.5)
Neurosyphilis	20 (10.9)
Bacterial meningitis	13 (7.1)
Cryptococcal meningitis	8 (4.3)
CD4 count (cells/mm^3) (*n*=128)	81 (32 - 197.5)
HIV viral load (cps/mL)	
0 - 50	0
50 - 1 000	10
>1 000	55
No record	72
Serum CRAg positive	10 (8.7)
ART (on treatment) (*n*=136)	45/136 (33.3)
Creatinine (μmol/L)	65 (49 - 83)
White cell count (×10^9/L)	6.89 (5.03 - 10.14)
Haemoglobin (g/dL)	11.4 (9.8 - 13.5)
Platelets (×10^9/L)	266.5 (169 - 344.5)
CRP (mg/L)	30 (6 - 96)
Outcome	
Discharged	144 (78.3)
Died	40 (21.7)
Length of hospital stay (days)	10.5 (4 - 23.5)

Data are expressed as median (IQR) or *n* (%).
CRAg = cryptococcal antigen test; EBV = Epstein–Barr Virus.

Table 2. Prevalence of herpesvirus categorised by HIV status

	All herpesviruses (*N*=204)	PLWH (*n*=137)	HIV negative (*n*=45)	HIV unknown (*n*=2)
EBV	152 (74.5)	118 (86.1)	33 (73.3)	1 (50)
CMV	19 (9.3)	16 (11.7)	3 (6.7)	0
VZV	11 (5.4)	9 (6.6)	2 (4.4)	0
HHV6	11 (5.4)	5 (3.6)	5 (11.1)	1 (50)
HSV2	6 (2.9)	6 (4.4)	0	0
HSV1	5 (2.5)	0	5 (11.1)	0

Data are expressed as *n* (%).Denominators = *n* (in column heading).
PLWH = people living with HIV.

(Table 3). Encephalopathy (*n*=5/19, 26.3%), seizures (*n*=5/19, 26.3%) and lower-limb weakness (*n*=5/19, 26.3%) were most common in patients with CMV. Those with HSV1 presented most frequently with seizures (*n*=2/5, 40%) and HSV2 with encephalopathy (*n*=3/6, 50%) and meningitis (*n*=2/6, 33.3%). Encephalopathy (*n*=38/152, 25%), followed by meningitis (*n*=29/152, 19.1%) had the highest prevalence in patients with EBV. In patients with HHV6, encephalopathy (*n*=4/11, 36.3%) and meningitis (*n*=2, 18.2%) were the most frequent clinical neurological syndromes.

EBV was the most frequently detected herpesvirus

EBV was the most frequently identified virus detected in CSF among PLWH and HIV-negative patients overall (Table 1). Patients with EBV-positive CSF were more likely to be HIV positive (p=0.05), have higher CD4 counts (100 v. 13 cells/μL; p<0.01), have higher creatinine values (67.5 v. 50 μmol/L; p=0.021) and have higher haemoglobin values (11.6 v. 10.35 g/dL; p=0.035) (Table 4). There were no significant differences between the two groups when comparing length of hospital stay and clinical outcomes in terms of in-hospital mortality.

Herpesviruses detection and physician-attributed cause of clinical syndrome

The herpesvirus detected in CSF was identified as the cause of the neurological clinical syndrome by the treating physician in 20 patients (*n*=20, 10.9%), of whom antiviral treatment was not administered to 1 patient with HHV6 (Table 5). Antiviral treatment

Table 3. Clinical neurological syndromes in patients with CSF herpesviruses

	Encephalopathy	Meningitis	Meningo-encephalitis	Stroke	Seizure	Lower-limb weakness
CMV	5/19 (26.3)	1/19 (5.3)	0	1/19 (5.3)	5/19 (26.3)	5/19 (26.3)
EBV	38/152 (25)	29/152 (19.1)	6/152 (3.9)	27/152 (17.8)	21/152 (13.8)	24/152 (15.8)
HSV1	1/5 (20)	0	0	0	2/5 (40)	1/5 (20)
HSV2	3/6 (50)	2/6 (33.3)	1/6 (16.7)	0	0	1/6 (16.7)
VZV	4/11 (36.3)	2/11 (18.2)	3/11 (27.3)	3/11 (27.3)	1/11 (9.1)	1/11 (9.1)
HHV6	4/11 (36.3)	2/11 (18.2)	1/11 (9.1)	1/11 (9.1)	1/11 (9.1)	1/11 (9.1)

Data are expressed as *n* (%).

Table 4. Clinical and laboratory characteristics characterised by CSF EBV status

	EBV positive (*n*=152)	EBV negative (*n*=32)	*p*-value
Age (years)	39 (31 - 46)	35.5 (25.5 - 42)	0.096
Female sex	79 (52.0)	21 (65.6)	0.16
Admission ward			0.019
Medical	134 (88.2)	26 (81.2)	-
ICU	3 (2.0)	0 (0.0)	-
High care	7 (4.6)	6 (18.8)	-
Surgical	8 (5.3)	0 (0.0)	-
Comorbidities			
Hypertension	22 (14.5)	4 (12.5)	0.77
Diabetes	4 (2.6)	1 (3.1)	0.88
Autoimmune	5 (9)	2 (14)	-
TB	45 (91.8)	4 (8.2)	-
Malignancy	4 (7)	1 (7)	-
HIV	117 (78.0)	19 (61.3)	**0.05**
CD4 count (cells/mm^3) (*n*=128)	100 (41 - 217)	13 (4 - 81)	**<0.001**
HIV viral load (cps/mL)			0.25
0 - 50	0	0	-
50 - 1 000	9	1	-
>1 000	47	8	-
No record	62	10	-
Serum CRAg positive	6 (6)	4 (21)	0.06
ART (on treatment) (*n*=136)	42 (36.2)	3 (15.8)	0.08
Creatinine (μmol/L)	67.5 (53 - 84.5)	50 (45 - 67)	**0.021**
White cell count (×10^9/L)	6.75 (5.3 - 9.78)	7.1 (3.31 - 13)	0.061
Haemoglobin (g/dL)	11.6 (10 -13.65)	10.35 (9.5 - 11.7)	**0.035**
Platelets (×10^9/L)	275 (174.5 - 347.5)	217 (151 - 336.5)	0.11
CRP (mg/L)	24.5 (6 - 96)	55.5 (8 - 91)	0.35
Outcome	0.34		-
Discharged	121 (79.6)	23 (71.9)	-
Died	31 (20.4)	9 (28.1)	-
Length of hospital stay (days)	11 (4 - 23)	9.5 (4.5 - 32)	0.76

Data are expressed as median (IQR) or *n* (%).
Bold indicates *p*-value ≤0.05 and statistical significance.
ICU = intensive care unit; CRAg = cryptococcal antigen test; EBV = Epstein–Barr Virus; ART = antiretroviral treatment.

was provided (intravenous acyclovir or ganciclovir) to 19 patients, 14 of whom received antiviral therapy appropriately. Three patients had a concomitant neurological diagnosis: one patient with GeneXpert-positive TB meningitis, one with presumed TB meningitis and one with HHV6/VZV with neurosyphilis and cryptococcal meningitis.

Cerebrospinal fluid analysis

Patients with VZV detected in CSF had the highest mean protein and lymphocyte counts, of 2.8 g/L and 80 cells/μL, respectively, followed by HSV2 (2.2 g/L and 10 cells/μL), EBV (2.1 g/L and 42 cells/μL), CMV (1.1 g/L and 6.4 cells/μL), HHV6 (1 g/L and 40 cells/μL) and HSV1 (0.8 g/L and 38 cells/μL). CSF protein counts were highest in patients with stroke (3.4 g/L), followed by meningitis (2.2 g/L), encephalopathy (2 g/L), meningoencephalitis (1.5 g/L) and encephalitis (0.8 g/L). All neurological clinical syndromes had a lymphocytic-predominant cell count, which was highest in the groups with meningitis, meningoencephalitis and encephalopathy.

Table 5. Characteristics of cases with clinician-diagnosed CSF herpesvirus-associated clinical syndrome (*N*=20)

HIV status	CD4 count (cells/μL)	Serum CRAg	ART	CSF virus 1	CSF virus 2	CSF protein (g/L)	CSF glucose (mmol/L)	CSF lymphocyte (/μL)	CSF PMN count (/ μL)	CSF RBC (/ μL)	CSF FTA/ VDRL	CSF GeneXpert	CSF CRAg	Clinical neurological syndrome	Modality	Findings	Outcome
NA		NA		HHV6		0.58	4.7	60	0	0	–	–		Meningitis	CT	Cerebral oedema	Discharged
+	195	NA	–	EBV		0.04	3.9	4	0	107	–	–		Encephalopathy	CT	Normal	Discharged
+	49	–	–	HSV2		3.91	0.7	46	12	0	–	+	–	Meningitis/ Encephalopathy	CT	Meningitis	Died
+	69	–	–	EBV	VZV	1.15	3	14	0	20			–	Encephalitis	CT	Normal	Discharged
–				HHV6		0.24	5.6	11	0	84			–	Meningoencephalitis/ encephalopathy	MRI	Autoimmune	Died
+	62	–	–	EBV	VZV	0.41	3.3	0	0	0	–	–	–	Meningitis	CT	Normal	Discharged
–				CMV		1.65	2.8	0	0	0				Encephalitis	MRI	Thrombosis	Discharged
+	75	–	–	EBV		0.35		0	0	44	–			Encephalitis	CT	PML	Died
–				VZV		1.72	2.4	101	153	5	–	–		Meningoencephalitis	CT	Normal	Discharged
+	217	NA	+	EBV	VZV	1.74	3	14	10	0				Meningoencephalitis	CT	Normal	Discharged
+	294	–	+	EBV	VZV	1.34	2.2	10	0	20	–	–	–	Stroke	CT	Infarct	Discharged
–				EBV	VZV	1.03	6.9	572	3	12	–	–	–	Meningitis	CT	Normal	Discharged
+	28	+	+	HHV6	VZV	0.78	3.4	0	0	2	+	–	+	Stroke	CT	Infarct	Discharged
–				HSV1		2.94	3.7	192	484	709		–		Lower-limb weakness	MRI	Transverse myelitis	Discharged
+	81	+	+	CMV		0.67	3.2	2	0	0		–	–	Meningitis	CT	Meningitis	Discharged
–				EBV		0.66	4.2	1	3	0		–		Seizures	CT	Infarct	Discharged
+	23	–	–	HSV2		0.66	3.5	0	0	28	–	–	–	Encephalopathy/ Meningoencephalitis	CT	Normal	Discharged
+	101	NA	–	CMV		2.06	2.4					–		Encephalopathy	MRI	Thrombosis	Died
+	11	–	–	CMV		0.89	2	0	0	0		–		Lower-limb weakness	CT	Normal	Discharged
+	172	–	–	EBV		0.04	3.7	13	4	0		–	–	Seizures/meningitis	CT	Normal	Discharged

NA = unknown.
+ = positive; – = negative; CRAg = cryptococcal antigen; ART = antiretroviral treatment; CSF = cerebrospinal fluid PMN = polymorphonuclear neutrophil; RBC = red blood cell; FTA/VDRL = fluorescent treponemal antibody/venereal disease research laboratory; HHV6 = human herpesvirus 6; CT = computed tomography; EBV = Epstein-Barr Virus; HSV2 = herpes simplex virus; VZV = varicella zoster virus; MRI = magnetic resonance imaging; CMV = cytomegalovirus; PML = Progressive Multifocal Leukoencephalopathy HSV1 = herpes simplex virus 1.

Outcomes (in-hospital mortality v. discharge)

One hundred and forty-four (78.3%) patients were discharged from hospital, and the in-hospital mortality rate was 21.7% (Table 1). The median length of hospital stay was 10.5 (IQR 4 - 23.5) days, with 15 (IQR 7 - 34) days for HIV-negative patients and 10 (IQR 4 - 23) days for PLWH (p=0.028). Of the 40 patients who died, 9 (28.1%) had a non-EBV herpesvirus detected in CSF; 9 patients had CMV detected in CSF, of whom 8 (88.9%) did not receive virus-specific treatment.

Discussion

This is the first study describing the clinical and demographic profile of patients with herpesviruses detected in CSF in a southern African setting. EBV was found to be the most prevalent herpesvirus. After EBV, the most frequent herpes viruses detected were CMV, VZV and HHV6. The herpesvirus was determined to be the cause of the clinical syndrome in a minority of cases and antiviral therapy was administered infrequently, with a third of all prescriptions for EBV. The prevalence of co-infection with HIV and TB in the study population was high.

The relevance of EBV DNA in CSF remains obscure, including in PLWH.[21] Its presence may signify active infection, inert virus or reactivation in the presence of another CNS pathogen.[21] Our findings are similar to those of a Zambian study that showed a very high prevalence of EBV in CSF.[12] Detection of EBV in CSF is not enough to conclude that it is the cause of a neurological clinical syndrome.[22] Co-infection rate with EBV and another CNS pathology is reported to be between 25% and 28%.[22] Our study describes TB co-infection rates within this range. There is no clear effective antiviral agent for EBV,[23] and it is of interest that a significant proportion of patients with EBV were still treated with an antiviral agent. Local data show a prevalence of AIDS-related primary CNS lymphoma ranging between 2% and 13%, and despite the oncogenic role of EBV in the disease, its presence in the CSF of PLWH is poorly predictive.[8] EBV viral loads of <10 000 copies/mL improve specificity and positive predictive value.[8] With the high prevalence in our study, guidelines are not clear regarding whether or how these patients should be followed up so that complications are detected early. Reassuringly, no patient with EBV detected in CSF had primary CNS lymphoma on head imaging.

Most patients with VZV, CMV or HSV2 were also PLWH. VZV is an important cause of vasculopathy and stroke.[14] Stroke was the most common clinical neurological syndrome among patients with VZV in the current study. VZV vasculopathy remains an important cause of disease morbidity and should always be considered when no clear cause is identified. Herpes zoster vaccines prevent reactivation.[24] The Centers for Disease Control recommends the recombinant herpes zoster vaccine (Shingrix) to all immunocompetent people 50 years and older and to any immunocompromised patients 19 years and older.[25] The majority of the VZV-positive patients in our study were immunocompromised and eligible for vaccination. However, the vaccine is not readily available in the public sector in South Africa.

CMV meningoencephalitis is a frequently encountered condition in the context of HIV, with a greater predilection for encephalitis as opposed to meningitis. This entity is rare in immunocompetent adults.[6] CMV associated with encephalitis/encephalopathy and/or stroke had a prevalence of 26.3% in PLWH in our study, and of concern is the large proportion that were not prescribed targeted antiviral therapy. A large proportion of patients with CMV detected in CSF did not receive antiviral therapy and died. Possible reasons for undertreatment of this group should be explored further. Nonetheless, it is prudent that patients with CMV detected in CSF presenting with a clinical neurological syndrome are referred to an infectious disease specialist if the treating team is not sure if antiviral treatment is indicated, as this may reduce mortality.

The frequency of HSV1 in this study was low. We found that, unlike the other herpesviruses, patients with HSV1 were not co-infected with HIV.[26] This contrasts with findings from a similar geographical region, where most of the patients had HIV.[27] HSV1 is common in immunocompromised patients, with extensive brain involvement and high mortality rates.[28] None of the patients in our study with HSV1 were PLWH, but we cannot make any finite postulations for this finding, due to the small study sample. On the other hand, patients with HSV2 were all HIV co-infected. HSV2 causes ulcerative lesions and is said to predispose to HIV acquisition.[29,30] All of the patients with HIV and HSV2 had a concurrent clinical syndrome that was either encephalopathy or meningoencephalitis. Patients with HSV2-associated encephalitis and meningoencephalitis commonly have underlying immunosuppression.[28,30].

HHV6 disease of the CNS is infrequent and, if suspected, is normally found in the context of severe T-cell depletion after HSCT.[7] If HHV6 disease occurs, encephalitis is the major neurological clinical syndrome.[17] Most of the patients with HHV6 in CSF also had another herpesvirus present, and none had undergone HSCT or solid-organ transplantation. It is reasonable to conclude that the majority of patients had chromosomal integrated HHV6 or reactivation of dormant virus.[31]

The prevalence of HIV in the sample was far higher than the background prevalence of HIV in the study setting.[32] Of concern is the large proportion of patients identified that were not on ART, which highlights the importance of achieving virological suppression to prevent viral reactivation or re-infection and its resultant complications.[33]

Strengths and limitations

The findings of this study provide insight into the frequency of herpesvirus detection in CSF locally. The retrospective nature of the study relied heavily on the importance of reliable documentation by treating physicians to identify symptoms, signs and diagnoses, which may have introduced bias due to the non-standardisation of clinical criteria. We only captured in-hospital data and outcomes, and it is possible that patients died after discharge or were transferred to a base/referring hospital. We limited our analysis to patients positive for herpesvirus in CSF. We cannot extrapolate our findings to all patients who are tested for these viruses and only to those who are positive; therefore the findings should be interpreted with caution. This study did not evaluate the clinical findings of all patients suspected of having a viral neurological syndrome, specifically those with negative CSF herpesvirus panels. As a result, odds ratios for particular associations could not be evaluated (i.e. VZV and stroke). Future studies should include a control group who test negative for herpesviruses on CSF; however, there will likely be challenges determining an appropriate control group in this patient population (any patient undergoing lumbar puncture, any patient with a neurological syndrome, etc.). Owing to limitations, we did not elaborate on the neurological syndromes in which a herpesvirus was not considered the cause by the attending physician/team. The large numbers of PLWH are likely to be owing to increased likelihood of detecting herpesviruses in this population or sampling bias due to study participants only being included from a tertiary hospital centre, thus this finding might not be representative of other settings. A prospective study design detailing clear inclusion parameters and definitions of the clinical neurological syndromes is a recommendation for future research.

Conclusion

EBV was the most common herpesvirus detected in CSF, but clinical significance is unclear. We found that patients with TB were more likely to be EBV positive on CSF, which may represent reactivation in these patients. Patients with CMV, VZV or HSV2 were more likely to be PLWH. Most patients with HSV1 or HHV6 were HIV negative. Although antiviral treatment is not indicated for EBV, we found that a third of all antiviral treatment was prescribed for EBV. CMV is a herpesvirus capable of causing various clinical neurological syndromes and should be considered a potential pathogen and treatment considered if detected in CSF in the correct context. The findings from this study highlight the undertreatment of CMV and overtreatment of EBV, and more awareness regarding the clinical indications for antiviral therapy in this setting is needed.

Data availability. Data are available from all authors on request.

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