Journal of Neurology (2023) 270:3914–3933
https://doi.org/10.1007/s00415-023-11735-w

ORIGINAL COMMUNICATION

Encephalitis in HIV-infected adults in the antiretroviral therapy era

Melissa Reimer-Mcatee[1,2,3] · Denisse Ramirez[1] · Casey Mcatee[4] · Alejandro Granillo[1] · Rodrigo Hasbun[1]

Received: 9 February 2023 / Revised: 18 April 2023 / Accepted: 18 April 2023 / Published online: 28 April 2023

Abstract

Introduction Encephalitis presents with high morbidity and mortality in both HIV-infected and HIV-negative patients. There are currently no studies comparing HIV-infected and HIV-negative patients admitted to the hospital with acute encephalitis.

Methods We conducted a multicenter, retrospective study of adults admitted to the hospital with a diagnosis of encephalitis in Houston, Texas between 2005 and 2020. We describe the clinical manifestations, etiology, and outcomes of these patients with a focus on those infected with HIV.

Results We identified 260 patients with encephalitis, 40 of whom were infected with HIV. Viral etiology was identified in 18 of the 40 HIV-infected patients (45.0%); bacterial in 9 (22.5%); parasitic in 5 (12.5%); fungal in 3 (7.5%); immune-mediated in 2 (5.0%). Eleven cases had unclear etiology (27.5%). More than one disease process was identified in 12 (30.0%) patients. HIV-infected persons were more likely to have neurosyphilis (8/40 vs. 1/220; OR 55; 95%CI 6.6–450), CMV encephalitis [5/18 vs. 1/30; OR 11.2 (1.18–105)], or VZV encephalitis (8/21 vs. 10/89; OR 4.82; 1.62–14.6) compared to the HIV-negative patients. Inpatient mortality was similar in the HIV-infected and HIV-negative patients, 15.0% vs 9.5% [$p=0.4$, OR 1.67 (0.63–4.44)], but one-year mortality was higher for the HIV-infected patients, 31.3% vs 16.0% [$p=0.04$, OR 2.40 (1.02–5.55)].

Conclusion This large, multicenter study shows that HIV-infected patients with encephalitis have a distinct pattern of disease when compared with HIV-negative patients, and that this population has nearly twice the odds of mortality in the year following hospitalization.

Keywords HIV · AIDS · Encephalitis · Outcomes · Altered mental status · Confusion

Introduction

Encephalitis is associated with high neurological morbidity and mortality and occurs with an estimated incidence of 3.5–7.5 cases/100,000 person-years [1-6]. Identifying the cause of encephalitis is challenging with the etiology frequently remaining unknown after thorough investigation [7-9]. Establishing the etiology of encephalitis in patients living with human immunodeficiency virus (HIV) is especially difficult given the patients' susceptibility to a wide variety of opportunistic infections as well as the direct neurological effects of the HIV virus itself in the form of HIV encephalitis [10-12] or CD8 + encephalitis [13-15].

HIV-infected patients are at risk for all causes of encephalitis seen in persons without HIV, as well as those that are specific to a person with decreased cellular immunity. Although *Cryptococcus neoformans*, cerebral toxoplasmosis, herpes viruses, and JC-associated progressive multifocal leukoencephalopathy causing encephalitis in HIV patients are well-described in case reports and case series [16-21], a large study with an analysis of the etiology of encephalitis in this patient population is lacking. To further clarify the diagnostic and therapeutic approaches to these patients, we conducted a study describing the clinical manifestations,

✉ Melissa Reimer-Mcatee
melissa.reimer@uth.tmc.edu;
melissa_reimer-mcatee@med.unc.edu;mel.reimer@gmail.com

✉ Rodrigo Hasbun
rodrigo.hasbun@uth.tmc.edu

1 Section of Infectious Diseases, UT Health McGovern Medical School, Houston, TX, USA

2 Institute for Global Health and Infectious Diseases, University of North Carolina UNC Project Malawi, Lilongwe, Malawi

3 Washington University in St. Louis, ACHIEVE Fogarty Global Health Program, Lilongwe, Malawi

4 Baylor College of Medicine, Houston, TX, USA

microbiology, etiology, and outcomes of acute encephalitis in adults with and without HIV.

Methods

We performed a retrospective cohort study of HIV-infected and HIV-negative adults admitted to 16 hospitals in Houston, Texas area between January 2005 and July 2020. Clinical information was obtained by a retrospective chart review of electronic medical records.

Case definition

Cases were initially screened by electronic search of ICD-9/10 billing codes. Due to low accuracy of encephalitis-related ICD codes [22], inclusion of each case was determined by manual evaluation by two physicians using the 2013 International Encephalitis Consortium (IEC) criteria. Thus, encephalitis was defined as new-onset altered mental status without alternative cause lasting > 24 h with at least two of the following: (A) fever 72 h before or after presentation, (B) new-onset seizures, (C) new-onset focal neurological findings, (D) white blood cell count > 5 cells/μL in the cerebrospinal fluid (CSF), (E) new neuroimaging findings, or (F) abnormal electroencephalogram consistent with encephalitis [23]. We excluded patients < 18 years of age, those that did not meet criteria for encephalitis based on the IEC guidelines, or if records were considered insufficient for inclusion. Patients without an HIV test performed were not included.

Data collection

Baseline characteristics were obtained, including demographic data (age, sex, and race), comorbidities, and signs and symptoms upon clinical presentation. Charlson comorbidity index was calculated and recorded based on the presence or absence of nineteen comorbid disease processes [24, 25]. Laboratory data, CSF white blood cell count (WBC) and differential, CSF glucose, CSF protein, serum WBC, and serological studies were recorded. Microbiological studies including blood and CSF cultures and molecular diagnostics were recorded. A summary of the laboratory and microbiological tests available to the ordering physician is included as a supplemental file.

The etiology of encephalitis was classified into seven categories: viral, bacterial, fungal, parasitic, prion disease, immune-mediated, or unknown. Some patients were included in more than one category, representing multiple disease processes at the time of presentation. Classification of neurosyphilis was based on the algorithm outlined by Marra et al. with an HIV-negative patient or HIV-infected patient with > 200 CD4 + cells/μL considered to have neurosyphilis if either (1) VDRL is positive in the CSF or; (2) if a serological test from the peripheral blood is positive, CSF WBC is > 20 cells/μL, and the patient has symptoms consistent with neurosyphilis. In HIV-infected patients with a positive serological test from peripheral blood, symptoms of neurosyphilis, and CD4 < 200 cells/μL, a lower limit of 6 WBC/μL was used [26]. A diagnosis of presumed cerebral toxoplasmosis was made based on clinical presentation, appearance of lesions on magnetic resonance imaging (MRI), and response to toxoplasmosis-directed therapy with decrease in size of lesions on follow-up MRI. Confirmed toxoplasmosis was made based on CSF *Toxoplasma gondii* PCR or *Toxoplasma gondii* identified on histopathology from autopsy.

Severity of disease course was indicated by admission to the intensive care unit (ICU), length of stay in the hospital (LOS), need for mechanical ventilation, renal failure, Sequential Organ Failure Assessment (SOFA) score > 3 [27], and Assessment of Physiology And Chronic Health Evaluation II (APACHE II) score > 10 [28]. Outcomes were assessed at time of discharge with the Glasgow Outcome Scale (GOS) [29]. In-hospital mortality was recorded for all patients during their hospitalization and one-year follow-up was recorded for those with available data in the electronic medical records of any of the 17 participating hospitals and affiliated clinics.

Ethical consideration

The study was approved by the UT Health Committee for the Protection of Human Subjects, by the Memorial Hermann Hospital Research Review Committee and the Harris Health Research Committee.

Statistical analysis

Categorical outcomes given HIV status were assessed for significant associations with Pearson's χ^2 test or Fisher's exact test when appropriate. Continuous data were compared using Welch's *t* test. Statistical analyses were performed with either IBM SPPS version 26 or **R** [30].

Results

Following initial screening using ICD-9/ICD-10 billing codes, 1241 adults admitted to the hospitals with a putative diagnosis of encephalitis were identified. Among these, 278 were included in the analysis based on IEC criteria. Eighteen patients (6.4%) did not have an HIV test performed and were excluded. Our analysis focused on the 260 (93.5%)

with known HIV status. All patients with HIV were infected with HIV-1; none were infected with HIV-2.

The demographic, clinical, and laboratory characteristics are shown in Table 1. Patients infected with HIV were younger than HIV-negative patients (median 43 years vs 49 years, $p < 0.001$). HIV-infected patients were more likely to be Black and had a higher Charlson comorbidity index ($p < 0.001$). There were no other significant differences regarding other demographics or presenting symptoms.

As shown in Table 2, the most common etiologies of encephalitis in HIV-infected patients were viral (45.0%), unknown (27.5%), neurosyphilis (20.0%), parasitic (12.5%), fungal (7.5%), and immune-mediated (5.0%). HIV-infected patients were less likely to have unknown etiologies and more likely to have neurosyphilis [$p < 0.001$, OR 55 (6.6–450)], parasitic ($p < 0.001$, OR unreportable) and fungal etiologies [$p = 0.005$, OR 8.8 (1.4–54.5)]. HIV-infected were more likely to have more than one etiology identified [$p < 0.001$, OR 13 (4.7–35.9].

Table 1 Baseline characteristics and clinical presentation of HIV-infected and HIV-negative adults with encephalitis

	HIV-infected $n = 40$	HIV-negative $n = 220$	p value
Demographic data			
Median age, years (IQR)	43 (32–46)	49 (31–63)	0.007
Age > 60 years, *n* (%)	1 (2.5)	70 (31.8)	< 0.001
Male, *n* (%)	23 (57.5)	118 (53.6)	0.844
Race/Ethnicity, *n* (%)			< 0.001
White	6 (15.0)	82 (37.2)	
Black	24 (60.0)	52 (23.6)	
Hispanic	7 (17.5)	52 (23.6)	
Asian	0	17 (7.7)	
Other	1 (2.5)	16 (7.2)	
Presenting signs and symptoms			
Fever, *n* (%)	24 (60.0)	130 (59.1)	0.965
Focal neurologic deficits*	21 (52.5)	95 (43.2)	0.275
Headache	17/36 (47.2)	99/189 (52.4)	0.570
Acute, < 5 days	17 (42.5)	109 (49.5)	0.355
Seizure on presentation	16 (40.0)	91 (41.4)	0.855
Psychiatric symptoms	16 (40.0)	82 (37.3)	0.759
Malaise	13/31 (41.9)	94/174 (54.0)	0.215
Memory deficits	13 (32.5)	66 (30.0)	0.765
Nausea	8/33 (24.2)	69/191 (36.1)	0.184
Neck stiffness	2/35 (5.7)	26/176 (14.8)	0.149
GCS**, median (IQR)	14 (10–15)	14 (10–15)	0.983
Charlson comorbidity index	6 (4–6)	0 (0–2)	< 0.001

*Focal neurologic deficits indicate hemiparesis, hemiplegia, or facial nerve palsy

**GCS = Glasgow coma scale

As shown in Table 3, the median CSF glucose was lower in HIV-infected patients ($p = 0.002$), but there was no difference in CSF WBC or CSF protein levels. Serum WBC level was lower in the HIV-infected cohort ($p < 0.001$). HIV-infected persons were more likely to have a positive VDRL [$p < 0.001$, OR 18.3 (1.8–183)], positive cytomegalovirus (CMV) PCR [$p = 0.022$, OR 11.2 (1.18–105)], or varicella zoster virus (VZV) PCR [$p = 0.003$, OR 4.82 (1.62–14.6)] compared to the HIV-negative patients. HIV-infected patients were more likely to have an abnormal MRI [$p < 0.001$, OR 15 (2.0–112)]. Of the 30 HIV-infected patients with abnormal MRI, 20 (66.7%) had reports of T2/FLAIR hyperintensity, 11 (36.7%) with intra-parenchymal lesions, 11 (36.7%) with white matter changes, 8 (26.7%) had report of restricted diffusion; five (16.7%) with leptomeningeal enhancement, 2 (6.7%) with ependymitis, and 3 (10.0%) with reports of acute ischemia. There were no significant differences in the results of other diagnostic tests between the two groups. The majority of HIV-infected patients had a CD4 < 200 cells/μL with a median level of 55 cells/μL. Three of the HIV-infected patients had a brain biopsy performed during the studied hospitalization. Two of these were diagnosed with primary CNS lymphoma. The third reported CD8 + predominant inflammation diagnostic for CD8 + -encephalitis. One HIV-infected patient had toxoplasmosis detected on brain lesions at autopsy.

As shown in Table 4, HIV-infected persons were more likely to have APACHE II score > 10 ($p = 0.005$) although there was no difference between the groups based on the SOFA score > 3 ($p = 0.7$). There were no significant differences between HIV-infected and HIV-negative patients in the need for intensive care unit admission, length of stay, need for mechanical ventilation, renal failure, or adverse clinical outcomes as defined by the Glasgow outcome scale. Most patients with encephalitis—whether HIV-infected (31/37, 83.7%) or HIV-negative (159/187, 85.0%)—were started on an antiviral medications during their hospitalization, although only 11/37 (29.7%) of the HIV-infected patients and 81/151 (58.6%) of the HIV-negative patients were initiated within 24 h of admission to the hospital. Inpatient mortality was similar in the HIV-infected and HIV-negative patients, 15.0% vs 9.5% [$p = 0.4$, OR 1.67 (0.63–4.44)], but one-year mortality was higher for the HIV-infected patients, 31.3% vs 16.0% ($p = 0.04$, OR 2.40 (1.02–5.55)].

Eight of the 22 HIV-infected patients that were known to survive > 1 year were on ART (36%) in comparison to 1/10 (10%) of the HIV-infected patients who died reported taking ART with an odds ratio of survival 5.14 (0.55, 48.97). The HIV RNA viral load of the one patient that died that reported taking ART was 11,200 copies/mL, concerning for non-adherence. The median CD4 + count of those that died was 33 cells/μL (IQR 16–136). Three (30.0%) had more than one diagnosis identified. Three (30.0%) had an unclear

Table 2 Etiology of encephalitis of HIV-infected and HIV-negative adults admitted to the hospital

	HIV-infected $n=40$	HIV-negative $n=220$	p value
Viral*	18 (45.0)	74 (33.6)	0.173
Bacterial**	9 (22.5)	15 (6.8)	0.118
Neurosyphilis	8 (20.0)	1 (0.005)	< 0.001
Mycobacterial	0	5 (2.3)	0.335
Parasitic***	5 (12.5)	0	< 0.001
Fungal$^{\phi}$	3 (7.5)	2 (0.9)	0.005
Immune-mediated$^{\phi\phi}$	2 (5.0)	37 (17.8)	0.056
Prion disease$^{\phi\phi\phi}$	0	1 (0.5)	1.00
CNS$^{\beta}$ malignancy	3 (7.5)	5 (2.3)	0.109
CNS lymphoma	3	0	
Glioblastoma multiforme	0	1	
Metastatic disease	0	4	
Prostate primary	0	2	
Diffuse large B cell lymphoma	0	1	
Renal cell carcinoma primary	0	1	
More than one diagnosis	12 (30.0)	7 (3.2)	< 0.001
Unclear	11 (27.5)	98 (44.5)	0.044

*HIV-infected: varicella zoster encephalitis (VZV) 8, cytomegalovirus (CMV) 5, John Cunningham virus (JCV) 2, Epstein Barr Virus (EBV) 2, enterovirus (EV) 1, St Louis encephalitis virus (StLE) 1, West Nile virus (WNV) 1. HIV-negative: WNV- 31, herpes simplex virus (HSV) 22, VZV 10, StLE 4, EBV 3, EV 2, CMV 1

**HIV-infected: Neurosyphilis 5, *Alpha-streptococcus* 1. HIV-negative: *Mycobacterium tuberculosis* 5, Neurosyphilis 1, *Staphylococcus aureus* 2, *Coagulase-negative Staphylococcus* 2, *Streptococcus pneumoniae* 2, *Citrobacter* sp. 1, *Enterococcus* sp. 1, Group G *Streptococcus* 1, Rickettsial encephalitis 1

***HIV-infected: *Toxoplasma gondii* 5

$^{\phi}$HIV-infected: *Cryptococcus neoformans* 2; Coccidioidomycosis 1. HIV-negative: *Cryptococcus neoformans* 1, Coccidioidomycosis 1

$^{\phi\phi}$HIV-Infected: CD8 + encephalitis 2. HIV-uninfected: NMDA encephalitis- 22, GAD65 + 5, Neurosarcoidosis 2, P/Q type Ca channel Ab + 2, Systemic Lupus Erythematous 2, Ach receptor Ab + 1, AMPA receptor Ab + 1, N-type Ca channel Ab + 1, Striated muscle Ab + 1, VGKC + 1, Immune-mediated encephalitis not otherwise specified 2

$^{\phi\phi\phi}$HIV-uninfected: Creutzfeldt–Jakob disease 1

$^{\beta}$CNS = Central nervous system

etiology of encephalitis at the time of death. Of the four that died after discharge, one was discharged home, one to acute rehabilitation center, and two to skilled nursing facilities. Table 5 provides a comprehensive summary of the pertinent diagnostics, diagnoses, and outcomes of each of the 40 patients with HIV admitted to the hospital with encephalitis.

Discussion

This large, multicenter cohort study adds valuable data to what is currently available on HIV-infected persons presenting to the hospital with encephalitis. The demographics of HIV-infected patients with encephalitis reflect the demographics of the HIV epidemic in Houston, Texas, with a higher proportion of HIV-infected patients being Black and younger age compared to HIV-negative patients.

The most notable result in our report is the one-year mortality, which is almost twice as high in the HIV-infected group compared to the HIV-negative cohort (31.3% vs 16.0%) with an odds ratio 2.38 (1.02–5.55). Our effect measure of increased odds of death among HIV-infected patients during hospitalization [OR 1.67 (0.63–3.65)] is similar to those previously reported by another large report of patients with encephalitis admitted to the hospital in the US between 2000 and 2010 [OR 1.70 (1.30–2.22)]; but, our analysis fails to reach statistical significance[1]. HIV-infected patients taking ART had an odds ratio of 5.14 (0.55, 48.97) of surviving one year after hospitalization compared to HIV-infected patients not taking ART. It is well-established that effective ART decreases mortality, but further studies focused on barriers and facilitators to medication adherence could be beneficial to for this vulnerable patient population.

Table 3 Diagnostic studies of HIV-infected and HIV-negative adults with encephalitis

	HIV-infected $n=40$	HIV-negative $n=220$	p value
Laboratory examinations			
CSF WBC, mg/dL, median (IQR)	21 (5–63)	41 (10–180)	0.462
CSF protein	94 (64–170)	76 (48–121)	0.221
CSF glucose	49 (37–59)	62 (49–76)	0.002
CSF VZV PCR-positive, *n* (%)	8/21 (38.1)	10/89 (11.2)	0.003
CSF CMV PCR-positive	5/18 (27.8)	1/30 (3.3)	0.022
CSF VDRL-positive	3/29 (10.3)	1/160 (0.6)	< 0.001
CSF JC Virus DNA PCR-positive	2/17 (11.8)	0/15	0.486
CSF EBV-positive	2/10 (20.0)	1/20 (5.0)	0.251
CSF Enterovirus PCR-positive	1/25 (4.0)	2/139 (1.4)	0.393
West Nile IgM	1/15 (6.7)	32/120 (26.7)	0.116
CSF HSV PCR	0/36	19/197 (9.6)	0.050
CSF HSV, VZV, Enterovirus PCR-obtained	12 (30.0)	64 (29.1)	0.907
CSF Autoimmune diagnostic test			
Anti-NMDA	0/1	22/59 (37.3)	
Anti-GAD-65	0	5	
Other autoimmune diagnostic tests*	0	7	
CD4 + T cell count, cells/μL, median (IQR)	55 (16–136)		
CD4 + T cell count < 200 cells/μL, *n* (%)	29 (72.5)		
HIV RNA VL, copies/mL, median (IQR)	85,800 (19,600–220,000)		
Serum WBC, median (IQR)	5.9 (4.2–7.3)	10 (7.3–14.2)	< 0.001
Imaging studies, *n* (%)			
Abnormal CT head**	14/37 (37.8)	58/202 (28.7)	0.266
Abnormal brain MRI***	30/31 (96.8)	122/185 (65.9)	< 0.001
Intervention, *n* (%)			
Antiviral medication administered during hospitalization	31/37 (83.8)	159/187 (85.0)	0.85
Antiviral medication administered within 24 h	11/37 (29.7)	81/151 (53.6)	0.009

CMV cytomegalovirus, *CSF* cerebrospinal fluid, *CT* computed tomography scan, *EBV* Epstein Barr Virus, *EV* Enterovirus, *JCV* John Cunningham virus, *HIV* Human Immunodeficiency Virus, *HSV* herpes simplex Virus, *MRI* Magnetic Resonance Imaging, *NMDA* N-methyl-D-aspartate, *PCR* Polymerase chain reaction test, *RNA* Ribonucleic acid, WNV *IgM* West Nile virus serum antibody, *VDRL* Venereal Disease Research Laboratory test, *VL* viral load, *VZV* varicella zoster encephalitis, *WBC* White blood cell count

*Other autoimmune diagnostic tests include acetylcholine receptor antibody, AMPA receptor antibody, Calcium channel antibody, N-type Calcium channel Antibody, P/Q type striated muscle antibody, VGKC antibody

**Abnormal CT includes report of cerebral edema, evidence of abscess, evidence of acute ischemia, hemorrhage, herniation, hypo-density, hyper-density, intra-parenchymal lesion, leptomeningeal enhancement, or leptomeningeal thickening, mass, ventriculitis, white matter abnormality

***Abnormal MRI includes report of demyelination, edema, ependymitis, hemorrhage increased T2/FLAIR hyperintensity, intra-parenchymal lesion, leptomeningeal enhancement or leptomeningeal thickening, leukoencephalopathy, mass, proventriculitis, restricted diffusion, ventriculitis, white matter changes

Another important issue to highlight is the number of patients without an etiology of encephalitis. This could be due to an incomplete differential diagnosis constructed by the clinical team, imperfect diagnostic tests, limited CSF available for diagnostic tests, or a combination of these. The number with an unidentified etiology in our HIV-negative cohort is similar to previous studies at 44.5% [3, 5, 7-9], but our HIV-infected cohort is lower than these reports at 27.5%. The difference between the HIV-infected and HIV-negative patients in the number that achieved a final diagnosis (72.5% vs 55.5%) may in part be due to more extensive evaluation in persons with HIV, however it is also more likely that HIV-infected persons have more than one disease process simultaneously [$p < 0.001$, OR 13 (4.7–35.9]. Eight of our HIV-infected patients were given a diagnosis of VZV encephalitis; in four of these (50.0%), VZV was not the only identified disease process. It is important for clinicians to be aware that one confirmed diagnosis may not indicate a complete work-up in patients with HIV.

Table 4 Indication of severity and outcomes of HIV-infected and HIV-negative patients with encephalitis

	HIV-infected $n=40$	HIV-negative $n=220$	p value
Outcomes			
Admission to ICU*, *n* (%)	15 (37.5)	112 (50.9)	0.278
Length of stay, median (IQR)	11 (7–22)	14 (7–27)	0.386
SOFA score > 3**, *n* (%)	19 (47.5)	101 (45.9)	0.676
APACHE II score > 10***, *n* (%)	26 (65.0)	96 (43.6)	0.005
Mechanical ventilation, *n* (%)	17 (42.5)	85 (42.1)	0.504
Renal failure, *n* (%)	9 (22.5)	47 (21.4)	0.770
Glasgow Outcome Scale, median (IQR)	4 (3–4)	4 (3–5)	0.268
Discharged home, *n* (%)	27 (67.5)	116 (52.7)	< 0.001
Death during hospitalization, *n* (%)	6 (15.0)	21 (9.5)	0.448
Death within one year, *n* (%)	10/32 (31.3)	29/181 (16.0)	0.040

*ICU = Intensive care unit

**Sequential organ failure assessment score

***Acute physiology and chronic health evaluation II

All guidelines for the management of encephalitis recommend PCR testing for HSV, VZV, and enterovirus be performed on CSF [23, 31-34], yet only 12 of our 40 patients with HIV had results for all three of these (30.0%). Our study shows that clinicians are better trained to consider HSV and ordered HSV PCR more often than enterovirus or VZV (90.0% vs 62.5% vs 52.5% in our HIV-infected patients). Only 18 of the 40 HIV-infected patients had results for CMV PCR (45.0%); only 29 had results for VDRL in the CSF (72.5%). CMV may have been low on the clinician's differential depending on the control of the HIV and CD4 + count of the patient, but guidelines for the management of encephalitis recommend testing for neurosyphilis in all immunosuppressed patients [23, 31-33].

HSV encephalitis is reported to be the most common etiology of viral encephalitis reported in the literature in immunocompetent patients [6, 35, 36]. Although surprising that none of our HIV-infected patients were diagnosed with HSV encephalitis, ours is not the only study to report a difference in the prevalence of HSV between the HIV-infected and HIV-negative patients. A multi-center study on the causes of encephalitis in England published in 2010 had similar results with HSV the etiology of 37/172 (22%) of the immunocompetent patients and 1/31 (3%) of the immunocompromised patients [4]. A separate study published in 2000 tested the CSF of 251 samples from 219 patients with HIV and neurologic symptoms for 5 herpes viruses and found only 3% samples positive for HSV (25% positive for CMV, 7% EBV, and 4% VZV) [37]. Since HSV encephalitis is thought most likely due to reactivation of prior infection, it seems immunodeficiency with HIV would increase the risk of HSV encephalitis, and yet the data from these two studies and ours show the opposite to be true. Further studies are needed to try to explain this puzzling result.

There is a notable discrepancy in the number of cases of West Nile Virus (WNV) encephalitis between HIV-infected (1/15, 6%) and HIV-negative patients (32/120, 26.7%), which is difficult to explain. This could in part be due to incomplete work-up since less than half of the HIV-infected patients were evaluated for WNV (15/40). The ordering clinicians may have been more focused on evaluation of diagnoses associated with HIV (neuro-syphilis, tuberculosis, and *Cryptococcus*) than those that can be seen in both HIV-infected and HIV-negative (WNV, enterovirus, and autoimmune encephalitis). If the remaining 25 HIV-infected patients with encephalitis would have had WNV serology ordered, perhaps additional cases would have been found. A second explanation for the lower number of cases of WNV in HIV-infected patients could be that other viruses seen in patients with HIV (VZV, CMV, and EBV) are most often due to reactivation of prior infection rather than acute infection seen with WNV. It is plausible that the risk of reactivation in the immunocompetent host that holds latent virus from prior infection is higher than risk of exposure to mosquito carrying WNV causing acute infection. A third possibility is a differential environmental exposure. Is it possible that patients with HIV are less likely to be exposed to the WNV vectors (mosquitos) than HIV-negative patients? Could patients with HIV be more concerned about spending extended periods of time outdoors (camping and hiking) knowing that they have a health condition that predisposes them to infection? This seems less likely than the first two reasons, but worth considering.

Although VZV PCR was only ordered in 52.5% of cases, it was a high yield test, with 8 of 21 tests ordered (38.1%) positive in HIV-infected patients. Although it may not be the only active disease process in an HIV-infected patient with encephalitis, it is important that clinicians consider VZV as

Table 5 Pertinent diagnostics, diagnoses, and outcomes of HIV-infected patients admitted to the hospital with encephalitis

Age/gender	CD4 + count	HIV VL	CSF HIV VL	ICU	LOS	CSF WBC	Lymph (%)	CSF protein	MRI	Pertinent diagnostics	Diagnosis	GOS	Disposition
44F	2	1,890,000	–	Y	54	7	10	62	T2/FLAIR hyperintensities of periventricular and cortical region; deep white matter changes	+ CMV PCR	CMV	4	Acute rehab, Died within 1 year
34F	3	45	–	Y	207	2		88	T2/FLAIR hyperintensities of the frontal, parietal, occipital, periventricular regions, bilateral thalami and cerebellum; leptomeningeal enhancement	+ JCV PCR	JCV	4	Home
58M	5	50,900	–	Y	31	130	12	276	T2/FLAIR hyperintensities of the periventricular region and deep white matter. Restricted diffusion of left cerebral peduncle	+ VZV PCR	VZV	3	LTAC

Table 5 (continued)

Age/gender	CD4 + count	HIV VL	CSF HIV VL	ICU	LOS	CSF WBC	Lymph (%)	CSF protein	MRI	Pertinent diagnostics	Diagnosis	GOS	Disposition
42F	5	245,000	–	N	23	0	–	31	Multiple, bilateral enhancing lesions in the bilateral temporal lobes and left occipital lobe with surrounding edema, largest lesion 1.5 cm. leptomeningeal enhancement Improvement of some of the lesions noted on repeat MRI following treatment for toxoplasmosis	Patient with previously diagnosed DLBCL with new CNS lesions. No biopsy performed this admission	CNS lymphoma, probable toxoplasmosis	3	SNF, Died within 1 year
21M	5	313,000	–	Y	8	2		88	Multiple, bilateral enhancing cerebral and cerebellar lesions with surrounding edema, largest lesion 1.6 cm in thalamic region. All lesions showed improvement on repeat MRI post-treatment for toxoplasmosis	No biopsy performed	Probable toxoplasmosis	3	Home

Table 5 (continued)

Age/gender	CD4 + count	HIV VL	CSF HIV VL	ICU	LOS	CSF WBC	Lymph (%)	CSF protein	MRI	Pertinent diagnostics	Diagnosis	GOS	Disposition
34M	8	91,700	–	N	1	4	60	94	Multiple, bilateral enhancing cerebral and cerebellar lesions with surrounding edema, largest in right temporal lobe 2.7 × 1.9 cm. Repeat CT showed improvement in lesions following treatment for *Cryptococcus* and toxoplasmosis	+ Cr Ag 1:1280 CSF fungal stain and culture negative	Possible *Cryptococcus* meningitis, probable toxoplasmosis	3	Home
40M	10	24,400	–	Y	32	10	58	64	T2/FLAIR hyperintensity in the right temporal and occipital region	+ VZV PCR	VZV	4	Home
43M	12	110,000	–	N	9	7	41	245	Periventricular T2/FLAIR hyperintensity	+ CMV PCR, + VZV PCR	CMV, VZV	5	Home, Died within 1 year
35M	16	128,000	–	Y	6	7	44	328	Leptomeningeal enhancement	Brain lesions + toxoplasmosis on autopsy	Toxoplasmosis	1	Death
26M	17	100,000	–	N	4	40	93	52	–	+ VDRL, + RPR 1:64	Neurosyphilis	5	Home

Table 5 (continued)

Age/gender	CD4 + count	HIV VL	CSF HIV VL	ICU	LOS	CSF WBC	Lymph (%)	CSF protein	MRI	Pertinent diagnostics	Diagnosis	GOS	Disposition
29F	26	175,000	–	N	28	20	78	124	Multiple enhancing lesions in the basal ganglia, corpus callosum, and periventricular parietal region; ependymal enhancement; hyperintensity of right medial temporal lobe with diffusion restriction indicating possible hemorrhage	+ JCV PCR Brain biopsy + CNS lymphoma	JC Virus, CNS lymphoma	3	Home
30F	26	19,600	–	N	15	15	99	76	T2/FLAIR hyperintensity of the bilateral internal capsule, caudate nucleus, and putamen	+ VZV PCR CSF	VZV	5	Home
42F	28	< 20	–	N	4	183	69	72	Diffuse gyral enhancement consistent with meningitis; multiple foci of increased hyperintensity consistent with acute infarcts; periventricular white matter changes	+ Cr Ag 1:16 in blood + CrAg in CSF	Cryptococcus	3	Acute rehab

Table 5 (continued)

Age/gender	CD4 + count	HIV VL	CSF HIV VL	ICU	LOS	CSF WBC	Lymph (%)	CSF protein	MRI	Pertinent diagnostics	Diagnosis	GOS	Disposition
32M	32	< 20	–		20	281	62	395	Increased T2/FLAIR signal of right basal ganglia, bilateral temporal lobes; white matter changes in the temporal lobes; nodular leptomeningeal enhancement	+ Coccidioides Ab blood 1:128 + Coccidioides Ag CSF 2.05 ng/mL + Coccidioides Ag urine 0.60 ng/mL	Coccidioidomycosis	3	Home
44M	32	154,000	–	Y	41	3		33	Multiple enhancing lesions with increased T2/FLAIR signal of basal ganglia and right parietal region. Largest lesion 3 × 2.3 cm	VZV PCR + Brain biopsy + CNS lymphoma	VZV, CNS lymphoma	1	Death
39F	34	180,000	–	Y	22	5	74	213	Bilateral ependymitis	+ CMV PCR, + WNV IgM blood	WNV, CMV	1	Death
56M	37	117,000	–	N	77	14	76	93	Diffuse white matter abnormality including periventricular region and deep white matter	Cr Ag, JCV PCR, HSV PCR, RPR, VZV PCR (-) CMV PCR, EBV PCR, EV PCR, VDRL not obtained. Bacterial, fungal, AFB cultures not obtained from CSF	Unclear	2	SNF, Died within 1 year
42F	39	132,000	–	N	8	44	74	279	T2/FLAIR hyperintensity in the cerebrum and cerebellum; leptomeningeal enhancement	VZV PCR +, VDRL (-), RPR 1:8	VZV, neurosyphilis	5	Home

Table 5 (continued)

Age/gender	CD4 + count	HIV VL	CSF HIV VL	ICU	LOS	CSF WBC	Lymph (%)	CSF protein	MRI	Pertinent diagnostics	Diagnosis	GOS	Disposition
29M	46	220,000	–	Y	8	6	87	256	Nodular leptomeningeal enhancement; severe communicating hydrocephalus	+ StLE Ab 1:32 + Toxoplasma PCR CSF CSF cytology, AFB stains, AFB cultures and TB PCR negative from sputum and CSF (−). Coccidioides Ab/Ag, Cr Ag, histoplasma Ag, WNV serology (−)	Toxoplasmosis, StLE *unclear if StLE contributed to clinical condition	1	Death
44M	51	60,100	–	N	24	178	90	165	Restricted diffusion in the cerebellum, basal ganglia, and pons	VZV PCR +	VZV with "locked-in syndrome"	2	Home
43M	59	438,000	–	Y	7	64	78	71	Diffuse symmetric white matter changes	Cr Ag, HSV PCR, JCV PCR, RPR (−) CMV PCR, EBV PCR, EV PCR, WNV Ab, arbovirus panel, autoimmune panel not obtained	Unclear	1	Death
45F	79	65,900	–	N	6	255	95	49	–	CMV PCR, Cr Ag, EV PCR, HSV PCR, RPR, WNV Ab (−) JCV PCR, EBV PCR, VZV PCR, arbovirus panel, autoimmune panel not obtained	Unclear	4	Home

Table 5 (continued)

Age/gender	CD4 + count	HIV VL	CSF HIV VL	ICU	LOS	CSF WBC	Lymph (%)	CSF protein	MRI	Pertinent diagnostics	Diagnosis	GOS	Disposition
58M	80	131,000	–	N	12	9	96	192	Diffuse deep white matter changes	Cr Ag, EV PCR, HSV PCR, JCV PCR, RPR, WNV Ab, arbovirus panel (−) CMV PCR, EBV PCR, VZV PCR, autoimmune panel not obtained	Unclear	3	Home with home hospice
31F	80	192,000	–	N	9	1		44	–	CMV PCR +	CMV	5	Home
39M	96	< 20	–	Y	27	1750 *RBC 55,000	13	82	–	Cr Ag, EV PCR, RPR (−) CMV PCR, EBV PCR, HSV PCR, JCV PCR, VZV PCR, WNV Ab, arbovirus panel, autoimmune panel not obtained	Unclear Portion of CSF sample lost. Patient treated with acyclovir for possible HSV/VZV encephalitis	3	Home
44M	99	71,411	–	N	8	31	56	74	Intraparenchymal hypo-density	CMV PCR +	CMV	4	Home
27M	110		–	N	7	18	90	170	Extensive T2/FLAIR hyperintensities involving bilateral cerebrum and cerebellum with possible involvement of the bilateral caudate nucleus	CMV PCR, HSV PCR, JCV PCR, VZV PCR, Cr Ag, WNV Ab (−) Arbovirus and autoimmune panel not obtained	Unclear	4	Home
41M	114	79,900	–	N	20	58	85	42	–	VZV PCR +, RPR 1:128, VDRL (−)	VZV, neurosyphilis	4	Home

Table 5 (continued)

Age/gender	CD4 + count	HIV VL	CSF HIV VL	ICU	LOS	CSF WBC	Lymph (%)	CSF protein	MRI	Pertinent diagnostics	Diagnosis	GOS	Disposition
52F	136	11,200	–	Y	11	31	89	76	Multiple areas of restricted diffusion concerning for acute ischemia; encephalomalacia of deep white matter including corpus callosum and periventricular regions	Cr Ag, CMV PCR, EV PCR, HSV PCR, JCV PCR, RPR, VZV PCR, WNV Ab (−) EBV PCR, arbovirus and autoimmune panel not obtained Autopsy reports diffuse leptomeningeal thickening; softening and discoloration of deep white and gray matter of R MCA territory consistent with acute ischemia	Unclear	1	Death
59F	184	212	–	N	14	180	62	313	Central parenchymal and cortical volume loss	Cr Ag, EV PCR, HSV PCR, VDRL (−) CMV PCR, EBV PCR, JCV PCR, RPR, VZV PCR, WNV Ab, arbovirus panel and autoimmune panel not ordered	Unclear Despite AFB microbiology (−), patient treated for tuberculous meningitis based on CSF results and possible exposure	3	Home
33M	228	37,900	–	N	11	66	96	115	T2/FLAIR hyperintensities of basal ganglia, thalamus, insula	VDRL +, RPR 1:1024	Neurosyphilis	5	Home

Table 5 (continued)

Age/gender	CD4 + count	HIV VL	CSF HIV VL	ICU	LOS	CSF WBC	Lymph (%)	CSF protein	MRI	Pertinent diagnostics	Diagnosis	GOS	Disposition
46F	229	2630	–	N	11	63	85	104	Diffuse white matter abnormality	CMV PCR, Cr Ag, EV PCR, HSV PCR, JCV PCR, RPR, VZV PCR, WNV Ab (−) EBV PCR, arbovirus panel and autoimmune panel not obtained	Unclear	5	Home
54F	314	6900	–	Y	31	22	95	124	T2/FLAIR hyperintensities of brainstem and periventricular region	Brain biopsy revealed CD8 + predominant inflammation. No CSF HIV VL obtained	CD8 + encephalitis	4	Home
24M	318	209,000	–	N	11	20	90	40	Normal	RPR 1:1. Cr Ag, EV PCR, HSV PCR, VDRL, WNV Ab (−) CMV PCR, EBV PCR, VZV PCR, WNV Ab, arbovirus panel and autoimmune panel not ordered	Unclear	5	AMA

Table 5 (continued)

Age/gender	CD4 + count	HIV VL	CSF HIV VL	ICU	LOS	CSF WBC	Lymph (%)	CSF protein	MRI	Pertinent diagnostics	Diagnosis	GOS	Disposition
48M	413	57,200	–	N	17	94	91	244	T2/FLAIR hyperintensities in the supratentorial and infratentorial white matter. Abnormal signal along the periventricular white matter with involvement of left genu of corpus callosum, posterior thalami, bilateral pons; acute infarction in the right pons	VDRL +, RPR 1:128 + EBV PCR	Neurosyphilis, EBV	4	Home
47F	423	< 20	–	N	5	2		98	–	+ EV PCR, Gram stain + gram positive cocci, bacterial culture + alpha streptococcus	EV, alpha streptococcus	4	Home
59M	443	118	< 20	Y	4	3		68	–	Cr Ag, EV PCR, HIV CSF VL < 20, HSV PCR, RPR (−) CMV PCR, EBV PCR, VZV PCR, WNV Ab, arbovirus panel and autoimmune panel not obtained	Unclear Possible CD8 + encephalitis	5	Home

Table 5 (continued)

Age/gender	CD4 + count	HIV VL	CSF HIV VL	ICU	LOS	CSF WBC	Lymph (%)	CSF protein	MRI	Pertinent diagnostics	Diagnosis	GOS	Disposition
71F	482	630	15,000	Y	16	31	93	186	Extensive T2 hyperintensities in deep white matter; periventricular enhancement of bilateral frontal and parietal regions	CSF HIV VL 15,000 CSF cytology with predominant T cell population with ratio DC4:CD8 30:58	CD8 + encephalitis	3	Acute rehab
49F	985	< 20	–	N	4	199	88	161	Restricted diffusion in corpus callosum	+ EBV PCR in CSF CMV PCR, Cr Ag, EV PCR, HSV PCR, RPR, VZV PCR, WNV Ab and arbovirus panel (−) Autoimmune panel not obtained	Unclear	5	Home
46M	1000	6230	–	N	7	44	79	67	–	RPR 1:1. Cr Ag, HSV PCR, VDRL, WNV Ab (−) CMV PCR, EV PCR, VZV PCR, arbovirus and autoimmune panel not obtained	Unclear	5	Home

In all places CMV PCR, EV PCR, EBV PCR, JCV PCR, HSV PCR, VZV PCR refer to tests performed in the cerebrospinal fluid. For each patient, CSF Gram stain, bacterial culture, fungal culture and AFB culture were ordered and negative unless otherwise specified. A diagnosis of *presumed cerebral toxoplasmosis* was made based on clinical presentation, appearance of lesions on MRI, and response to therapy with decrease in size of lesions on follow-up MRI. *Confirmed toxoplasmosis* was made based on CSF *Toxoplasma gondii* PCR or autopsy findings. Two patients with + EBV PCR may have had EBV contributing to clinical presentation, but in neither case was EBV thought to be the primary disease process. Neither had a lesion concerning for CNS lymphoma but it was suggested that both patients follow in the outpatient setting for repeat imaging and close monitoring

CSF cerebrospinal fluid, *Cr Ag* Cryptococcal Antigen, *CMV* Cytomegalovirus, *DLBCL* Diffuse Large B cell Lymphoma, *EBV* Epstein Barr Virus, *EV* Enterovirus, *JCV* John Cunningham virus, *HIV* Human Immunodeficiency Virus, *HSV* Herpes Simplex Virus, *MRI* Magnetic Resonance Imaging, *PCR* Polymerase chain reaction test, *RBC* Reb blood cells, *RPR* Rapid Plasma Reagin, *Rehab* rehabilitation center, *SNF* Skilled nursing facility, *StLE* St Louis encephalitis virus, *WNV Ab* West Nile virus serum antibody, *VDRL* Venereal Disease Research Laboratory test, *VL* viral load, *VZV* Varicella zoster encephalitis

well as HSV in any patient with encephalitis given the potential benefits of administration of antiviral medication [38].

Some of the tests not ordered may have been considered by the clinician, but clinicians are often faced with the challenge of prioritizing tests in the setting of limited CSF since the differential for encephalitis is broad, and the amount of cerebrospinal fluid available for analysis is limited. Institutions with multiplex PCR testing on CSF samples available to the clinician have the advantage of a more complete work-up using less CSF. This is especially beneficial in persons with HIV since the recommended diagnostic tests in an immunocompromised patient with encephalitis are extensive, and there could be more than one disease process occurring in the same presentation.

Reports in the literature estimate an immune-mediated process the etiology in 21–33% of cases of encephalitis [4, 9]. However, a work-up for immune-mediated encephalitis was performed in only 2 (5.0%) of the HIV-infected patients in our study. As clinicians become more aware of the overlap of these presentations, cases of autoimmune encephalitis will appropriately be differentiated from presumed infectious encephalitis. Although the proportion of infectious vs immune-mediated etiology more often favors an infectious process in HIV-infected patients compared to HIV-negative patients, this may become less pronounced than in years past, as more patients with HIV achieve viral suppression on ART.

The two HIV-infected patients in our report classified as immune-mediated etiology were diagnosed with HIV-associated CD8 + encephalitis (HIV-CD8E). HIV-CD8E is an inflammatory disease with infiltration of CD8 + T cells into the cerebral parenchyma and should be considered in HIV-infected patients on ART [13-15]. Although biopsy provides definitive diagnosis, CSF HIV viral load is a non-invasive way to test for viral escape, the presence of which supports the diagnosis of HIV-CD8E and provides sufficient evidence to warrant treatment with steroids.

The first patient had a CSF HIV viral load of 15,000 copies/mL despite a peripheral HIV viral load of 630 copies/mL, supporting the diagnosis of HIV-CD8E with viral escape. The second patient had a brain biopsy consistent with HIV-CD8E; no HIV viral load was obtained from the CSF. Both of these had MRI findings classically seen with HIV-CD8E with T2/FLAIR hyperintensities of the periventricular region (both patients), deep white matter (first patient), and brainstem (second patient). A third patient was considered *possible* HIV-CD8E based on clinical presentation and response to steroids. The patient, a 41-year-old male was brought to the hospital by family for acute altered mental status. Work up during the hospitalization was negative and he was started empirically on corticosteroids for the suspicion of HIV-CD8E. He experienced clinical improvement and was discharged home. An MRI was not performed. The CSF HIV viral load resulted was < 20 copies/mL. Although the authors of this paper agree with the treatment of steroids based on the possibility of the diagnosis of HIV-CD8E, we classified this patient as having an unclear diagnosis given the incomplete work-up and undetectable HIV viral load in the CSF.

A recent case series of 23 patients with confirmed HIV-CD8E provides a thorough summary of what is known about HIV-CD8E [13]. Of the 16 patients with available CSF, 11 (68.8%) had increased viral load in the CSF with HIV viral load suppressed in the peripheral blood (viral escape) [13]. Only two of the nine patients on ART (22.2%) in our study had an HIV viral load performed on the CSF to evaluate for HIV-CD8E. If more of the patients in our study had a HIV viral load from the CSF or brain biopsy, there may have been more diagnosed with HIV-CD8E than the two we identified. With an increased proportion of patients living with HIV achieving viral suppression, HIV-CD8E is a disease process that should be considered in patients with HIV on ART.

It should be noted that we used a broad definition for classification of neurosyphilis. Given the low sensitivity of VDRL in CSF [39, 40], we followed the treatment algorithm outlined by Marra et al. as explained in the methods [13, 14]. This resulted in eight patients classified as neurosyphilis even though CSF VDRL was positive in only three.

Strengths and limitations

Strengths of our study include the large sample size allowing for a comparison of HIV-infected and HIV-negative patients with encephalitis. This was a multicenter study with patients from 17 hospitals reflective of a diverse patient population and socioeconomic class. We included only cases that met the definition of encephalitis by IEC definition and provided a thorough report of the diagnostic tests ordered and interventions.

Weaknesses include the retrospective nature of the study with missing data that could have limited the conclusions of the study, including data related to outcome for patients that received subsequent medical care in a different healthcare system. Although it may have been appropriate in the clinical setting, the gaps in data from unordered diagnostic tests create the potential for selection bias, where only those with higher clinical suspicion have certain diagnostic tests ordered.

Another weakness of our study is that results may not be generalizable to other parts of the country or outside of the United States since the etiology of encephalitis varies by geographical location. In Houston, Texas, it is important to evaluate for West Nile virus during summer months, but our study did not have patients diagnosed with other vector-borne pathogens, such as Japanese encephalitis, Dengue virus, or tick-borne encephalitis virus, which should be

considerations in other parts of the world. For example, we identified two cases of coccidioidomycosis in patients that traveled to the western United States, but a clinician practicing in the western United States would likely see a higher proportion of patients with central nervous system (CNS) coccidioidomycosis. Similarly, *Mycobacterium tuberculosis* would be expected to be higher in many parts of the world than what was reported in our study, especially in the HIV-infected population.

Conclusion

This report demonstrates the severity of illness of patients presenting to the hospital with encephalitis. The high rates of mortality seen in HIV-infected patients presenting to the hospital with encephalitis highlight the importance of appropriate utilization of available diagnostic tests to allow for rapid intervention in this vulnerable population.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00415-023-11735-w.

Funding Fogarty International Center (D43TW0009340, D43TW012275): Grant A Starr Foundation.

Declarations

Conflicts of interest Rodrigo Hasbun has research support and personal fees from Biofire®. No other authors have any potential conflicts of interest. Melissa Reimer-McAtee was funded by NIH Fogarty Global Health Research Training Grants when analyzing the data and writing the manuscript [grant numbers D43TW0009340, D43TW012275]. The work was also supported by the Grant A Starr Foundation. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or Grant A Starr Foundation.

References

1. George BP, Schneider EB, Venkatesan A (2014) Encephalitis hospitalization rates and inpatient mortality in the United States, 2000–2010. PLoS ONE 9(9):e104169. https://doi.org/10.1371/journal.pone.0104169. (**Published 2014 Sep 5**)
2. Granerod J, Crowcroft NS (2007) The epidemiology of acute encephalitis. Neuropsychol Rehabil 17(4–5):406–428. https://doi.org/10.1080/09602010600989620. (**PMID: 17676528**)
3. Huppatz C, Durrheim DN, Levi C, Dalton C, Williams D et al (2009) Etiology of encephalitis in Australia, 1990–2007. Emerg Infect Dis 15:1359–1365
4. Granerod J, Ambrose HE, Davies NW (2010) Causes of encephalitis and differences in their clinical presentation in England: a multicenter, population-based prospective study. Lancet Infect Dis 10(12):835–844
5. Kulkarni MA, Lecocq AC, Artsob H, Drebot MA, Ogden NH (2012) Epidemiology and aetiology of encephalitis in Canada, 1994–2008: a case for undiagnosed arboviral agents? Epidemiol Infect 141:2243–2255
6. Barbadoro P, Marigliano A, Ricciardi A, D'Errico MM, Prospero E (2012) Trend of hospital utilization for encephalitis. Epidemiol Infect 140(4):753–764. https://doi.org/10.1017/S0950268811001002. (**Epub 2011 Jun 21. PMID: 21733247**)
7. Hasbun R, Rosenthal N, Balada-Llasat JM, Chung J, Duff S, Bozzette S, Zimmer L, Ginocchio CC (2017) Epidemiology of meningitis and encephalitis in the United States, 2011–2014. Clin Infect Dis 65(3):359–363. https://doi.org/10.1093/cid/cix319. (**PMID: 28419350**)
8. Glaser CA, Gilliam S, Schnurr D (2003) In search of encephalitis etiologies: diagnostic challenges in the California encephalitis project, 1998–2000. Clin Infect Dis 36:731–742
9. Granerod J, Tam CC, Crowcroft NS, Davies NWS, Borchert M, Thomas SL (2010) Challenge of the unknown. A systematic review of acute encephalitis in non-outbreak situations. Neurology 75(September (10)):924–932
10. Antinori A, Arendt G, Becker JT et al (2007) Updated research nosology for HIV-associated neurocognitive disorders. Neurology 69:1789–1799
11. Saylor D et al (2016) HIV-associated neurocognitive disorder-pathogenesis and prospects for treatment. Nat Rev Neurol 12(4):234–248
12. Heaton R et al (2010) HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER study. Neurology 75(23):2087–2096
13. Lucas SB et al (2021) HIV-associated CD8 encephalitis: a UK case series and review of histopathologically confirmed cases. Front Neurol 12:628296–628296 (**Web**)
14. Zarkali A, Gorgoraptis N, Miller R et al (2017) CD8+ encephalitis: a severe but treatable HIV-related acute encephalopathy. Pract Neurol 17:42–46
15. Lescure FX, Moulignier A, Savatovsky J, Amiel C, Carcelain G, Molina JM, Gallien S, Pacanovski J, Pialoux G, Adle-Biassette H, Gray F (2013) CD8 encephalitis in HIV-infected patients receiving cART: a treatable entity. Clin Infect Dis 57(1):101–108. https://doi.org/10.1093/cid/cit175. (**Epub 2013 Mar 20. PMID: 23515205**)
16. Rakhmanova AG, Giaurgieva OKh (1999) Klinicheskoe techenie kriptokokkoza pri BICh-infektsii [Clinical course of cryptococcosis in HIV infection]. Klin Med (Mosk) 77(1):39–42 (**Russian. PMID: 10097505**)
17. Baradkar V, Mathur M, De A, Kumar S, Rathi M (2009) Prevalence and clinical presentation of *Cryptococcal meningitis* among HIV seropositive patients. Indian J Sex Transm Dis AIDS 30(1):19–22. https://doi.org/10.4103/0253-7184.55474. (**PMID: 21938109; PMCID: PMC3168034**)
18. Pereira-Chioccola VL, Vidal JE, Su C (2009) *Toxoplasma gondii* infection and cerebral toxoplasmosis in HIV-infected patients. Future Microbiol 4(10):1363–1379. https://doi.org/10.2217/fmb.09.89. (**PMID: 19995194**)
19. Chrétien F, Bélec L, Hilton DA, Flament-Saillour M, Guillon F, Wingertsmann L, Baudrimont M, de Truchis P, Keohane C, Vital C, Love S, Gray F (1996) Herpes simplex virus type 1 encephalitis in acquired immunodeficiency syndrome. Neuropathol Appl Neurobiol 22(5):394–404. https://doi.org/10.1111/j.1365-2990.1996.tb00909.x. (**PMID: 8930949**)
20. Gray F, Bélec L, Lescs MC, Chrétien F, Ciardi A, Hassine D, Flament-Saillour M, de Truchis P, Clair B, Scaravilli F (1994) Varicella-zoster virus infection of the central nervous system in the acquired immune deficiency syndrome. Brain 117(Pt 5):987–999. https://doi.org/10.1093/brain/117.5.987. (**PMID: 7953606**)
21. Berger JR, Chauhan A, Galey D, Nath A (2001) Epidemiological evidence and molecular basis of interactions between HIV and JC virus. J Neurovirol 7(4):329–338. https://doi.org/10.1080/13550280152537193. (**PMID: 11517412**)

22. Samannodi M, Hansen M, Hasbun R (2019) Lack of accuracy of the international classification of disease, ninth (ICD-9) codes in identifying patients with encephalitis. J Neurol 266(4):1034–1035
23. Venkatesan A, Tunkel AR, Bloch KC (2013) Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis. Consortium Clin Infect Dis 57(October (8)):1114–1128
24. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 40:373–383. https://doi.org/10.1016/0021-9681(87)90171-8
25. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P (2011) Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol 173:676–682. https://doi.org/10.1093/aje/kwq433
26. Gonzalez H, Koralnik IJ, Marra CM (2019) Neurosyphilis. Semin Neurol 39(4):448–455
27. Vincent JL, de Mendonça A, Cantraine F, Moreno R, Takala J, Suter PM, Sprung CL, Colardyn F, Blecher S (1998) Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med 26(11):1793–1800. https://doi.org/10.1097/00003246-199811000-00016
28. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) APACHE II: a severity of disease classification system. Crit Care Med 13(10):818–829 (**PMID: 3928249**)
29. Jennett B, Teasdale G, Braakman R, Minderhoud J, Knill-Jones R (1976) Predicting outcome in individual patients after severe head injury. Lancet 1(7968):1031–1034. https://doi.org/10.1016/s0140-6736(76)92215-7. (**PMID: 57446**)
30. R Core Team (2021) R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna. https://www.R-project.org/
31. Tunkel AR, Glaser CA, Bloch KC (2008) The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 47(August (3)):303–327
32. Solomon T, Michael BD, Smith PE (2012) Management of suspected viral encephalitis in adults —Association of British Neurologists and British Infection Association National Guidelines. J Infect 64:347–373
33. Britton PN, Eastwood K, Brew BJ, Nagree Y, Jones CA (2015) Consensus guidelines for the investigation and management of encephalitis. Med J Aust 202:576–577
34. Stahl JP, Azouvi P, Bruneel F, De Broucker T (2017) Guidelines on the management of infectious encephalitis in adults. Med Mal Infect 47:179–194
35. Boucher A, Herrmann JL, Morand P et al (2017) Epidemiology of infectious encephalitis causes in 2016. Med Mal Infect 47:221–235
36. Venkatesan A, Murphy OC (2018) Viral Encephalitis. Neurol Clin 36(4):705–724. https://doi.org/10.1016/j.ncl.2018.07.001. (**Epub 2018 Sep 20. PMID: 30366550**)
37. Quereda C, Corral I, Laguna F et al (2000) Diagnostic utility of a multiplex herpesvirus PCR assay performed with cerebrospinal fluid from human immunodeficiency virus-infected patients with neurological disorders. J Clin Microbiol 38(8):3061–3067. https://doi.org/10.1128/JCM.38.8.3061-3067.2000
38. Pahud BA, Glaser CA, Dekker CL, Arvin AM, Schmid DS (2011) Varicella zoster disease of the central nervous system: epidemiological, clinical, and laboratory features 10 years after the introduction of the varicella vaccine. J Infect Dis 203(3):316–323. https://doi.org/10.1093/infdis/jiq066. (**Epub 2010 Dec 21. PMID: 21177308; PMCID: PMC3071104**)
39. Marra CM, Tantalo LC, Maxwell CL, Dougherty K, Wood B (2004) Alternative cerebrospinal fluid tests to diagnose neurosyphilis in HIV-infected individuals. Neurology 63(1):85–88. https://doi.org/10.1212/01.wnl.0000131902.69113.34. (**PMID: 15249615**)
40. Marra CM, Maxwell CL, Smith SL, Lukehart SA, Rompalo AM, Eaton M, Stoner BP, Augenbraun M, Barker DE, Corbett JJ, Zajackowski M, Raines C, Nerad J, Kee R, Barnett SH (2004) Cerebrospinal fluid abnormalities in patients with syphilis: association with clinical and laboratory features. J Infect Dis 189(3):369–376. https://doi.org/10.1086/381227. (**Epub 2004 Jan 27. PMID: 14745693**)