JVIN Journal of Vascular and Interventional Neurology
OFFICIAL JOURNAL OF THE ZEENAT QURESHI STROKE INSTITUTE

Human Immunodeficiency Viral Infection and Status Epilepticus in United States (2002–2009)

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Abstract

Objective—To determine the association between human immunodeficiency virus (HIV) infection and status epilepticus and compare the outcomes of patients with status epilepticus with or without underlying HIV infection.

Methods—Patients with primary diagnosis of status epilepticus (cases) and status asthmaticus (controls) were identified from the 2002–2009 Nationwide Inpatient Sample (NIS) which is representative of all admissions in the United States. We performed logistic regression analysis adjusting for age, gender, co-morbid conditions, including hypertension, diabetes mellitus (DM), renal failure, alcohol use, and opportunistic infections. We compared the in hospital outcomes among patients admitted with status epilepticus in strata defined by underlying HIV infection.

Results—The rate of concurrent status epilepticus and HIV has increased over the last 7 years in hospitalized patients with status epilepticus in United States (0.14%–0.27% $p<0.0001$). The HIV infection was significantly associated with status epilepticus (odds ratio [OR]: 2.2; 95% confidence interval [CI]: 1.8–2.6; $p<0.0001$)) after adjusting for age, gender, opportunistic infections, and cardiovascular risk factors. The in-hospital mortality was significantly higher while discharge with none or minimal disability was significantly lower in status epilepticus patients with underlying HIV infection (17.5% vs. 9.9%, $p<0.0001$) and (50.4% vs. 63.3%, $p<0.0001$), respectively.

Conclusions—Our study suggests that there is a direct association between HIV infection and status epilepticus. The proportion of patients admitted with concurrent status epilepticus and HIV infections is increasing and such patients have higher rates of poor discharge outcomes.

Keywords

human immunodeficiency viral infection; status epilepticus; seizures

INTRODUCTION

Human immunodeficiency virus (HIV)-infected patients often present with new onset seizures. New onset seizures are usually secondary to intracranial mass lesions, opportunistic infections, drugs used for treatment of HIV infection [1,2] or opportunistic infections and/or metabolic abnormalities [3]. However, no apparent reason for the seizures is identified in a significant proportion of patients [4–8] (6–46%). The direct neurotropic effect of HIV virus has been implicated in such cases [8–11]. An undetermined proportion of such patients develop status epilepticus. However, it remains unknown whether HIV infection is a risk factor for status epilepticus because of the small sample sizes of most studies and the lack of well-designed case–control studies [4–8]. Furthermore, the influence of underlying HIV infection and associated conditions on the outcomes of

Vol. 8, No. 3, pp. 56–61. Published July, 2015.

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status epilepticus patients is not described. We performed this case–control study to identify the association between HIV infection and status epilepticus and study the trends in occurrence and comparative outcomes of patients with concurrent HIV infection and status epilepticus.

MATERIALS AND METHODS

We used in-hospital data for all admissions between 2002–2009 from the Nationwide Inpatient Sample (NIS) which is part of the Healthcare Cost and Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality(AHRQ) [12] for our analyses. Briefly, NIS is the largest all-payer inpatient care database in the United States focusing on identification, tracking, and analyzing national trends in health care utilization, access, charges, quality, and outcomes based on data derived from approximately a 20% stratified sample of U.S. community hospitals; approximately 5 to 8 million hospital stays and all discharge data from approximately 1,000 hospitals. The data comprise more than 100 clinical and nonclinical variables associated with hospital stays, including primary and secondary diagnoses, primary and secondary procedures, patients' admission and discharge status, patient demographic information (e.g., sex, age, race/ethnicity, expected payment source, total charges, and length of stay). Detailed information on the design of the NIS is available at http://www.hcup-us.ahrq.gov/.

Identification of Patients and Control Group

We used the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis code 345.3 to identify the patients admitted with status epilepticus. This approach has been used previously to estimate in-hospital mortality in a large sample at United States [13]. Patients who had underlying HIV/AIDS were identified by the following ICD-9-CM codes: 042, 0420–0422, 0429, 0430–0433, 0439, 0440, 0449, 07953, 27910, 27919, 79571, 7958, and V08. These codes have been used in various studies to calculate the national estimates of HIV/AIDS infection [14]. We selected status asthmaticus as our control group, as there is no demonstrated relationship between asthma and HIV infection [15,16] and this approach has been used in previous studies [17]. Status asthmaticus patients were identified using ICD-9-CM codes (493.01, 493.11, and 493.2x) as discharge diagnoses in patient records, and this approach has been used previously to generate national estimates and mortality indicators[18–20].

Ascertainment of Potential Confounders

We ascertained patients' age, sex, and race/ethnicity for cases and controls. Cardiovascular risk factor, such as hypertension, diabetes mellitus, renal failure, alcohol use, and drug abuse information, was obtained from the AHRQ comorbidity data collected for each patient in case and control groups. The presence of underlying infections was determined using ICD-9-CM diagnosis codes such as meningitis (320.xx, 321.xx, and 322.xx), encephalitis (323.xx), intracranial abscess (324.xx/326.xx), and toxoplasmosis (130.xx).

Ascertainment of Outcome Measures

We ascertained patients' length of stay, discharge status, medical complications, and procedures performed and total hospitalization charges for patients who were admitted with status epilepticus. ICD-9-CM secondary diagnosis codes were used to identify patients with in-hospital associated complications such as pneumonia (486, 481, 482.8, 482.3), urinary tract infection (599.0, 590.9), and sepsis (995.91, 996.64, 038, 995.92, 999.3). Discharge status is categorized into routine, home health care, short-term hospital, and other facility including intermediate care and skilled nursing home, or death). We categorized routine discharge as none or minimal disability, any other discharge status as moderate to severe disability.

Statistical Analysis

We used the SAS 9.1 software (SAS Institute Inc., Cary, NC) to convert raw counts generated from the NIS database into weighted counts that we used to generate national estimates. The statistical analysis was performed based on these weighted numbers and incorporated the complex sampling of NIS, following HCUP recommendations [12]. We used the chi-square test for the comparison of categorical data and analysis of variance for continuous data with a $P < 0.05$ considered statistically significant. We estimated the annual incidence of concurrent status epilepticus and HIV infections and displayed the data in a line graph. We identified significant changes across the study period using trend p values that were computed by including year as a continuous variable in the logistic regression models while adjusting for the NIS survey design. We subsequently used logistic regression analysis to identify the association between status epilepticus and the presence of HIV infection. We adjusted for age and gender in the initial models and subsequently adjusted for opportunistic infection, cardiovascular risk factors, and/or metabolic abnormalities. Statistical hypotheses were tested using $p = 0.05$ as the level of significance.

Table 1. Clinical characteristics and outcomes of patients with status epilepticus with and without underlying human immunodeficiency viral infection in United States 2002–2009

	Status epilepticus			Multivariable model adjusting for age, gender, and race/ethnicity		
	No HIV infection	Concurrent HIV infection	*p* value	Odds ratio (OR)	95 % confidence interval (CI)	*p* value
Overall number	**258323 (98.47%)**	**4031 (1.53%)**				
Age (years, 95% CI)	41.05 (39.6–42.5)	42.95 (42.0–43.8)	< 0.0001	1.005	(1.004–1.006)	0.0007
Men	1,34,112 (52.08)	2845 (70.57)	< 0.0001	2.147	(1.817–2.538)	< 0.0001
Race/ethnicity*						
White	1,12,461 (57.17)	670 (20.16)		reference		
African-Americans	45,916 (23.34)	2,090 (62.94)	<.0001	7.409	(6.092–9.010)	< 0.0001
Hispanic	25,187 (12.80)	432 (13.01)		2.927	(2.221–3.856)	
Other	13,122 (6.67)	129 (3.87)		1.908	(1.519–2.397)	
Comorbid conditions						
Hypertension	73,362 (28.6)	1,193 (29.8)	0.5177	0.911	(0.737–1.125)	0.3862
Diabetes mellitus	33,824 (13.09)	414(10.26)	0.0380	0.616	(0.471–0.807)	0.0004
Renal failure	16,522 (6.5)	584 (14.6)	< 0.0001	2.27	(1.790–2.879)	<0.0001
Alcohol use	19,981 (7.8)	508 (12.7)	0.0007	1.481	(1.171–1.874)	0.001
Drug abuse	14,418 (5.6%)	758 (19.0%)	< 0.0001	3.697	(3.025–4.519)	< 0.0001
Infections						
Meningitis	2,419 (0.9)	236 (5.8)	< 0.0001	6.77	(4.820–9.509)	< 0.0001
Encephalitis	2,232(0.8)	122 (3.0)	0.0044	3.008	(1.826–4.953)	< 0.0001
Intracranial abscess	1,153 (0.4)	33 (0.8)	0.2829	2.01	(0.936–4.316)	0.0735
Cytomeglovirus	105 (0.04)	107 (2.65)	0.0005	118.643	(57.334–245.514)	< 0.0001
Toxoplasmosis	19 (0.01)	518 (12.8)	< 0.0001			
Leukoencephlopathy	38 (0.02)	178 (4.4)	< 0.0001			
Hospital teaching status						
Rural	24,506 (9.52)	198 (4.94)		reference		
Urban nonteaching	90,418 (35.14)	1,225 (30.53)	0.0001	1.552	(1.042–2.311)	< 0.0001
Urban teaching	1,42,335 (55.32)	2,589 (64.51)		2.194	(1.486–3.239)	
Hospital location						
Northeast	49,843 (19.29)	1,190 (29.53)		reference		
Northcentral	57,024 (22.07)	527 (13.07)	< 0.0001	0.302	(0.214–0.427)	<.0001
South	1,01,197 (39.17)	1,991 (49.38)		0.903	(0.762–1.071)	
West	50,259 (19.45)	322 (8.01)		0.289	(0.217–0.386)	
Medical complications						
Pneumonia	19,698 (7.6)	421 (10.4)	0.0415	1.501	(1.173–1.919)	0.0012
Urinary tract infection	36,030 (13.9)	593(14.7)	0.5668	1.174	(0.937–1.470)	0.1639
Sepsis	15,023 (5.8)	476 (11.8)	< 0.0001	2.088	(1.641–2.657)	< 0.0001
Deep venous thrombosis	3,160 (1.2)	74 (1.8)	0.2553	1.567	(0.913–2.688)	0.1029
Discharge status						
Length of hospital stay (Days, 95% CI)	8.01 (7.8–8.2)	12.6 (10.9–14.3)	< 0.0001	1.011	(1.008–1.014)	< 0.0001
Hospital charges ($, 95% CI)	53,402 (50,883–55,920)	83,006 (69,235–96,775)	< 0.0001	1.016	(1.012–1.020)	< 0.0001
None to mild disability	1,63,636 (63.3)	2,034 (50.4)	< 0.0001	0.513	(0.421–0.624)	< 0.0001
Moderate to severe disability	68,428 (26.4)	1,276 (31.6)	0.0063	1.289	(1.069–1.554)	0.008
In-hospital mortality	25,672 (9.9)	704 (17.5)	< 0.0001	2.028	(1.637–2.514)	<0.0001

RESULTS

A total of 1,36,855 estimated patients were admitted with a diagnosis of status epilepticus in the United States during the study duration; 4,031 (1.53%) had concurrent HIV infection. The mean age in years (95% confidence interval [CI]) was significantly lower in status epilepticus patients without concurrent HIV infection: 41.1 (39.6–42.5) versus 42.9 (42.0–43.8), $p \leq 0.0001$) compared with those with concurrent HIV infection. The proportion of men was higher among patients with status epilepticus who had concurrent HIV infection (70.5% vs. 52.1%, $p < 0.0001$). The proportion of African Americans was higher among patients with status epilepticus who had concurrent HIV infection (62.9% vs. 23.3%, $p < 0.0001$). The mean age of HIV-admitted patients has increased from 41.4 years (95% CI: 41.3–41.5) to 45.6 (95% CI: 45.5–45.7) $p < 0.0001$ from 2002 to 2009. The rates of meningitis, encephalitis, cytomegalovirus, toxoplasmosis, and leukoencephalopathy were significantly higher among patients with an underlying HIV infection (Table 1). The proportion of patients with hypertension, coagulopathy, renal failure, or alcohol use was lower in patients with status epilepticus who had an underlying HIV infection.

The mean length of stay of 12.6 days (95% CI: 10.9–14.3) was higher in status epilepticus patients than 8 days (95% CI: 7.8–8.2) observed in patients without concurrent HIV infection (Table 1). The in-hospital mortality was significantly higher, while none to minimal disability was significantly lower in patients with concurrent HIV infection (17.5% vs. 9.9%, $p < 0.0001$) and (50.4% vs. 63.3%, $p < 0.0001$), respectively. The mean hospital charges were significantly higher in patients with concurrent HIV infection ($83,006 vs. $53,402 $p < 0.0001$). There was a higher rate of admission to urban teaching hospitals in patients with underlying HIV

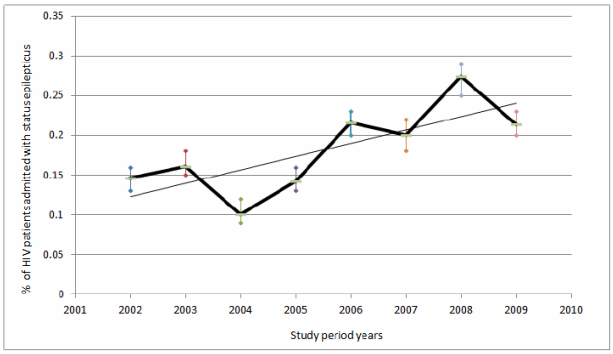

Figure 1. Trends in overall proportion of status epilepticus admissions associated with HIV in the United States: 2002–2009

Table 2. Results of the multivariate regression model determining the association between status epilepticus and underlying HIV infection using status asthmaticus as control group.

	Odds ratio (95 % CI)	*p* value
Unadjusted	5.762 (4.856–6.837)	< 0.0001
Adjusted for age and gender ¥	3.733 (3.144–4.432)	< 0.0001
Adjusted for risk factors ¥	3.285 (2.748–3.927)	< 0.0001
Adjusted for opportunistic infections ¥,ǂ	2.201 (1.823–2.657)	< 0.0001

CI: confidence interval

¥ model adjust for age and gender

ǂ model adjust for diabetes mellitus, hypertension, renal failure meningitis, alcohol use, drug abuse, central nervous system infections

infection. The rate of concurrent status epilepticus and HIV infection had increased over the 8 years in hospitalized patients in United States (0.14%–0.27%, $p < 0.0001$) (Figure 1).

In the case–control analysis, a total of 3,00,384 patients admitted with status asthmaticus were included in the control group. After adjusting for age, gender, hypertension, diabetes mellitus, renal failure, meningitis, encephalitis, cytomegalovirus, toxoplasmosis, drug abuse, and leukoencephalopathy, the presence of HIV infection was significantly associated with status epilepticus (odds ratio [OR]: 2.2, 95% CI: 1.8–2.6, $p < 0.0001$) (Table 2).

DISCUSSION

To our knowledge, this is the first nationally representative study that shows the clinical outcomes, trend, and association between status epilepticus and HIV infection. We observed a male and African American predominance in patients with concurrent status epilepticus and HIV infection which is consistent with the patient demographic of the HIV/AIDS-seropositive patients in United States. We also found statistically significant higher in-hospital mortality in status epileticus patients with HIV infection. This finding is in accordance with a previously published retrospective study of 119 patients from Ethiopia with status epilepticus, in which HIV infection and its central nervous system complications were predictors of mortality [21].

Ovbiagele et al [22] reported that there is an increased incidence of ischemic stroke in patients with HIV infection, and we saw a similar trend of increasing incidence of concurrent status epilepticus and HIV infection in our study. There is approximately 40% increase in status epilepticus with coexisting HIV infection (2002 vs. 2009) indicating the possibility of circumstances unique to HIV-infected patients. A more plausible explanation could be that these trends reflect consequences of broad use of combination antiretroviral therapies in HIV-infected patients. First, combination antiretroviral therapy increases life expectancy, and as such inadvertently boosts the risk of status epilepticus due to neurotropic effects of HIV infection. Longer exposure to HIV, even at low viral load levels, may allow for the direct effects of the virus to increase the incidence of status epilepticus .The increase in status epilepticus also coincides with the introduction of combination antiretroviral drugs and antiepileptic drugs and increased usage of these drugs in subsequent years.

In our study, we found an association between HIV infection and status epilepticus after adjusting for drug abuse, and opportunistic infections. We believe that the same underlying pathogenic process in patients with HIV is responsible for both increasing the predisposition to status epileticus and subsequent poor clinical outcomes. The presence of meningitis, encephalitis, cytomegalovirus, toxoplasmosis, and leukoencephalopathy in HIV-infected patients is expected to increase the predisposition to occurrence and subsequent poor outcomes in status epilepticus patients. However, the association between HIV infection and status epilepticus was seen even after adjusting for these conditions suggesting the role of additional mechanisms. Two studies have indirectly evaluated the underlying mechanism for new onset of seizures in patients with HIV infection and generated similar results. Modi et al [23] suggested that new onset seizures in the HIV-infected patients may be associated with direct neurotropic effect of HIV infection. In this study, single-photon emission computerized tomography (SPECT) scan findings suggested that the HIV virus induces a focal metabolic abnormality or encephalopathy. Another possibility is the presence of comorbidities such as renal failure observed more frequently

among HIV-infected patients increase the likelihood of status epilepticus and associated poor outcomes. Such association was noted in a previous study [3] which reported that hypomagnesemia or renal failure is associated with new-onset seizures in HIV-infected individuals.

Our study has some important limitations. The identification of patients with status epilepticus and HIV infection depended upon the accuracy of ICD-9-CM code utilization. We also lack information related to the stage of HIV infection. Individuals with advanced disease might be at higher risk of developing epilepsy and status epilepticus. Due to lack of data regarding exact medical treatment undertaken, we are unable to determine whether more aggressive treatment with earlier institution of midalozam infusion and/or empiric treatment of infections would have improved the outcome in HIV-infected patients. It is possible that status epilepticus with poor outcome is a consequence of severe brain disease in HIV-infected patients and therefore not amenable to reduction in death and disability. We were not able to control for the type and duration of antiretroviral medication and antiepileptic drugs used, but it is possible that the broad use and the combination of antiretroviral agents and Antiepileptic drugs in HIV-infected patients may increase the risk of status epilepticus by inducing metabolic abnormalities.

We conclude that HIV-infected patients are at higher risk for status epilepticus and poor discharge outcomes. We believe that this study provides a nationwide perspective, which may have some important implications on health planning and management of HIV-infected individuals. We have demonstrated a direct association of HIV infection and status epilepticus that needs to be further analyzed in experimental and clinical research studies to see whether HIV-induced infection predisposes to genesis and propagation of seizures. Moreover, future clinical research can clarify the side effects of current antiretroviral medications and its relation with status epilepticus. Considering direct relationship and poor outcomes, HIV testing should be considered in all acute admission of status epilepticus.

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