HIV Seroprevalence among Hospital Inpatients with Neuropsychiatric and other Central Nervous System Disorders

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ABSTRACT

Objective: *To determine the seroprevalence of HIV among inpatients with neuropsychiatric and other central nervous system (CNS) disorders at the University Hospital of the West Indies (UHWI).*
Methods: *Sera and data of hospital inpatients with disorders of the CNS were prospectively investigated and reviewed at the Virology Laboratory, UHWI, over the period January 1 to December 31, 2007. The study population included inpatients with a principal diagnosis of a neuropsychiatric or other CNS disorder and for whom a serological analysis for HIV had been requested.*
The CNS disorders were categorized as follows: neuropsychiatric disorder (eg schizophrenia), CNS infection (eg viral, bacterial), motor and psychogenic dysfunction not included in other categories (eg seizures), gross structural brain lesion (eg tumours) and other. HIV prevalence rates were calculated and compared according to age, gender and diagnostic category.
Results: *Eighty-two patients were included. Sixty-one per cent were males and 39% females. The mean age in years (± SD) was 37.6 (± 16.3). There were significant differences in prevalence rates according to diagnostic category (*$p = 0.026$*). All of the patients with psychiatric disorders (*$n = 40$*) were HIV-negative and 25% (3 out of 12) of patients with CNS infection were HIV-positive. There were no statistically significant associations demonstrated between HIV and age or gender (*$p > 0.05$*).*
Conclusion: *Clinicians should have a high index of suspicion for HIV infection when faced with patients with CNS infection. Further research is needed to clearly identify the reasons for the comparatively low prevalence of HIV among the psychiatric patients included in this study.*

Key words: AIDS, CNS, HIV, Neuropsychiatry

Seroprevalencia del VIH entre Pacientes Hospitalizados con Trastornos Neuropsiquiátricos, y Otros Desórdenes del Sistema Nervioso Central

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RESUMEN

Objetivo: *Determinar la seroprevalencia de VIH entre pacientes hospitalizados con trastornos neuropsiquiátricos, y otros desórdenes del sistema nervioso central (SNC) en el Hospital Universitario de West Indies (UHWI).*
Métodos: *Los sueros y datos de los pacientes hospitalizados con desórdenes del SNC, fueron investigados y analizados en el Laboratorio de Virología, UHWI, durante el período comprendido entre el 1ero. de enero al 31 de diciembre de 2007. La población del estudio incluyó pacientes hospitalizados con un diagnóstico principal de trastorno neuropsiquiátrico u otros desórdenes del SNC. A estos pacientes se les había ordenado un análisis serológico de VIH. Los trastornos del SNC se categorizaron como sigue: trastornos neuropsiquiátricos (p.ej. esquizofrenia), infecciones del SNC (*p.ej. *virales, bacterianas), disfunciones psicogénicas y motoras no incluidas en otras categorías (*p.ej. *ataques), lesiones cerebrales estructurales severas (p.ej. tumores), y otros. Las tasas de prevalencia de VIH fueron calculadas y comparadas de acuerdo con la edad, el género y la categoría de diagnóstico.*
Resultados: *Se incluyeron ochenta y dos pacientes. El sesenta y uno por ciento eran varones y el 39%*

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*hembras. La edad promedio en años (± SD) fue 37.6 (± 16.3). Hubo diferencias significativas en las tasas de prevalencia según la categoría de diagnóstico (*p = *0.026). Todos los pacientes con trastornos psiquiátricos (n = 40) fueron VIH negativos y 25% (3 de 12) de los pacientes con infección del SNC fueron VIH positivos. Sin embargo, no se presentaron asociaciones estadísticamente significativas entre el VIH y la edad o el género (*p > *0.05).*

Conclusión: *Los clínicos deben tener un índice alto de sospecha de infección de VIH frente a los pacientes con infección del SNC. Se requieren más investigaciones a fin de identificar claramente las razones para una prevalencia comparativamente baja de VIH entre los pacientes psiquiátricos incluidos en este estudio.*

Palabras claves: SIDA, SNC, VIH, neuropsiquiatría

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INTRODUCTION

Despite significant progress in HIV treatment approaches and their increasing accessibility worldwide, the number of persons living with HIV/AIDS continues to grow (1). In 2007, between 30 and 36 million people were living with HIV around the world. In Jamaica, HIV adult prevalence is approximately 1.6% and about 27 000 persons are living with the condition (1).

The rate of HIV infection varies among different demographic groups. One high-risk population that has been reported is that of persons with neuropsychiatric disorders. Numerous studies have demonstrated a significant association between HIV infection and neuropsychiatric disorders (2–4). It has been suggested that causal relationships may exist in both directions, *ie* that having a neuropsychiatric disorder may predispose persons to being infected with HIV and *vice-versa*. It is believed, for example, that poverty, homelessness, sexual abuse and unsafe sexual practices are common in persons with neuropsychiatric disorders and place them at increased risk of acquiring HIV (4). Substance abuse is another important intermediary factor (4, 5). Conversely, adjustment issues and HIV infection severity (6) have been identified as risk factors for neuropsychiatric disorders in persons living with HIV.

Whereas a bidirectional causal association between neuropsychiatric disorders and HIV infection has been proposed, the linkage between HIV infection and other CNS disorders would appear to arise primarily by virtue of a heightened predisposition to CNS afflictions in persons with HIV and not *vice-versa*.

Neurologic disease is the first manifestation of symptomatic HIV infection in roughly 10–20% of persons (7) while about 60% of patients with advanced HIV disease will have clinically evident neurologic dysfunction during the course of their illness (8). In the United States of America and the European Union where antiretroviral therapy is readily available, peripheral neuropathy and HIV-associated cognitive dysfunction (including AIDS dementia) account for the largest proportion of neurologic disease burden. In developing countries, opportunistic infections of the central nervous system (CNS) account for most of the reported neurologic morbidity and mortality in AIDS; this includes but is not limited to: cryptococcal meningitis, fulminant bacterial meningitis, neurotuberculosis, toxoplasmosis and neurosyphilis (8–10).

The human immunodeficiency virus crosses the blood-brain barrier and enters the nervous system early, probably concomitant with initial systemic infection (11). It has been cultured from brain, nerve and cerebrospinal fluid (CSF) of persons at all stages of HIV disease, including those without neurological signs or symptoms (12, 13).

The development of neuropsychiatric manifestations depends on a number of factors, such as antiretroviral treatment history, degree of immunosuppression and the molecular biology of the viral strain, particularly its neurovirulence. Human immunodeficiency virus is classified among the lentiviruses, a family of viruses characterized in part by their tendency to cause chronic neurologic disease in their animal hosts (14). The initial "seeding" of the nervous system by HIV-1 is usually asymptomatic, although acute aseptic meningitis, encephalitis and inflammatory polyneuropathy may occur in acute HIV infection (15).

HIV-1 does not directly infect central or peripheral neurons, astrocytes or oligodendroglial cells. Latent or low-level HIV infection in the CNS is maintained by virus-infected cells of the monocyte/macrophage lineage. "Indirect effects" of macrophage activation – such as dysregulation of cytokines and chemokines, free-radical (oxidative stress) injury and secretion of soluble factors that are potently neurotoxic have been implicated as effectors of nervous system injury in HIV (8, 11).

Despite reports, including studies from the Caribbean (4) linking neuropsychiatric disorders to HIV infection, it has been the authors' anecdotal experience that HIV infection appeared to be rarely encountered in persons who were accessing the acute inpatient psychiatric services at the University Hospital of the West Indies in Jamaica. This study was undertaken in order to explore this and to demonstrate any significant association between neuropsychiatric disorders and HIV infection (or lack thereof) in these patients.

The principal null hypothesis is that the rate of HIV infection among patients with neuropsychiatric disorders

who undergo HIV screening will be the same as the rate among patients with other CNS disorders. However, apart from their role as a comparison group, the inclusion of patients with other CNS disorders in this study allows an exploration of the degree to which these various CNS conditions may be associated with HIV infection. This is useful from the point of view of identifying patient populations that may have a high association with HIV infection and for whom it would be prudent to have a high index of clinical suspicion.

SUBJECTS AND METHODS

Approval for this study was sought and received from the Faculty of Medical Sciences, The University of the West Indies/University Hospital of the West Indies Ethics Committee. Over the period, January 1, 2007 to December 31, 2007, data from patients' laboratory requisition forms and laboratory records were prospectively extracted according to the following inclusion criteria:

- The patient was age 18 years or older and admitted to hospital
- A HIV test had been requested as part of the patient's clinical management
- The principal diagnosis was a central nervous system (CNS) disorder.

All patients meeting these criteria over the period under investigation were included in the study. Essentially, persons with non-neuropsychiatric CNS disorders acted as a comparison group for persons with neuropsychiatric illnesses. These two groups were highly comparable from the point of view that they both had CNS disorders and were hospital inpatients. It was also expected that distributions of age and gender would be comparable.

The following data were extracted from the laboratory requisition forms and laboratory records: age, gender, HIV status and principal diagnosis. For each patient, the principal diagnosis was placed into one of the following categories: CNS infection (including viral, bacterial, fungal or protozoal causes), motor and psychogenic dysfunction not included in other categories (*eg* delirium, seizures), neuropsychiatric disorder (*eg* schizophrenia, bipolar disorder) or gross structural brain lesion (*eg* tumours). There was also an "other" category which contained a single case of Systemic Lupus Erythematosus (SLE) cerebritis. All these categories were based on clinicians' suspected diagnosis at the time that the HIV testing was being requested and not on final confirmed diagnoses.

Serological analysis for HIV was done using the ELISA test, with confirmation by Western Blot. Sera were also investigated for other bacterial, viral and opportunistic infections which included *cryptococus neoformans, toxoplasma gondii*, herpes viruses and bacterial infections.

Basic socio-demographic characteristics of the patients were explored and HIV prevalence rates calculated. These rates were compared according to age, gender and principal diagnosis. Statistical analyses included the Fisher's Exact and *t*-tests and were performed as appropriate using the Statistical Package for the Social Sciences (SPSS; version 12.0).

RESULTS

Eighty-two patients participated in the study. Sixty-one per cent were male (n = 50) and 39% female (n = 32). Ages ranged from 18 to 98 years. The mean age (± SD) in years was 37.6 (± 16.3) years [Table 1].

A *t*-test showed no significant difference in age when persons with neuropsychiatric disorders (mean age ± SD = 29.8 ± 11.0 years) were compared with persons with non-neuropsychiatric CNS disorders (mean age ± SD = 30.1 ± 23.5 years). However, chi-square analysis showed a significant difference ($p < 0.001$) in gender distribution between these two groups. Seventy-five per cent of persons with neuropsychiatric disorders were of male gender compared to only 43.1% of all other participants.

Thirteen per cent (n = 40) of all patients (n = 307) admitted to the acute psychiatric ward of the hospital during the study period were included in the study. It was not possible to determine the percentage of patients with other CNS disorders who were included. Of the total sample of 82 patients, 7.3% (n = 6) were HIV-positive and 92.7% (n = 76) were HIV- negative (Table 1).

No statistically significant differences were found in HIV status when both genders were compared ($p = 0.674$; Fisher's Exact test). Neither was there any statistically significant difference in HIV status with respect to age ($p = 0.448$; *t*-test) [Table 1].

Table 1: Age and gender among HIV-positive and HIV-negative inpatients admitted with a CNS disorder as the principal diagnosis

	HIV-positive patients	HIV-negative patients	Overall sample of patients
Number of patients	6 (7.3%)	76 (92.7%)	82 (100%)
Gender (M:F)	1: 1	1.6: 1	1.6: 1
Mean age ± SD	42.5 ± 15.1	37.3 ± 16.4	37.6 ± 16.3

Patients' diagnoses were distributed as follows: non-neuropsychiatric disorders 51% (42/82) and neuropsychiatric disorders 49% (40/82). Non-neuropsychiatric manifestations included: motor and psychogenic dysfunction not included in other categories (32%), CNS infections (15%), gross structural brain lesions (4%) and "other" (SLE cerebritis – 1%) [Table 2].

There were significant differences in rates of HIV positivity among the various diagnostic categories ($p = 0.026$; Fisher's Exact test) [Table 2]. All patients with neuropsychiatric disorders (n = 40) and brain lesions (n = 3) were HIV-negative. On the other hand, 25% (3 out of 12) of persons with CNS infections were HIV-positive as were 11.5%

(3 out of 26) of those with motor and psychogenic dysfunction not included in other categories (Table 2).

Table 2: HIV status by diagnostic category among inpatients admitted with a CNS disorder as the principal diagnosis

	HIV-positive patients	HIV-negative patients	Total
CNS infection	3 (25.0%)	9 (75.0%)	12 (100%)
Motor and psychogenic dysfunction not included in other categories	3 (11.5%)	23 (88.5%)	26 (100%)
Neuroppsychiatric disorder	0 (0%)	40 (100%)	40 (100%)
Gross structural brain lesion	0 (0%)	3 (100%)	3(100%)
Other	0 (0%)	1 (1000%)	1(100%)
Total	**6 (7.3%)**	**76 (92.7%)**	**82 (100%)**

Fisher's Exact = 10.12; $p = 0.026$

DISCUSSION

Although most of the literature points to a heightened risk of HIV infection in persons with neuropsychiatric disorders, our findings suggest a trend to the opposite. However, this type of result is not without precedent. Collins *et al* (16), in a systematic review of HIV and neuropsychiatric disorders, reported that, in developing countries, HIV infection rates among persons with neuropsychiatric disorders ranged from 0 to 28.3% and that these rates showed no significant difference when compared with rates in the relevant general population. The authors of that study also speculated that higher levels of family involvement and institutionalized care of patients with neuropsychiatric disorders in lower income countries may mitigate against risk behaviour and consequent HIV infection.

Another important consideration is that some studies which have demonstrated a high prevalence of HIV among psychiatric patients (3, 4) have been conducted in long-stay mental hospitals. This is in contrast to the short-stay acute psychiatric unit from which the patients with psychiatric diagnoses who were included in this study were drawn. This difference is suggestive of the possibility that institutionalization may be more important than psychiatric illness *per se* as a risk factor for HIV among persons with psychiatric diagnoses. Collins *et al* (16) have postulated that institutional control of persons' lives may be protective of HIV infection, A larger study is needed to investigate this in our setting.

The prevalence of HIV in patients presenting with CNS infections (25%) in this study warrants a comment despite the small sample size and case selection. Compared to the general population, HIV seropositive individuals are at increased risk for both opportunistic infections of the CNS, as well as community-acquired bacterial or viral meningitides (7). Additionally, an early form of aseptic, HIV-associated meningitis develops within days to weeks after HIV infection. It appears as a mononucleosis-like illness and is rarely associated with encephalitis. Patients with this syndrome have primary HIV meningoencephalitis (11).

Opportunistic CNS infections due to cryptococcosis, coccidiomycosis, histoplasmosis or other fungal infections are AIDS-defining events and occur typically with very low $CD4^+$ lymphocyte counts. Among the opportunistic viral infections of the CNS, the most important are the herpes viruses: herpes simplex Types 1 and 2 (HSV-1 and -2), herpes varicella-zoster (VZV) and CMV. Each can cause a meningoencephalitis with mental status changes and focal neurologic findings (17). Progressive multifocal leukoencephalopathy (PML) is another opportunistic infection caused by the JC virus, a ubiquitous polyoma virus that affects approximately 4–8% of patients with advanced HIV disease (18).

The incidence of CNS toxoplasmosis has declined dramatically among patients receiving PCP prophylaxis, and further declined among patients treated with effective antiretroviral therapy. Earlier reports described frequencies of 3–40% reflecting the considerable regional variation in exposure to the parasite (8).

This study's findings reinforce the need to have standards of clinical practice which would facilitate the detection of HIV in persons with CNS infections. Although the specific types of CNS infections affecting patients in this study were not explored, this would be a useful subject to investigate in future studies. Such research would enable even more specific recommendations to be made to facilitate prevention and early diagnosis of HIV among vulnerable patient groups.

The absence of universal HIV screening may have resulted in some selection bias in this study. Therefore, only cautious generalizations can be made about the findings. Another limitation of this study arises from the fact that the diagnoses used in the analyses were based on data from laboratory requisition forms and were not confirmed as being present in the respective patients. The study could also have been strengthened by increasing the sample size.

Limitations notwithstanding, the findings from the study would suggest that clinicians should have a fairly high index of suspicion for HIV infection in patients with infectious CNS disorders and it would be valuable to sensitize medical personnel about this issue. Finally, the apparently low rate of HIV infection among patients with psychiatric disorders does not mean that the relationship between HIV and neuropsychiatric disorders should be ignored. Rather, further research is needed to identify and clarify the reasons for this finding which may help to inform risk reduction strategies in other populations.

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