ORIGINAL ARTICLE

Analysis of HIV-related mortality data in a tertiary South African neurology unit, 2006 - 2012

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Background. South Africa (SA) has a high prevalence of HIV infection with almost 11% of the population aged >2 years living with HIV. At the Steve Biko Academic Hospital, Pretoria, the Neurology Department has seen a steady increase in HIV-related neurology patients.

Objective. To evaluate the mortality data of this unit as it relates to HIV infection.

Methods. The study was a retrospective analysis of records. Patient mortality statistics for 2006, 2008, 2010 and 2012 were analysed regarding cause of death, sex, age and HIV status.

Results. During 2006, 85 patients died: 33% were HIV-positive, 13% were HIV-negative and 54% had not tested for HIV. By 2010, these figures were 50%, 22% and 28%, respectively, changing little in 2012 (48%, 28% and 24%, respectively). Causes of death in the HIV-positive group were meningitis in 58% – with tuberculous meningitis the most common aetiology – followed by strokes (14%), space-occupying lesions (8%) and status epilepticus (7%). Among HIV-positive patients aged 20 - 30 years, a larger proportion of young women died than men. In the combined untested and HIV-negative group, strokes accounted for the vast majority of deaths.

Conclusion. Neurological complications of HIV remain common in SA and contribute significantly to the overall mortality in our tertiary neurology unit, with TB posing a serious threat. A strong corps of clinical neurologists with training in infective neurology is needed urgently in the coming years to care for this growing number of patients.

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The AIDS epidemic in South Africa (SA) is continuing. The Department of Health estimated that the national HIV prevalence among women attending antenatal clinics was 29.4% in 2009 and 29.5% in 2011, with a higher prevalence in KwaZulu-Natal (37.4%) and Mpumalanga (36.7%) provinces.[1,2] Furthermore, an alarming HIV incidence of 10.9% has been reported among the population aged >2 years.[3] Death notification data in SA show that the death rate among young women (25 - 34 years) more than quadrupled between 1997 and 2004, and that among men (30 - 39 years) more than doubled, presumably in part due to HIV infection.[4] Unfortunately, mortality data are difficult to analyse, as the majority of HIV-related deaths are misclassified. Thus, the ascertainment of deaths related to HIV remains a big concern.[5,6]

Neurological complications of HIV infection are common. In the era prior to highly active antiretroviral therapy (HAART), neurological disorders were the first manifestation of AIDS in 7 - 20% of patients and prevalence rates of opportunistic neurological infections, including cryptococcal meningitis (CM), tuberculous meningitis and progressive multifocal leukoencephalopathy (PML), ranged from 39 - 70%. Toxoplasmic encephalitis and primary central nervous system (CNS) lymphoma were common causes of space-occupying lesions in HIV-positive patients.[7] In SA, the neurological complications that resulted in hospital admissions included bacterial and fungal meningitis, mass lesions – especially due to toxoplasmosis and tuberculosis (TB) – spinal cord disorders and peripheral nerve disorders. Primary CNS lymphoma was rarely seen.[8] One study showed TB as the most common cause of focal brain lesions in HIV-positive patients,[9] but very few cases of PML had been reported until a recent study showed that it was a common cause of white-matter lesions in an academic hospital in Pretoria.[10]

The clinical spectrum of neurological manifestations in HIV-positive patients has changed somewhat since the arrival of HAART, and several studies have confirmed that the incidence rates of neurological diseases, such as HIV-associated dementia and CNS opportunistic infections, are decreasing.[11] Even so, a Nigerian study showed that about one-third of patients receiving HAART presented to hospital with a neurological problem, including neurocognitive problems (53%), distal sensory neuropathy (16.4%), meningitis (6.4%), myopathies (5.2%), myelopathies (2.4%) and strokes (2%).[12]

In the Neurology Department of Steve Biko Academic Hospital, Pretoria, clinicians have the impression that there

has been a steady increase in HIV-related neurology cases. This article evaluates the mortality data of this tertiary neurology unit as it relates to HIV infection.

Methods

The patient mortality statistics of the neurology unit at Steve Biko Academic Hospital were reviewed for years 2006, 2008, 2010 and 2012; alternate years were chosen on the presumption that data would not change significantly from one year to the next. The hospital has 830 beds and serves as a major tertiary referral centre in Gauteng Province. The Department of Neurology admits patients from the emergency department, the neurology outpatient department and from referral hospitals. The statistics from the morbidity and mortality meetings are stored in the department and were analysed in this study in terms of cause of death, sex, age and HIV status. The HIV status of a patient is determined whenever a clinical indication exists and knowledge of the HIV infection would influence management. The cause of death was determined by the treating neurologists' best clinical opinion in the large majority of cases, since autopsies are often not feasible in our resource-limited setting. Ethics approval of the study was granted by the University of Pretoria.

Results

The total number of neurological admissions was 533, 446, 510 and 460 in 2006, 2008, 2010 and 2012, respectively. The total number of deaths was 85, 73, 80 and 61, respectively (Table 1).

Of the 85 patients who died in 2006, 28 (33%) were HIV-positive (12 females, 16 males), 11 (13%) were HIV-negative (6 females, 5 males) and 46 (54%) had not had their HIV status tested (26 females, 20 males). In the HIV-positive group, meningitis was the most common cause of death (75%), with TB the most common aetiology, followed by CM. Strokes were the second most common cause of death (14%). The HIV-negative group had miscellaneous causes of death (strokes, cancer-related and hypoxia). In 54%, the HIV status had not been determined; the most common cause of death in these patients was stroke (41%), followed by meningitis (17%).

Of the 73 patients who died in 2008, 31 (42%; 17 females, 14 males) were HIV-positive; again, infective causes of death were most common at 71%, with TB meningitis in 47% of meningitis cases, followed by CM in 26%. Strokes accounted for 23% of HIV-related deaths. The HIV-negative group included 13 patients (18%) with miscellaneous causes of death (strokes, complications of chronic neurological conditions, etc.). In 40% of patients, testing for HIV had not been requested; of these, two-thirds died as a result of stroke (66%), 17% from complications of status epilepticus and 10% from meningitis.

In 2010, 80 patients died. Most had been tested for HIV, and half were HIV-positive: 40 (50%; 22 females, 18 males) had a cause of death related to HIV infection. Meningitis and other infective disorders were the cause of death in 63% (TB 56%, cryptococcal 22%, *S. pneumoniae* 17%) and 18% died from seizure complications. Miscellaneous causes accounted for the rest of the deaths (strokes, various space-occupying lesions, etc.). $CD4^+$ counts were determined for nearly 70% of HIV-positive patients (mean 62×10^6 cells/l; range $2 - 200 \times 10^6$). Eighteen patients (22%) were HIV-negative, with miscellaneous causes of death (strokes 44%, meningitis, Wernicke encephalopathy, chronic neurological disorders, etc.). In 28% (22 patients), HIV testing had not been performed, and stroke was the most common cause of death (55%); 4 (14%) died of status epilepticus complications. Meningitis, metastatic disease and space-occupying lesions were other causes of death.

In 2012, 61 patients died: 29 (48%) were HIV-positive (20 females, 9 males), 17 (28%) were HIV-negative and 15 (24%) had not been tested. Again, the majority of HIV-positive patients died of infective causes (20; 69%), with TB meningitis being the most common cause of death in the meningitis group (80%). Strokes accounted for 17% of deaths. $CD4^+$ counts were available in 21/29 patients and ranged from $13 - 1\,021 \times 10^6$ cells/l (mean 145×10^6). From the retrospective data, it was possible to ascertain that 14 patients had not been receiving antiretroviral therapy (ART), 4 were receiving ART, and this information was not available for 11. Of the 17 deceased patients (28% of total) who were HIV-negative, the majority died from strokes (8/17; 47%), meningitis (4/17; 24%) and other miscellaneous causes. HIV testing had not been performed in 15 (24%) patients; most of these patients died from strokes (10/15; 67%) and meningitis (3/15; 20%). Fig. 1 shows the HIV status of patients over the period that the study was conducted.

Over the study period, 71 female and 57 male HIV-positive patients died. Their age ranges were 14 - 64 and 17 - 61 years for females and males, respectively. The age profiles showed a clear difference in the age at death between the sexes, with a much higher proportion of women dying at age 20 - 30 years than men in the HIV-positive group (19 v. 5, respectively) (Fig. 2).

When combining the results of the 4 years of the study, the causes of death in the HIV-positive patients included meningitis (58%), strokes (14%), space-occupying lesions (8%), status epilepticus (7%) and PML (5%) (Fig. 3). Meningitis was most commonly tuberculous (50%), followed by cryptococcal (30%) and bacterial (12%). Causes of death in the combined HIV-negative and HIV-unknown group are shown in Fig. 4.

Discussion

It is well-known that HIV leads to a wide spectrum of neurological complications, ranging from immunological dysregulation to diseases caused by immunosuppression, such as cerebral toxoplasmosis, PML and primary CNS lymphoma, and to HIV-driven disorders such as dementia and polyneuropathies.[13,14] Secondary conditions related to HAART and reactive psychiatric disorders also occur. Up to 40% of HIV-infected patients may have a neurological disorder[15] and post-

Table 1. Patient admissions, deaths and HIV status over the study period

	2006	2008	2010	2012
Patients admitted, *N*	533	446	510	460
Deaths, *n* (%)	85 (15.9)	83 (16.3)	80 (15.6)	61 (13.2)
Deceased who were HIV-positive, %	33	42	50	48

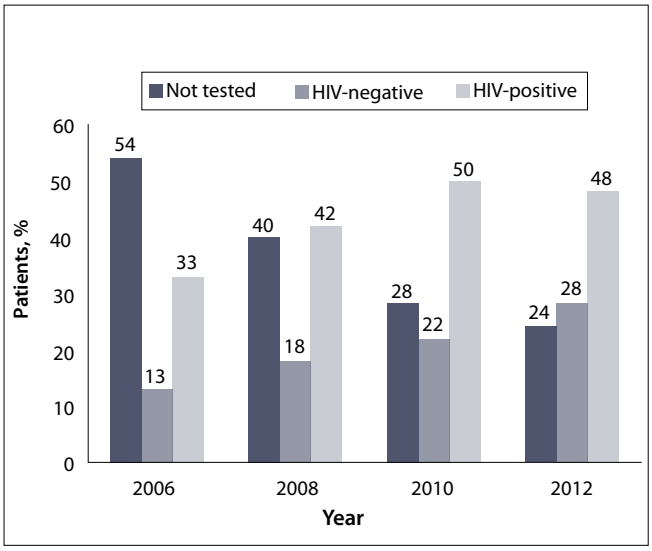

Fig. 1. HIV status of patients over the study period, indicating a positive trend for HIV infection.

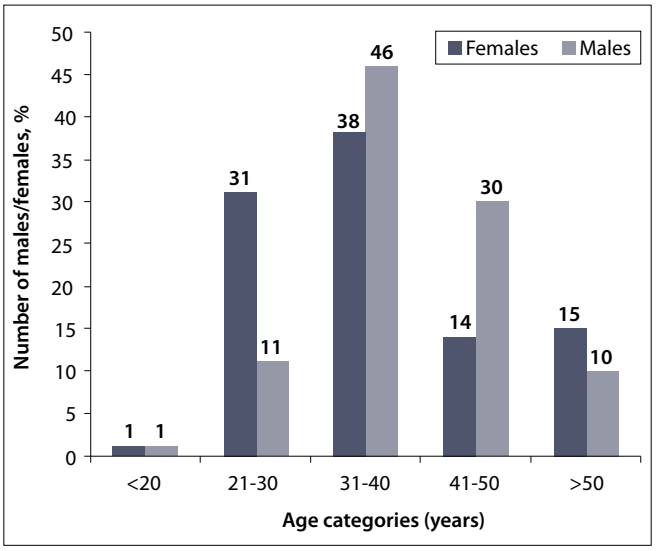

Fig. 2. Age categories of HIV-positive patients, suggesting that females died of neurological complications of HIV infection at a younger age than their male counterparts.

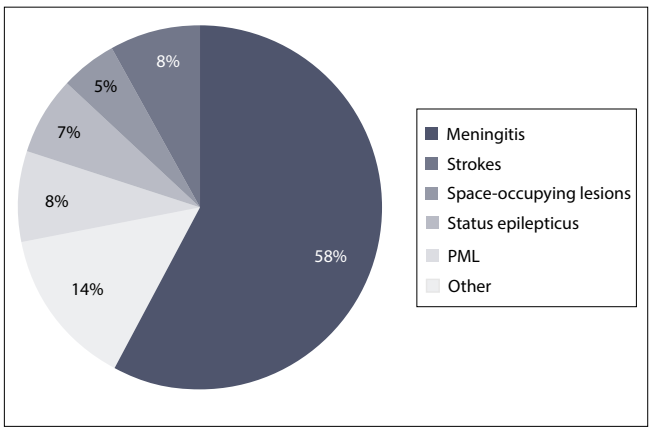

Fig. 3. Cause of death in the HIV-positive patients.

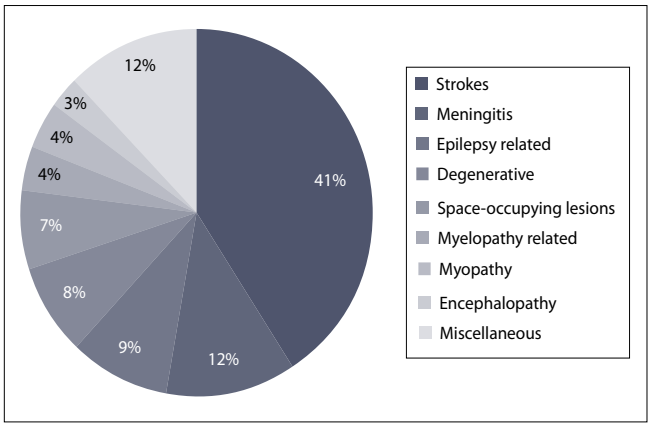

Fig. 4. Cause of death in the combined HIV-negative and HIV-unknown patients.

mortem studies show an even higher proportion of CNS pathology with HIV infection.[16]

Over the study period, an increasing number of patients had been tested for HIV infection – from 45% in 2006 to 70% in 2010 and almost 80% in 2012, with HIV infection proven in 34% in 2006 and approximately 50% in 2010 and 2012. Thus, HIV-related neurological disorders are the leading cause of death in our tertiary unit, with at least half of all deaths currently directly related to HIV infection. According to the South African National HIV Survey of 2008, 10.9% of South Africans aged >2 years were infected with HIV in 2008, which compared with 11.4% in 2002 and 10.8% in 2005, showed some stabilisation.[3] However, the prevalence was still growing in people aged >25 years (from 15.6% in 2005 to 16.8% in 2008), which may be reflected by our findings. Many people were unaware of their HIV status and were not receiving HAART, although this was not formally assessed in this study. Patients were also often referred late in the course of their neurological illness, making reversal of established pathology a challenge.

In this study, infective causes of death in HIV-positive patients were preponderant, with TB the most common aetiology. Several previous post-mortem studies have shown that infections as a cause of death constitute the largest proportion in HIV-positive individuals. A study from Botswana[17] concluded that TB was the leading cause of death in HIV-positive adults, followed by pneumonia and Kaposi's sarcoma. Another study compared causes of death and mortality rates during the pre-, early and late HAART eras, finding that even with HAART, infections remained the leading cause of death in HIV-positive patients.[18] A recent study[19] showed that the presence of neurological disorders in treated HIV/AIDS patients negatively affected survival, with the highest mortality hazard ratio occurring in those patients who had opportunistic infections of the CNS.[19]

A high index of suspicion should be maintained for CM and tuberculous meningitis in the primary healthcare (PHC) setting, since many patients were referred with neurological problems that were already irreversible. The new guidelines for the prevention, diagnosis and management of CM[20] may go a long way in addressing the problem of late diagnosis of CM, and routine screening for cryptococcal antigen and urgent follow-up in patients with a $CD4^+$ count <100 cells/µl should be seen as a necessity in all PHC facilities. Tuberculous meningitis is often misdiagnosed, even if a lumbar puncture is performed, since cerebrospinal fluid (CSF) results are not always typical. A high index of suspicion is essential, and patients

should be started empirically on anti-TB treatment, even if it means that some patients may be treated unnecessarily.[21]

Our mortality data did not include information on ART. This information should, in future, be added to our statistics for analysis, as the current impression is that many patients are still unaware of their HIV status and are treatment-naive. Earlier awareness and initiation of ART before immunosuppression should lead to reduced mortality.

Among the HIV-positive patients in the 20 - 29-year age group, the proportion of women who passed away was much higher than men. This finding may be related to the results of the South African National HIV Survey of 2008,[3] which revealed that the HIV prevalence is disproportionally high for females compared with males, peaking in the 25 - 29-year age group, with one-third being HIV-positive. In males, the prevalence was found to peak in the 30 - 35-year age group (25% HIV-positive), which is also comparable to our findings where most male deaths occurred at age 30 - 39 years. Intergenerational sex may be a contributory factor to the high HIV prevalence in young women, many of whom have partners who are ≥5 years older – this number has increased from 9.6% in 2005 to 14.5% in 2008. Young girls may be particularly vulnerable in such relationships since they lack the skills and power to insist on condom use.[3,22]

Conclusion

Our findings show that neurological complications of HIV infection remain common in SA and contribute significantly to the overall mortality in our tertiary neurology unit. TB remains a significant threat, with many young patients dying as a result of this infection. In the next few years, a strong corps of clinical neurologists with special training in infective disorders is urgently needed to provide optimal care for this large number of patients.

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