Spectrum of central nervous system disorders in hospitalized HIV/AIDS patients (2009–2011) at a major HIV/AIDS referral center in Beijing, China

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ABSTRACT

Objective: To describe the spectrum of central nervous system (CNS) disorders and the contribution of neurological immune reconstitution inflammatory syndrome (IRIS) in hospitalized HIV/AIDS patients in You'an Hospital, Beijing China.

Study design & methods: A retrospective observational study conducted over a 24-month period in You'an Hospital, a public sector referral hospital in Beijing, China. This study enrolled HIV seropositive patients who were admitted for developing new or recurrent neurological and (or) psychiatric symptoms from September 2009 to August 2011. Medical records were reviewed, demographic and clinical data were collected. Patients with peripheral neuropathy and those in delirium were excluded from this study.

Results: Of the total 620 HIV/AIDS hospital admissions from September 2009 to August 2011, 60 patients (9.7%) were hospitalized for CNS complications. The diagnosis of HIV infection was made after hospital admission in 16 of the 60 patients (26.7%), and 34 of them (56.7%) were already on antiretroviral therapy (ART) at the point of admission. The median CD4 cell count in these subjects was 39 (21–133) cells/mm³, and 93.3% (56/60) of these patients belonged to stage IV HIV disease according to World Health Organization (WHO) classification. The most frequent diagnosis in these subjects included cryptococcal meningitis (CM, n = 13, 22%), cerebral toxoplasmosis (n = 10, 17%), and CNS tuberculosis (n = 7, 11.7%). The overall mortality was 13% (8/60) and the case-fatality rates were: cryptococcal meningitis 7.7% (1/13), cerebral toxoplasmosis 20% (2/10) and tuberculous meningitis 28.6% (2/7). Of the 34 patients who were on ART, paradoxical neurological IRIS (the conditions of their existing CNS disorders get paradoxically worse after ART because of an exuberant inflammatory response directed towards opportunistic pathogens) was diagnosed in 4 patients (11.8%), 2 of whom related to TB infection (out of 5 TB patients, 40%), and the other 2 related to CM (out of 8 patients, 25%).

Conclusion: Opportunistic infections, such as cryptococcal meningitis, cerebral toxoplasmosis and CNS tuberculosis were the most frequent diagnosis of CNS disease in hospitalized HIV/AIDS patients in You'an Hospital, Beijing, China. About 10% patients on ART were diagnosed as neurological IRIS in such a group of patients.

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1. Introduction

Antiretroviral therapy (ART) has been highly successful in slowing the progress of immunodeficiency in persons infected with HIV (human immunodeficiency virus), and partially restores immune function, reduced the incidence of opportunistic infections and decreased mortality rates. However, although systemic viral load can be undetectable, the virus remains sequestered in anatomically privileged sites within the body such as brain, which can cause central nervous system (CNS) disease itself. Furthermore, in a subset of patients, new CNS infections will occur or the conditions of their existing CNS disorders will get paradoxically worse in spite of the commencement of ART because of an exuberant inflammatory response directed towards opportunistic pathogens [1], termed unmasking immune reconstitution inflammatory syndrome (IRIS) or paradoxical IRIS [2].

CNS disease is a major cause of morbidity and mortality among human immunodeficiency virus (HIV)-infected patients [3,4]. About 40% to 70% of HIV/AIDS patients develop symptomatic neurological disorders during the course of their illness [3], and about 10%–20% have neurologic symptoms as an initial manifestation of acquired immunodeficiency syndrome (AIDS) [4,5]. Because of limited laboratory services and facilities for diagnosis, short of ART medicine and delayed..
antiviral treatment, the CNS complications in HIV-infected patients are especially hazardous in developing countries. Studies done indicating that the major causes of neurological disorders in HIV/AIDS patients are opportunistic infections in developing countries [6–10], but data on the incidence and pattern of CNS complications in Chinese HIV/AIDS patients are rare, studies on the contribution of neurological IRIS in China are especially few, which is important because of the poor prognosis. In this study, we tried to describe the spectrum of CNS disease and determine the contribution of neurological IRIS in hospitalized HIV/AIDS patients in China, which will provide useful information to clinicians.

2. Patients and methods

This is a retrospective observational study at You’an Hospital affiliated to the Capital Medical University, Beijing, China, which is a major referral center for the treatment of HIV disease. In this study, HIV/AIDS patients (≥ 13 years old) admitted to You’an Hospital from September 2009 to August 2011 (24 months) with a complaint of new or recurrent neurological or psychiatric symptoms/signs were included. Patients with delirium secondary to general medical conditions (sepsis due to a non-neurological infection or metabolic abnormality), psychosis and peripheral neuropathy were excluded. Medical records that were retrieved to data such as age, gender, marital status, duration between HIV infection and the hospital admission, CD4 T cell counts, presenting symptoms and signs, reports of previous and current clinical investigations done, diagnosis, treatment, treatment outcome at hospital discharge, were obtained. HIV infection was confirmed by a combination of ELISA and Western Blot. Because of the shortage of laboratory services and facilities for diagnosis, only partial opportunistic infections were culture-confirmed diagnosed, other opportunistic infections, HIV-associated dementia, progressive multifocal leukoencephalopathy, neurosyphilis, et al., were diagnosed by experienced clinical experts based on clinical manifestations; cerebral infarction and encephalopathy were diagnosed by imaging expert and neurologist; Guillain–Barre syndrome/chronic inflammatory demyelinating polyneuropathy was diagnosed by neurologist based on CSF examination, neurological examination and clinical manifestations; clinical staging of HIV/AIDS was determined based on the World Health Organization (WHO) staging system for HIV infection and disease [10]. The ethics committee of You’an Hospital approved the study and patient confidentiality was maintained by de-identifying patient data and using a unique ID number for each patient.

3. Definitions

The following were the definitions used for patient classifications: according to the international network for the study of HIV-associated IRIS (INSHI) consensus working case definition [2,11], the diagnosis of paradoxical TB-IRIS required i) diagnosis of active TB prior to ART initiation, ii) response to antitubercular treatment and, iii) development of recurrent, new or worsening symptoms/signs of neurological TB within three months of starting ART; and iv) was diagnosed with TB after initiation of ART and, v) subsequently, developed a neurological paradoxical reaction after starting antitubercular therapy that did not have an alternative explanation. The diagnosis of paradoxical CM-IRIS required i) diagnosis of CM prior to ART, ii) initial response to antifungal treatment with improvement of symptoms/signs and, iii) presentation with CM recurrence that was culture negative within 12 months of ART initiation (or any positive cryptococcal culture within 3 months of antifungal therapy). ‘ART-associated cryptococcosis’ or ‘ART-associated TB’ refers to the patients who were diagnosed as cryptococcosis or TB after initiation, reintroduction, or switch after previous ART failure. When IRIS was suspected, alternative diagnoses were evaluated by history, examination, laboratory, lumbar puncture, and/or radiological investigations. The diagnosis of a culture positive CM relapse on ART required i) re-presentation with CSF fungal culture positive CM and, ii) occurrence more than three months after start of antifungal therapy. New diagnosis of CM or TB refers to CM and TB which occurs more than one year after ART.

4. Results

Sixty HIV/AIDS patients had CNS complications from among all 620 HIV/AIDS patients admitted between September 2009 and August 2011 and who were part of this retrospective observational study. The incidence of CNS diseases in You’an admissions was 9.7% (60 out of 620 HIV/AIDS patients). Table 1 summarizes the clinical and demographic characteristics of the 60 patients. Briefly, The percentage of males (76.7%) was almost 3 times that of females, the median age was 36 years (range 13–76), median CD4 count was 39 cells/mm³ (range 21–133 for IQR), 53.3% of the cases were below 50 cells/mm³ (53.3%), 16 patients (26.7%) had CD4 counts between 50 and 200 cells/mm³, only 12 patients (20.0%) had CD4 counts above 200 cells/mm³; and 53 patients (93.3%) were stage IV according to the WHO staging system for HIV infection and disease. The diagnosis of HIV infection was established after current admission in 16 patients (26.7%); 34 patients (56.7%) were

| Male (n,%): | 46 (76.7%) |
| Age in years, median (range): | 36 (13–76) |
| Culture-confirmed diagnosis (n,%): | 14 (23.3%) |
| Diagnosis of HIV infection after current admission: | 16 (26.7%) |
| Nadir CD4⁺ count, cells/mm³, median (IQR): | 29 (21–133) |
| WHO stage, n (%): | 2 (3.3%) |
| Stage IV: | 56 (93.3%) |
| ART regimen, n (%): | 34 (56.7%) |
| AZT/3TC/NVP: | 7 (20.6%) |
| D4T/3TC/NVP: | 9 (26.5%) |
| D4T/3TC/EFV: | 9 (26.5%) |
| D4T/3TC/LPV/r: | 2 (5.9%) |
| Duration since ART beginning (n,%): | 29 (85.3%) |
| <1 year: | 2 (5.9%) |
| 1–2 years: | 3 (8.8%) |

Table 1 Characteristics and outcomes of 60 HIV/AIDS patients hospitalized in You’an Hospital between September 2009 and August 2011 with a complaint for CNS deterioration.
on ART when they were admitted to the hospital, but most of them began the ART within one year or only a few weeks (29/34, 85.3%) prior to hospital admission. Among the 60 patients, 14 (23.3%) had a culture-confirmed diagnosis, while others were diagnosed by experienced clinical experts based on clinical manifestations.

Table 2 shows that the three most frequent diagnoses were: Cryptococcal meningitis (n = 13, 21.7%), cerebral toxoplasmosis (n = 10, 16.7%), followed by CNS tuberculosis (n = 7, 11.7%). Other diagnoses included: Cerebral infarction (n = 5, 8.3%), HIV-encephalopathy (n = 5, 8.3%), Guillian-Barre syndrome/chronic inflammatory demyelinating polyneuropathy (n = 4, 6.7%), CMV encephalitis (n = 3, 5%), fungal infection other than cryptococcal, (n = 3, 5%), neurosyphilis (n = 2, 3.3%), CNS infections of unknown origin, (n = 1, 2%). Poor outcome was defined as patients who remained in the same clinical condition or deteriorated. Improved patients were patients who showed partial or complete recovery.

### Table 2
The spectrum of central nervous system (CNS) disease in 60 hospitalized HIV/AIDS patients.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>CD4 cells/mm³, median (range)</th>
<th>Outcome at hospital discharge n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptococcal meningitis</td>
<td>32 (7–337)</td>
<td>Improved 10 (76.9%) Poor 2 (15.4%) Dead 1 (7.7%)</td>
</tr>
<tr>
<td>Cerebral toxoplasmosis</td>
<td>36 (8–179)</td>
<td>Improved 6 (60%) Poor 2 (20%) Dead 2 (20%)</td>
</tr>
<tr>
<td>CNS tuberculosis</td>
<td>14 (2–511)</td>
<td>Improved 3 (42.9%) Poor 2 (28.6%) Dead 2 (28.6%)</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>266 (133–350)</td>
<td>Improved 4 (80.0%) Poor 1 (20%) Dead 0</td>
</tr>
<tr>
<td>HAD, 5 (8.3%)</td>
<td>84 (30–206)</td>
<td>Improved 3 (60%) Poor 2 (40%) Dead 0</td>
</tr>
<tr>
<td>GBS/CIDP, 4 (6.7%)</td>
<td>28 (19–285)</td>
<td>Improved 3 (75%) Poor 1 (25%) Dead 0</td>
</tr>
<tr>
<td>CMV encephalitis</td>
<td>72 (30–85)</td>
<td>Improved 2 (66.7%) Poor 1 (33.3%) Dead 0</td>
</tr>
<tr>
<td>Fungal infection other than Cryptococcal, 3 (5%)</td>
<td>17 (4–205)</td>
<td>Improved 1 (33.3%) Poor 1 (33.3%) Dead 1 (33.3%)</td>
</tr>
<tr>
<td>Neurosyphilis, 2 (3.3%)</td>
<td>269 (29–509)</td>
<td>Poor 2 (100%) Good 0 Good 0</td>
</tr>
<tr>
<td>PML, 2 (3.3%)</td>
<td>33 (30–36)</td>
<td>Poor 0 Good 2 (100%) Good 0</td>
</tr>
<tr>
<td>CNS infections of unknown origin, 2 (3.3%)</td>
<td>56 (22–90)</td>
<td>Poor 0 Good 1 (50%) Good 1 (50%)</td>
</tr>
<tr>
<td>Others, 4 (6.6%)</td>
<td>235 (10–719)</td>
<td>Poor 2 (50%) Good 1 (25%) Good 0</td>
</tr>
<tr>
<td>Total, 60 (100%)</td>
<td>37 (2–719)</td>
<td>Poor 37 (61.7%) Good 15 (25%) Good 8 (13.3%)</td>
</tr>
</tbody>
</table>

HAD = HIV-associated dementia; GBS/CIDP = Guillian-Barre syndrome/chronic inflammatory demyelinating polyneuropathy; PML = Progressive multifocal leukoencephalopathy; Others = Intracranial space occupying lesion of unknown origin (n = 1), encephalorrhagia (n = 1), VZV encephalitis (n = 1), bacterial meningitis (n = 1). Poor outcome was defined as patients who remained in the same clinical condition or deteriorated. Improved patients were patients who showed partial or complete recovery.

### 5. Discussion

Neurological complications are very common in HIV disease. Every site of the neuro-axis can be involved, and can occur at any time right from seroconversion to late stage HIV [12,13]. Conditions may result from direct viral impairment, indirect immune-deficiency driven opportunistic infections, AIDS-defining cancers, antiretroviral (ARV) drug therapy, or less well elucidated associations, such as vascular events.

Since the widespread of ART, the epidemiology of neurological disease has declined substantially. Garvey et al. studied a large cohort (n = 30954) of adults with HIV infection between 1996 and 2007 in UK. The incidence of all CNS disorders declined significantly from an overall rate of 13.1 per 1000 per year in 1996–1997 to 1.0 per 1000 per year in 2006–2007 [14]. But in developing countries, because of the difficulty to diagnose the HIV infection and antiviral treatment detention, the incidence of CNS complications in HIV-infected patients is still very high. In the 620 patients we reviewed, 60 patients were diagnosed with CNS complications, the incidence of CNS deterioration in HIV/AIDS patients admitted patients in You’an Hospital from September 2009 to August 2011 was 9.7% (60/620), which is still very high, but substantially lower than that reported by previous studies done in HIV/AIDS patients in Nairobi (21.2%) [15] and Nigeria (15.8%) [8]. Since, in our study we
excluded all the patients with psychosis and peripheral diseases and included patients with a complaint of new or recurrent neurological or psychiatric symptom/sign, and the incidence is most likely an underestimate of the true incidence, because patients with mild symptoms or signs are usually overlooked. A prospective study using careful neuropsychological testing and examination to screening all the admitted patients will uncover much more asymptomatic patients. Furthermore, most of our patients were highly selected group of patients with advanced disease stage in whom the neurologic symptoms might be overshadowed by overwhelming systemic illness, and this might also partly contribute to the low prevalence. The increased incidence of HIV associated CNS disorders in males as compared to females and the disease presentation at a mean age of 36 is similar to other reported studies [7,8,16].

Ideally, patients with HIV infection would be identified prior to advanced immunosuppression. However, epidemiologic data indicate that it is often difficult to identify HIV infection in its early stages even in the developed world [17]. It was estimated that about 740,000 HIV-infected patients living in China by 2009, and more than 80,000 of them had received ART since 2002 on National Free Antiretroviral Treatment Program (NFATP) in China [18], but according to the data from the national HIV epidemiology and treatment databases in China, the median CD4 count was 201 cells/mm³ (IQR 71–315) at HIV diagnosis and 194 cells/mm³ (range 73–293) when first declared eligible for treatment [19]. In our study, about one third (26.7%) of cases did not know their HIV condition before their current central nervous system complications. Almost all patients were in late-stage of HIV disease at presentation (3.3% stage III and 93.3% stage IV), and more than half of patients have a CD4 count below 50 cells/mm³, which was also consistent with previous studies [8].

There are conflicting reports on the spectrum of neurological diseases in patients with HIV/AIDS. Our study indicated that opportunistic infections were the major reason of CNS disorders in hospitalized HIV/AIDS patients, which was consistent with the collison of some previous studies [6–9,16,20,21]. However, other studies show that HIV-associated dementia (HAD) and HIV associated encephalitis (HIVE), which are now included under the umbrella term called HIV associated neurological disorders (HAND), are the most common CNS disorders in HIV/AIDS patients. In a study from India [15], HAD was present in 33.65% patients, followed by CNS infections in 21.63% patients. According to the reports in Asia pacific region, the prevalence of HAD continues at high rates of 15%–50% [22]. For the CNS opportunistic infections, the relationship to immunosuppression due to HIV infection appears to be relatively indirect, while in HAD, the CNS damage is most likely through direct mechanisms of HIV replication. Some studies have reported that the incidence of HAD rises as patient survival longer after accepting antiretroviral therapy, so the AIDS patients, the incidence of HAD may be higher [15,22]. On the contrary, in the naive patients with severe immune suppression the incidence of HAD might be lower than the incidence of CNS opportunistic infections. In addition, the lack of adequate screening techniques and readily available imaging studies in patients might contribute to the lower HAD prevalence observed in our study.

The spectrum of HIV-associated nervous disorders may be influenced by differences in the epidemiology of opportunistic infections affecting the nervous system, and the use of ART. The most frequent CNS disorders identified in our study were cryptococcal meningitis (21.7%), cerebral toxoplasmosis (16.7%) and CNS tuberculosis (11.7%), which accounted for at least 50% of cases. This may be due to the high incidence of TB in China, and profound immunosuppression at ART initiation. Some previous studies done in developing countries [6,16,23] had the same results but a little higher frequencies of cerebral toxoplasmosis and CNS tuberculosis. And in a study from India [12], cerebral toxoplasmosis was detected in 8.8% (5/57) which is very low compared to our finding. Tuberculous meningitis are rare findings in HIV/AIDS patients with neurologic manifestations in United States [4]. Because of the inadequate facilities for brain biopsy, only 14 (23.3%) patients had pathogens culture-confirmed diagnosed, while all the other patients were empirically treated. The number of patients with presumed diagnosis of primary CNS lymphoma was very low in our cases probably due to failure to do brain biopsy when empirical therapy for toxoplasmosis failed.

Our study suggests that IRIS has emerged as an important early complication of ART in resource-limited settings, especially in patients with tuberculosis and CM. According to the previous study, paradoxical CM-IRIS and TB-IRIS may occur in up to 30% of patients following ART initiation [24–26]. Consistent with these observations, in our study, of the 34 ART patients, paradoxical neurological IRIS was diagnosed in 4 patients (11.8%), related to TB in 2 out of 5 patients (40%) and related to CM in 2 out of 8 patients (25%). The overall incidence of IRIS is dependent on the population studied and the burden of underlying opportunistic infections. Although the overall mortality associated with IRIS is low, the patients with CNS involvement have poor prognosis and require aggressive therapeutic management. In majority of IRIS cases, mortality and hospitalization rates are particularly high when tuberculosis or cryptococcal-IRIS affects the CNS [27]. Neurological deterioration is an important cause of poor prognosis and death after starting ART. The management of neurological IRIS is problematic, in that no diagnostic test exists and treatment strategies are based on anecdotal case reports [27]. High mortality rates have been associated with both CM-IRIS (up to 66%) [26] and neurological TB-IRIS (at least 13%, at 6-months follow-up) [28]. It is different from the treatment of opportunistic infections caused by unsuccessful ART, as it is believed that IRIS is caused by an exuberant inflammatory response directed towards opportunistic pathogens when ART partially restores immune function. The general approach to the treatment of IRIS is to continue ART and provide antimicrobial therapy for the infection, and in some cases corticosteroid therapy may be beneficial. In our study 4 IRIS patients were treated with corticosteroid of which 2 CM-IRIS patients showed improvement and the 2TB-IRIS patients died. Mortality in 2TB-IRIS patients may be attributed to the high resistance rate of TB in China [29] and low tolerance to anti-TB drugs, given that most of our patients had late stage disease and were in poor general health condition.

There were several limitations of our study, which include the use of retrospective medical records to collect data, which might have led to referral bias, that resulted in inclusion of individuals who developed mild disease that would otherwise never be identified. Etiological diagnosis was difficult in some patients because of limited availability of laboratory services and lack of facilities for neuroimaging studies, resulting in partial diagnosis or error in diagnosis. Despite all of these shortcomings, our study findings suggest that cryptococcal meningitis, cerebral toxoplasmosis and CNS tuberculosis were the most frequent diagnosis in admitted HIV/AIDS patients with neurological disorders, and that neurological IRIS occurred in over 10% of ART patients in our patient cohort at the You’an Hospital in China. These findings warrant a more in-depth study in the future since in resource constrained settings, patients present with advanced immunosuppression and the morbidity associated with this condition will continue to pose a major challenge to clinicians.

Conflict of interest

None.

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Author contributions

LD — Conceived experimental design, obtained clinical and laboratory data, reviewed patient charts, data analysis and manuscript writing;
SM — data analysis of patients and manuscript writing; CG, TZ, WW, TL, TJ — Clinical and laboratory analysis and patient enrollment, clinical evaluation of patients; HW — Clinical evaluation of patients and funding support for study and NL — Clinical evaluation of patients and funding support for study.

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