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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 Hospial, 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/mm^3, 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.

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

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antiviral treatment, the CNS complications in HIV-infected patients are especially hazardous in developing countries. Studies done indicating that the major causes of neurologic 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; Guillian–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 ARTor 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/mm^3 (range 21–133 for IQR), 53.3% of the cases were below 50 cells/mm^3 (53.3%), 16 patients (26.7%) had CD4 counts between 50 and 200 cells/mm^3, only 12 patients (20.0%) had CD4 counts above 200 cells/mm^3; 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

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.

Male (n,%)	46 (76.7%)
Age in years, median (range)	36 (13–76)
Culture-confirmed diagnosed (n,%)	14 (23.3%)
Diagnosis of HIV infection after current admission	16 (26.7%)
Nadir CD4$^+$ count, cells/mm^3, median (IQR)	39 (21–133)
<50	32 (53.3%)
50–200	16 (26.7%)
>200	12 (20.0%)
WHO stage, n (%)	
Stage II	2 (3.3%)
Stage III	2 (3.3%)
Stage IV	56 (93.3%)
On ART (n, %)	34 (56.7%)
ART regimen, n (%)	
AZT/3TC/NVP	7 (20.6%)
D4T/3TC/NVP	9 (26.5%)
AZT/3TC/EFV	9 (26.5%)
D4T/3TC/EFV	7 (20.6%)
AZT/3TC/LPV/r	2 (5.9%)
Duration since ART beginning (n, %)	
<1 year	29 (85.3%)
1–2 years	2 (5.9%)
>2 year	3 (8.8%)

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