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NEUROCYSTICERCOSIS IN THE HIV ERA: A CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT

The prevalence of HIV is increasing in countries where neurocysticercosis is endemic. Co-infection rates are expected to rise; however, no systematic reviews of the subject are available. We performed a literature review of neurocysticercosis (NCC) occurring in HIV-infected patients and described the clinical and immunophenotypic characteristics of a NCC case presenting with probable immune reconstitution inflammatory syndrome. We identified 27 cases of NCC-HIV co-infection. The most frequent presentation (61%) was with multiple parenchymal lesions. Seven patients (30%) had other concomitant neurologic infections (e.g., tuberculosis, toxoplasmosis). Thirteen patients received cysticidal therapy, and 85% responded to therapy. Only three patients died (12%). NCC should be included in the differential diagnosis of neurologic infections in HIV patients in endemic populations. Consideration of the patient's immune status should alert the clinician to potential atypical presentations.

INTRODUCTION

Neurocysticercosis (NCC) is caused by Taenia solium and is the most common helminth infection of the central nervous system (CNS). Cysticercosis is endemic in most of the developing world, particularly where pigs are raised (Garcia *et al*., 2006). Clinical manifestations of neurocysticercosis depend on the number, size, and location of CNS lesions and on the intensity of the host immune response (Garcia *et al*., 2005; Serpa *et al*., 2006). Infection with HIV is becoming more frequent in cysticercosis areas, and NCC has been associated with up to 27% of CNS lesions in HIV-infected individuals presenting with neurologic symptoms in South Africa (Modi *et al*., 2004). Despite that, there is very little literature on the presentation, treatment, and outcomes of patients with NCC and HIV infection. The introduction of highly active antiretroviral therapy (HAART) has decreased the mortality and morbidity associated with HIV infection. However, in some patients, immune recovery leads to an inflammatory condition termed immune reconstitution inflammatory syndrome (IRIS). IRIS presents with clinical worsening of an opportunistic infection under treatment or uncovering of a subclinical infection (Shelburne *et al*., 2006).

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Several case reports have described the effects of HIV infection on the clinical course of NCC (Soto Hernandez *et al*., 1996; Thornton *et al*., 1992; Delobel *et al*., 2004; Prasad *et al*., 2006; White *et al*., 1995; Moskowitz *et al*., 1984; Mason *et al*., 1992); however, systematic reviews addressing this co-infection are lacking. Here we report a patient with AIDS who presented with an intense inflammatory reaction to NCC after starting HAART. We also systematically reviewed the literature to summarize all of the reported cases of NCC in HIV-infected individuals.

MATERIALS AND METHODS

For the literature review, we searched the English literature in November 2015 with PubMed using the search terms [HIV AND neurocysticercosis], [HIV AND cysticercosis], and [AIDS AND cysticercosis]. We also searched references from previous literature. Positive and negative controls were used.

RESULTS

Literature review. We identified 27 cases, including ours, with HIV and NCC co-infection reported in the literature (Table 1). The most frequent presentation of NCC in HIV patients was with multiple parenchymal lesions (enhancing or non-

enhancing cysts) seen in 61% of cases (14 of 23; data were not available in 4 cases). Other presentations included single parenchymal lesions in four patients (17%), atypical forms (giant brain cyst and spinal epidural lesion) in two (9%), and mixed forms (parenchymal, subarachnoidal, and ventricular) in three (13%). Seven patients (30%) had other concomitant CNS infections. Among those, toxoplasmosis encephalitis/abscess and tuberculous brain abscess were the most commonly described.

Fifteen patients (56%) had either serum or cerebrospinal fluid (CSF) serology positive for cysticercosis. Thirteen patients received cysticercal therapy, and 85% of these patients responded to therapy. Only three patients died, for a mortality rate of 12%. All deaths were during the pre-HAART era. Because of the limited amount of available information, we were not able to assess the association between CD4 cell counts and type of NCC lesions.

TABLE 1
NCC cases reported in HIV-infected patients

Case number, author (reference), year	Age/sex	CD4 count	Radiologic findings	Comorbidities	Treatment	Outcome
1 Moskowitz and others [11], 1984	22/F	NA	Multiple parenchymal enhancing lesions	Toxoplasma encephalitis, tuberculous abscess	None	Died
2 Thornton and others [7], 1992	40/M	NA	Multiple parenchymal and subarachnoid lesions	Generalized lymphadenopathy	Albendazole, steroids	Improved
3 Thornton and others [7], 1992	30/M	NA	Multiple parenchymal viable cysts	Oral candidiasis, generalized lymphadenopathy	Albendazole, steroids	No improvement
4 Thornton and others [7], 1992	36/M	NA	Multiple parenchymal viable cysts	Generalized lymphadenopathy	Praziquantel	Recurrent seizures
5 Thornton and others [7], 1992	25/M	NA	Multiple parenchymal viable cysts	Oral candidiasis, thrombocytopenia	None	Died
6 Jessurun and others [23], 1992	NA	NA	NA	NA	NA	Died
7–9 Mason and others [12], 1992	NA	NA	NA	NA	NA	NA
10 White and others [10], 1995	29/M	NA	Multiple parenchymal viable cysts	Cryptococcal meningitis	None	Improved
11 Soto and others [6], 1995	29/M	150	Giant parenchymal cystic lesion	None	Surgical excision, albendazole	Improved
12 Soto and others [6], 1995	41/F	NA	Single parenchymal and subarachnoid lesions	Herpes zoster, toxoplasma encephalitis	V/P shunt	Improved
13 Delobel and others [8], 2004	45/M	241	Single parenchymal and lumbar epidural cyst	Toxoplasma encephalitis	Surgical spinal cyst removal, albendazole	Improved
14–19 Modi and others [4], 2004	NA	106–768	Single (3), and multiple (3) parenchymal lesions	None	Albendazole	Improved
20–22 Modi and others [4], 2004	NA	30–104	Multiple parenchymal lesions	Tuberculosis and toxoplasma encephalitis	Albendazole	Improved
23 Prasad and others [9], 2006	51/F	350	Multiple parenchymal enhancing lesions	Bacterial brain abscess	Albendazole	Improved
24 Prasad and others [9], 2006	40/M	32	Multiple parenchymal enhancing lesions	Toxoplasma encephalitis	None	Improved
25 Prasad and others [9], 2006	72/M	105	Multiple parenchymal enhancing and nonenhancing lesions	None	Albendazole, steroids	Improved
26 Chianura and others [24], 2006	22/F	473	Multiple parenchymal, ventricular, and subarachnoidal cysts	None	Albendazole, steroids	Improved

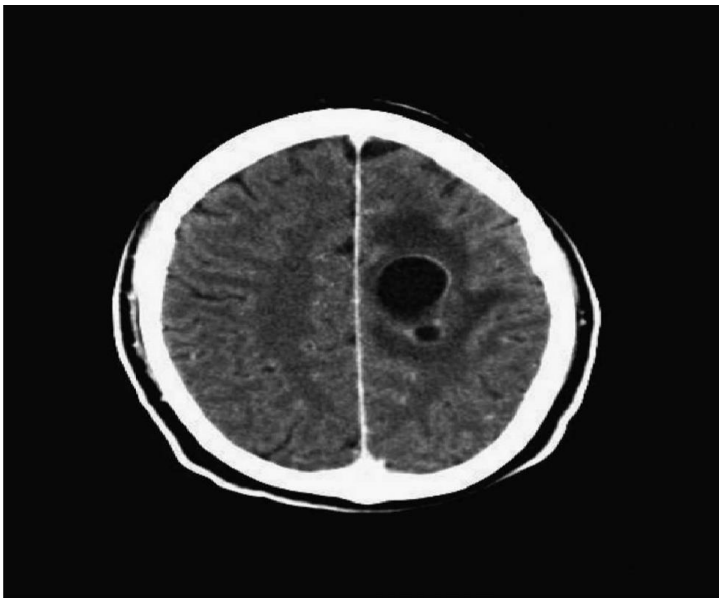

Figure 1. Computed tomography of head with contrast revealing a 4.5 × 3 × 2-cm hypodense lesion with surrounding edema in the left posterior frontal lobe

CASE REPORT

The patient was a 35-year-old man diagnosed with HIV in 2014. His initial CD4+ T-cell count was 103/mm3, and his HIV RNA viral load was 546,000 copies/mL. Shortly after diagnosis, he began efavirenz, tenofovir, and lamivudine, which led to a marked improvement in his CD4+ T-cell count and suppression of HIV RNA viral load. Two months after starting HAART, his HIV viral load had fallen to < 400 copies/mL, and his CD4+ lymphocyte count had risen to 238/mm3. He presented to Jawaharlal Nehru Medical College emergency in September 2015 with new onset generalized tonic-clonic seizures. He also complained of headaches and right-sided hemiparesis for 16 and 2 months, respectively.

Computed tomography (CT) of the head with contrast revealed an enhancing 4.5 × 3 × 2-cm cystic lesion with surrounding edema located in the left posterior frontal region. No evidence of hydrocephalus or midline shift was observed (Figure 1). Magnetic resonance imaging (MRI) of the brain with gadolinium did not disclose any further lesions. Laboratory studies revealed a normal complete blood count, CD4 count of 462/mm3, and HIV RNA viral load < 400 copies/mL. Chest x-ray and serologic tests for syphilis, cryptococcal antigen, and toxoplasma IgG were negative.

DISCUSSION

Despite the wide endemicity of cysticercosis and HIV infection, < 30 cases of NCC have been reported in HIV infected patients. Clearly, given the growing problem of HIV infection in India, Sub-Saharan Africa, and other areas endemic for cysticercal disease, more research on how to treat co-infected patients is needed. Nonetheless, based on our review, some important observations are noted. Approximately one third (7 of 22) of patients with NCC and HIV presented with at least one other neurologic infection at the time of diagnosis.

This high rate of co-infections suggests that in some, if not most of these cases, NCC was an incidental finding in patients undergoing imaging studies for other causes. The range of causes with similar clinical and neuroimaging manifestations also complicates the diagnosis of NCC, such that some patients, including ours. More than one half of our patients had a positive cysticercal serology, which underscores its importance for the noninvasive diagnosis of the infection. The response rate to cysticidal therapy in HIV patients was 85%, similar to that reported in the literature for the general population. (Garcia *et al.,* 2005). This may be attributable to several factors, namely, less inflammatory response after administration of cysticidal drugs as a result of impaired cellular immunity, improved outcome of patients with parenchymal lesions (viable or enhancing) after receiving antiparasitic drugs,(Del Brutto *et al*., 2006) or resolution of symptoms produced by specific therapy for CNS infections other than NCC. Compared with series of NCC in patients without HIV, we noted a high case fatality rate (12%). Other HIV-associated conditions may have also contributed to this high mortality rate. Although it is possible that patients present with more severe forms of disease as a result of the underlying HIV infection, we found no clear evidence of this. Alternatively, there may be selection bias toward disproportionate diagnosis or reporting of severe cases. No fatal cases were observed in the HAART era. In regard to our patient, the onset of clinical symptoms and signs clearly correlated with the recovery of the immune system as documented by an undetectable HIV RNA viral load and an increase in the CD4+ T-lymphocyte count. Thus, based on this correlative evidence, this patient meets current case definitions for IRIS (Robertson *et al*., 2006). However, it is impossible to be certain that this did not reflect the natural history of NCC, in which symptoms typically develop after a prolonged latent period. Our patient developed headaches shortly after recovery of the CD4+ cell count to > 200/mm3, but only developed hemiparesis and seizures when the CD4+ cell numbers rose to > 400/mm3. In NCC, there is normally a chronic immune response with multiple cell types (plasma cells, B and T lymphocytes, macrophages, and mast cells) that together secrete Th1 and Th2 cytokines (inflammatory and anti-inflammatory cytokines). Viable parasites seem to induce Th2 and regulatory cytokines and suppress the host Th1 response. In contrast, death of the cysticerci is associated predominantly with Th1 cytokines. (Restrepo *et al*., 2001; White *et al*., 1997) Seizures in NCC are thought to result from the inflammatory response to release of parasite antigens at the time of parasite death, (Stringer *et al*., 2003) and this response may be mediated by host molecules including substance P.(Robinson *et al*., 2002) HAART leads to a protective immune response against a wide variety of pathogens in HIV/AIDS patients. However, a profound, pathologic inflammatory reaction termed IRIS occurs in some patients in response to subclinical or previously recognized microbial infections. The spectrum of IRIS is varied and consists of clinical worsening of a treated opportunistic infection, atypical appearance of an unrecognized infection, or even autoimmune disorders.

(Shelburne *et al*., 2006) Low baseline CD4+ lymphocyte count, higher HIV RNAviral load, and faster and more marked elevation in CD4+ lymphocyte count coupled with a rapid fall of the HIV RNA viral load after initiation of HAART have been linked to IRIS cases. (Shelburne *et al*., 2005; Lipman and Breen, 2006) In this case, the patient had a low nadir CD4+ T-lymphocyte count (103/mm3) and a high initial viral load of 546,000 copies/mL. Although some authors have suggested that patients with higher CD4+ T lymphocyte counts are more likely to develop symptomatic NCC needing treatment,(Modi *et al*., 2004; Prasad *et al*., 2006) whereas patients with advanced HIV and lower CD4+ T lymphocyte counts present with either asymptomatic or atypical lesions (giant cysts and racemose forms),(Soto Hernandez *et al*., 1996; Delobel *et al*., 2004; White *et al*., 1995) we found no clear evidence to support these hypotheses. Theoretically, giant cysts could be caused by an uncontrolled parasitic growth as a result of the impaired cell-mediated immune response, as has been documented in echinococcal disease, (Sailer *et al*., 1997) but we could not confirm this proposed relationship. The immunopathogenesis of IRIS is poorly understood. Initial descriptions showed that activated memory cells (CD4+CD45RO+) account for the early incremental phase of CD4+ cell recovery after effective HAART. Naïve activated CD4+ cells (CD4+CD45RA+CD62L+) do not reappear until several months of therapy (Shelburne *et al*., 2006). CD4+ T cells are required to sustain a CD8+ cytotoxic

T-cell response during certain infections such as chronic viral infections. Thus, after HAART, rapid recovery of CD4+ T-cell count may induce a strong CD8+ cytotoxic T-cell response that likely initiates the immune cascade leading to IRIS. Uncontrolled studies have shown a preponderance of CD8+ T cells in cerebral biopsies from HIV patients with IRIS (Venkataramana *et al*., 2006). This finding was also observed in the analysis of the immunophenotype of our case. In brief, NCC co-infection is likely to be increasingly recognized in patients with HIV and should be included in the differential diagnosis of CNS infections in HIV patients. Epidemiologic factors should be studied, and consideration of the patient's immune status should alert the clinician to potential atypical presentations. NCC also needs to be considered in endemic populations even when there are atypical manifestations (e.g., giant cysticerci) or lesions suggestive of other infections (e.g.,enhancing lesions compatible with toxoplasmosis). Further studies are necessary to clarify the pathogenesis, diagnosis, and therapeutic response of NCC in the setting of HIV infection.

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