

Full Length Research Paper

AIDS and epilepsy

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The aim of this study was to describe the prevalence of epilepsy among Sudanese AIDS patients and to study the underlying causes and types of epilepsy. About 700 AIDS patients were included in this cross sectional hospital based study. Almost 5.71% of the patients had epilepsy and 50% of them had generalized convulsion. Encephalitis was found to be the commonest cause of epilepsy followed by meningitis, brain abscess, CNS lymphoma and toxoplasmosis. The EEGs showed abnormal discharge in 28 patients (70%). AIDS is a great mimicker. It can be present in almost any neurological manifestation. Epilepsy is not an uncommon neurological manifestation associated with AIDS.

Key words: AIDS, epilepsy, Sudanese patients.

INTRODUCTION

Since its independence in 1956, Sudan has witnessed only eleven years of peace. The civil wars, inter-ethnic conflicts, floods, droughts and variant patterns of rain, have had adverse effects on the economic and the developmental status of the whole country. More over, Sudan shares extensive borders with nine countries, several of which have high HIV/AIDS prevalence. The population of Sudan according to 1993 census was 26 millions. The annual growth rate also increased from 1.9 to 2.6%. Rural urban migration has been steady and high. HIV/AIDS pandemic have "Humanity's social and economic disaster with far reaching implications for individual communities and countries. No other disease has so dramatically highlighted the current disparities and inequities in health care access, economic opportunity and the protection of basic human rights.

Antenatal care attendance showed prevalence of 1% with regional variations. However, among certain population groups the trend is critically alarming. There are regional variations in the prevalence of HIV infection with higher prevalence in southern, eastern, Khartoum and White Nile states.

Heterosexual transmission accounts for 94% of infections with prenatal transmission accounting to 2.4%. HIV belongs to the retroviruses group. AIDS was first discovered in June, 1981. HIV, by far is the most common immunodeficiency disorder encountered in clinical prac-

tice which is transmitted by intercourse, heterosexual or homosexual, administration of infected blood or blood products, contaminated needles and from infected mothers to their infants (Epstein and Gendelman, 1993; Lipton and Gendelman, 1995). HIV virus causes an infection that leads to profound immune-suppression.

The clinical manifestations of AIDS depend on the level of immunity, which is reflected by the CD4 and T cell count. The clinical expression of HIV infection is very diverse, varying from a healthy carrier state to potentially fatal opportunistic disease (Perry, 1996). The clinical manifestations associated with HIV infection vary in different populations, possibly due to the relative frequency of endemic infections (Simpson and Tagliati, 1994). HIV is known to affect most of the systems including the CNS. The Neurological complications of AIDS are due either to a direct effect of the virus, AIDS related cancer such as lymphoma, or to opportunistic infections like toxoplasmosis (Price, 1996; Sidtis and Price, 1990). The neurological complications of AIDS range from acute febrile illness at the time of seroconversion to late onset dementia related to specific brain damage by the virus. HIV may cause damage to the brain causing encephalitis; it may affect the membranes surrounding the brain (meningitis). It may also cause difficulties in thinking and behavioral changes (Brew and Miller, 1993; Clifford, 2000). AIDS dementia complex is a well recognized complication of HIV infection (McArthur, 1987). Peripheral neuropathy, retinitis, myelopathy, demyelination and cerebral space occupying lesions, can all be seen during the course of the disease (Geldmacher, 2003).

Epilepsy is a condition in which someone has unpro-

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voked seizures at two or more separate times in their life. A seizure is an abnormal electrical discharge within the brain resulting in involuntary change in movement, sensation, perception, behavior, and/or level of consciousness. Epilepsy is either generalized or partial, there are different varieties of generalized epilepsy, the most famous one is grand mal epilepsy. Others types of generalized epilepsy include petit mal epilepsy, typical absence, atypical absence, tonic epilepsy and myoclonic epilepsy. Partial epilepsy is either complex partial if there is associated loss of consciousness or simple partial if there is no loss of consciousness. Also, epilepsy can be classified as primary or idiopathic when there is no underlying cause or secondary, when there is an identifiable cause e.g., asphyxia, head injury, tumor, stroke, infection like meningitis (Browne and Holmes, 2001).

The incidence of epilepsy increased in the African countries (8 times to that in the developed countries) due to increased incidence of infections like meningitis, encephalitis and AIDS. AIDS can cause epilepsy through different mechanism: (1) HIV does not directly infect nerve cells. HIV may either infect or disturb cells (macrophages and microglia) that nurture and maintain the brain. The infected macrophages and microglia then produce toxins that set off a chain reaction that kill neurons (brain cells); (2) AIDS-related cancers, such as CNS lymphoma; (3) Opportunistic infections may also affect the nervous system causing epilepsy e.g. cerebral toxoplasmosis, a common opportunistic infection in AIDS patients; (4) Progressive multifocal leukoencephalopathy (PML), a disorder that can also occur in patients with AIDS. (5) Brain Abscess (what ever the underlying cause). (6) Meningitis especially *Cryptococcus meningitis* (Sevigny et al., 2007).

Objectives

This study investigated the presence of epilepsy among Sudanese AIDS patients.

METHODS

Study design

This is a descriptive cross-sectional hospital based study.

Study area

The study was carried out at Khartoum state Hospitals, during the period March 1998 to November 2008. Khartoum state has a surface area of 20140 Km and a population of 5,548,000. The state is divided politically and administratively into 7 localities and 24 administrative units. The central location of the state is subject to continuous population influx from other states almost on a daily basis for work, education, health services, marketing and some for residence. A total of 700 AIDS patients were included in the study, all gave their verbal consent to participate in the study. Ethical approval was received from the local ethics committee prior to the start of the study. The diagnosis of epilepsy and its subtypes was

made by a neurologist based on the clinical signs and symptoms. A full detailed history was taken from each patient and a proper systemic and neurological examination was performed by the authors. The presenting symptoms include history of convulsions, headache, loss of consciousness, mental symptoms, such as confusion and forgetfulness and family history of epilepsy. The history also included symptoms in favour of HIV infection like fever, weight loss and extreme fatigue, chronic diarrhea and difficult or painful swallowing due to *Candida* infection. The physical signs were grouped into general, systemic and neurological. The following investigations were done, when indicated: TWBC and differential, urine analysis, blood urea and electrolyte, ESR, HB% and blood picture, CSF analysis, ELISA was done for each patient and the diagnosis was confirmed by Weston blot. CPK, NC study, EMG, EEG, Brain MRI and serology for toxoplasmosis and syphilis were done if needed.

RESULTS

Neurological disorders were found in 31% of the patients (mean age of 23.2 ± 4.0 years). Table 1 gives the occurrence of the different manifestations.

Out of 700 AIDS patients 40 presented with convulsion, 20 had partial epilepsy (12 had complex partial epilepsy and 8 had simple partial epilepsy) while 20 had generalized epilepsy. All patients with CNS lymphoma had secondary epilepsy; most of them had partial epilepsy (5 patients). The study showed that all patients with brain abscess presented with convulsion (5 had partial epilepsy while 2 had generalized convulsion). Eight out of 14 patients with meningitis experienced more than two attack of convulsion (5 had generalize seizure and 3 had partial seizure). It did appear that 5 out of 7 patients with toxoplasmosis had epilepsy (3 had generalize epilepsy and 2 had partial epilepsy). Regarding those who had encephalitis including PML (10CASES) nine patients had epilepsy (6 had generalize epilepsy and 3 had partial epilepsy). No obvious underlying cause was detected in four patients (2 had partial epilepsy and 2 had generalize epilepsy). The EEGs showed abnormal discharge (epileptiform features) in 28 patients (70%).

DISCUSSION

Up to 70% of HIV patients develop neurological complications. Neurological complications, including seizures, from the human immunodeficiency virus (HIV) may arise from HIV itself, opportunistic infections, tumors, or drug-related complications. Seizures can occur at any disease stage (Nath et al., 2000).

Regarding the underlying causes of seizures among our patients, the incidence was very high among those who had CNS lymphoma and brain abscesses unlike what was mentioned by Pesola and Westfal (1998). The differences are due to long duration of our study (11 years) and late presentation of our patients. The study showed that 5.7% of the patients presented with convulsion unlike what was described by Holtzman et al. (1989) where seizures were the presenting symptom of HIV in-

Table 1. Neurological disorders among 700 AIDS patients.

Neurological	Number of patients	(%)
Encephalitis including PML	63	9
Proximal myopathy	35	5
Peripheral neuropathy	28	18
Retinitis	28	4
Meningitis	14	2
Brain abscess and Toxoplasmosis	7	1
CVA	7	1
Guillian-bare syndrome	7	1
<i>Transverse myelitis</i>	7	1
<i>Cerebellar ataxia</i>	7	1
CNS LYMPHOMA	7	1

fection in 18 of 100 cases (Holtzman et al., 1989). But the result of this research is similar to what was reported by Pascual-Sedano in a prospective study of new-onset seizures in HIV-infected patients where he found a new-onset seizure occurred during the study period in 5% of subjects. Of these, 82% had AIDS per the 1993 CDC AIDS definition, it was found that the leading causes of seizures were: drug toxicity (47%), intracranial lesions (35%), metabolic derangement or unknown (18%). It did appear that 50% of the patients had generalized epilepsy, unlike what was reported by Labar and Harden, 1997, where they found that generalized convulsions constituted 75% of seizures among patients with AIDS (Holtzman et al., 1989). In the Pascual-Sedano study, the type of first seizure was: generalized (71%), simple partial motor (12%), simple partial with secondary generalization (18%) (Pascual-Sedano et al., 1999).

The EEGs in our AIDS patients frequently show epileptiform features similar to what was reported by Harden and colleagues where they found low-amplitude slow, monotonous EEGs associated with AIDS dementia complex. Our study regarding EEGs analysis is different from what was reported by Gabuzda et al., 1988, where they described routine EEGs in a series of AIDS patients (generalized slowing (38%), focal slowing (19%), epileptiform activity (6%), unremarkable (37%)), the differences are due to late presentation of our patients and to the inability of having EEGs recorded within the first 48 h which was due to practical difficulties. When compared to the work of other researchers, Brain MRI was found to be very sensitive to support the diagnosis of brain lesions associated with AIDS, EEG, CNS, lymphoma, Toxoplasmosis and brain abscesses.

AIDS encephalopathy

This is the most common neurological manifestation of AIDS. Encephalopathy or what is known as AIDS dementia complex (ADC) is a brain disorder in people with AIDS

characterized by cognitive impairment that manifests as severe irreparable memory loss and disorientation, thus affecting the ability to function in social or work settings. The incidence of HIV encephalopathy is increasing, along with the increasing incidence of AIDS. It usually develops in advanced AIDS when CD4+ lymphocyte counts fall below 200 cells/mm. It was present in 9% of the patients. The mechanism by which HIV infection leads to ADC is likely multifactorial. Theories include: (1) Cellular proteins where the widespread pathologic damage may occur via indirect cellular responses with the secretion of chemokines, proinflammatory cytokines, nitrous oxide and other neurotoxic factors; (2) Damage to neurons may occur through the actions of specific HIV proteins, including gp120, gp41, Tat, Nef, Vpr and Rev.; (3) CNS damage by humoral immune mechanisms, as evidenced by the presence of anti-CNS antibodies in AIDS patients with dementia; (4) Altered neurotransmitter release; (5) Increases in excitatory amino acids and free intracellular calcium. Disturbances of cognitive function may be the first symptoms. Early signs of HIV encephalopathy include apathy, inattention, impaired concentration forgetfulness, mood swing. Symptoms typically progress over months, but may fluctuate or remain stable.

Other neurological symptoms that can be found in an encephalopathy include myoclonus (twitching of muscles or muscle groups), nystagmus (involuntary eye movements), tremor, muscle atrophy and weakness, disequilibrium (and unsteady gait), paraesthesiae (sensory disturbances), hypothalamic dysfunction, orthostatic intolerance and postural hypotension. More serious neurological symptoms such as seizures can also be found in AIDS encephalopathy. Diffuse cortical atrophy is the most common finding on CT and MRI. Both can help to rule out other conditions that might be causing the symptoms. Electroencephalogram EEG reveals generalized slowing in the later stages of ADC. In spite of the fact that seizures are rare among patients with encephalopathy but a considerable number of the patients were presented with convulsion, this may be due to co-

existent of other abnormalities such as electrolyte disturbances (McArthur, 2004).

Progressive multifocal leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML) is a rare disorder that damages the material (myelin) that covers and protects nerves in the white matter of the brain, it is most common among individuals with acquired immune deficiency syndrome (AIDS). The disease occurs in 4% of adults with AIDS. Typical symptoms associated with PML are diverse, since they are related to the location and amount of damage in the brain and evolve over the course of several days to several weeks. The most prominent symptoms are Headaches, Loss of coordination, clumsiness, Loss of language ability (aphasia), Memory loss, Vision problems, Weakness of the legs and arms that gets worse, seizure and sometimes, personality changes (De Gans and Portegies, 1989).

HIV-associated CNS lymphoma

HIV-associated CNS lymphoma is a diffuse, large-cell non-Hodgkin lymphoma that usually occurs in the brain. It is a late complication of HIV infection. HIV-associated CNS lymphoma is typically of B-cell origin. Development of this opportunistic neoplasm is associated with CD4+ lymphocyte counts less than 100 cells/mm³. Non-focal, non-specific symptoms occur in more than 50% of patients; mental status changes in one third; symptoms of increased intracranial pressure (headache, nausea/vomiting) and/or generalized seizures in 9%. Focal symptoms in 30 to 42% of cases, including weakness or numbness, partial seizures and cranial nerve palsies (visual changes, double vision, facial numbness, facial weakness, hearing loss and/or swallowing difficulties). A hypodense or hyperdense lesions that enhances in a nodular, homogeneous, or ring like pattern where observed on CT scan of the brain. Unlike what was mentioned in the literature, Patients with CNS lymphoma had secondary epilepsy while most of them had partial epilepsy (5 patients) this is due to the late presentation of the patients in addition to inappropriate management of the patients (HAART with radiation is the mainstay of treatment) (Forsyth and DeAngelis, 1996).

Toxoplasma gondii

Toxoplasma gondii is an obligate intracellular protozoan with a worldwide distribution. Transmission occurs from the ingestion of uncooked, infected meat or from cats via a nematode vector. Toxoplasmosis is one of the most common opportunistic infections in AIDS, so cases of CNS toxoplasmosis have increased dramatically since 1981. Toxoplasmosis is responsible for over one-third of

neurologic symptoms in AIDS patients. CNS toxoplasmosis results from infection by the intracellular parasite *Toxoplasma gondii*. It is usually due to reactivation of old CNS lesions or to hematogenous spread of a previously acquired infection. For most HIV-infected patients, toxoplasmic encephalitis develops after the CD4 count falls below 100. Clinical CNS toxoplasmosis occurs in 3 - 10% of patients with AIDS. Nervous system complications include encephalitis, large brain lesions in the course of AIDS and, rarely, myelitis, polyradiculoneuritis and polymyositis. In a pregnant woman, infection during the first two trimesters of pregnancy, this can result in a massive injury to the fetal encephalon, producing brain malformations, encephalopathies, psychomotor delay and chorioretinitis and epilepsy. Reported seizure rates range from 18 to 29% and may include partial, complex partial and generalized seizures. The CT scan is very suggestive as it shows multiple ring-enhancing cysts surrounded by perilesional edema. Diagnosis is supported by resolution of clinical signs and brain lesions in response to treatment. Diagnosis is more difficult when the CT scan shows a single image suggestive of abscess, or when normal. *Toxoplasma* serology contributes little to the diagnosis. The MRI detects multiple T2 hypersignals with mass effect. Brain biopsy, performed less often nowadays, shows areas of necrosis with parasitic infestation. A very important argument favoring the diagnosis is the effectiveness of the specific treatment, resulting in clinical and imaging resolution in over 80% of cases (Porter, 1992).

Brain abscess

Brain abscess is a serious, life-threatening emergency with direct consequences on morbidity, and mortality has decreased because of advances in diagnostic modalities, antibiotic regimens and early surgical interventions. The clinical course ranges from indolent to fulminant. Most symptoms are as a result of the size and location of the space-occupying lesion or lesions. The triad of fever, headache (often severe and on the side of the abscess) and focal neurologic deficit occurs in less than half of patients. The frequency of common symptoms and signs is as follows: Headache (70%), Mental status changes (may indicate cerebral edema) (65%), Focal neurologic deficits (65%), Fever (50%), Seizures (25 - 35%), Nausea and vomiting (40%), Nuchal rigidity (25%), Papilledema (25%). A suddenly worsening headache, followed by emerging signs of meningismus, is often associated with rupture of the abscess. The diagnosis is strongly suspected from CT or MRI brain (Offiah and Turnbull, 2006). Like non compromised individual patients with AIDS, can be present with acute or chronic meningitis and can also be present with persistent or recurrent meningeal pleocytosis with or without meningeal symptoms. Different forms of meningitis are associated with HIV infection. They may be classified according to the etiologic agent

as cryptococcal, tuberculous, syphilitic, or *Listeria* species; others are lymphomatous or aseptic. Although HIV-seropositive individuals are at increased risk of certain types of meningitis, evidence suggests that they are also more likely than the general population to develop community-acquired bacterial or viral meningitides. 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. Meningitides due to cryptococcosis, coccidioidomycosis, histoplasmosis, or other fungal infection are AIDS-defining events and occur typically with very low CD4+ lymphocyte counts. An asymptomatic form is found in one third of patients. Patients present with malaise, fever, stiff neck, photophobia, and headache. Less common findings are confusion, somnolence, seizure and personality changes. Cryptococcosis is the most common systemic fungal infection in AIDS and it is on the rise with the rapid spread of AIDS. Without treatment, Cryptococcosis is invariably fatal. The incidence of cryptococcal meningitis, formerly a relatively rare disease, has markedly increased in recent years due to the frequent occurrence of the opportunistic infection in human immunodeficiency virus positive patients, mainly in places where protease inhibitor, nucleoside reverse transcriptase and non-nucleoside reverse transcriptase drugs remains unavailable. The fungus is acquired by inhalation and causes the initial lesion in the lungs; the pulmonary stage of infection is usually a symptomatic. The fungus disseminates in debilitated patients, usually involving the meninges (Durand et al., 1993).

Conclusion

AIDS is a great mimicker. The physician cannot be over-cautious to include it in his/her differential diagnosis of otherwise unexplained neurological symptoms and signs. Epilepsy is not an uncommon neurological manifestation associated with AIDS.

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