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Introduction- At least one-third of the 35.3 million people living with HIV worldwide are infected with latent tuberculosis. Tuberculosis is the most common presenting illness among people living with HIV, including those who are taking antiretroviral treatment. There were an estimated 1.1 million HIV positive new TB cases globally in 2012. Around 75% of these people live in sub-Saharan Africa. Despite its great burden, neurological manifestations have not been described yet in patients with HIV-active tuberculosis, although tuberculosis and HIV have synergistic influence on immunity system which may contribute to change in prevalence or severity of CNS involvement in patients with HIV-active TB co infection. Objectives: To study neu rological manifestations in patients with HIV-active tuberculosis.

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Neurological Manifestations among Patients with HIV – Active Tuberculosis Co Infection

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Despite its great burden, neurological manifestations have not been described yet in patients with HIV-active tuberculosis, although tuberculosis and HIV have synergistic influence on immunity system which may contribute to change in prevalence or severity of CNS involvement in patients with HIV-active TB co infection.

Objectives: To study neurological manifestations in patients with HIV-active tuberculosis

Methodology: A case series study of 58 consecutive patients with laboratory confirmed HIV- active tuberculosis co infection attending tertiary hospital for tuberculosis treatment was conducted. Data about neurological symptoms and signs – conducted by a neurologist- were collected from each patient.

Results: 24% of 58 patients were found to have neurological manifestations in clinical assessment.

Conclusion: The frequency of neurological manifestations among patients with HIV-active TB co infection was found to be higher compared to that of patients with HIV only;

I. Introduction

Sudan is the largest country in Africa, covering one eighth of the continent surface with an area of 2.5 million kms2. More than 2000 km from north to south, having diverse environment due to different climatic zones, extending from the great desert to equatorial rainy forests. 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. Moreover, Sudan shares extensive borders with nine countries, several of which have high HIV/AIDS prevalence. The population of Sudan according to1993 census was 26 millions. The annual growth rate also increased from 1.9 percent to 2.6 percent. Rural –urban migration has been steady and high. HIV/AIDS pandemic has become human'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.

HIV belongs to the retroviruses group. AIDS was first discovered in June 1981. HIV is by far the most common immunodeficiency disorder encountered in clinical practice, it is transmitted by intercourse, heterosexual or homosexual, administration of infected blood or blood products, contaminated needles and from infected mothers to their infants. (1, 2) 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. (3-4) The clinical manifestations associated with HIV infection vary in different populations, possibly due to the relative frequency of endemic infections. 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 or to the coexistent AIDS related cancer such as lymphoma, or to opportunistic infections like toxoplasmosis. (5, 6) The neurological complications of AIDS range from acute febrile illness at the time of sero conversion 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. (7,8). AIDS dementia complex is a well-recognized complication of HIV infection (9). Peripheral neuropathy, retinitis, myelopathy, demyelination and cerebral space occupying lesions, all can be seen during the course of the disease. (10)

Tuberculosis (TB) is an ancient disease. Egyptian mummified remnants dated to 3400 BC showed evidence of Pott's disease1. A recent resurgence of TB in both developing and developed countries had been observed. Several factors had

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contributed to this serious phenomenon including the increasing prevalence of HIV infection. TB of the central nervous system is a common clinical problem in developing countries. Its incidence is directly proportional to the prevalence of TB infection2. No part of central nervous system is spared. (11, 12) Infection of the meninges by tubercle bacilli is usually caused by rupture of subependyma tubercle into subarachnoid space rather than by haematogenous seeding in the meninges. The clinical manifestations of central nervous system involvement depend on the site affected. Neurological manifestations are common in patients with TB. However, high index of suspicion is needed to avoid delay in diagnosis and management. Pott's paraplegia and peripheral neuropathy were highly prevalent. (13, 14)

The paraesthesias seen in patients who presented with neurological complications- may be due to antituberculous chemotherapy, neuropathic numbness, or concomitant HIV infection17. Sphincteric disturbance in form of urine retention occurred in 10% of tuberclous patients; it is associated with Pott's paraplegia and indicates severe damage to the spinal cord. (15-16)

Cranial nerves involvement may be part of the manifestations of tuberculous meningitis especially basal meningitis, tuberculoma or may be due to coexistent diseases like HIV infection .Convulsions may be due to increase intracranial pressure in cases of tuberculoma, abscess formation, hydrocephalus complicating tuberculous meningitis, or coexistent HIV. (17, 18-19-20)

II. Objectives

To study neurological manifestations in patients with HIV-active tuberculosis.

III. Methods

The study was carried out at Bashair Teaching Hospital and Abo Anga Teaching Hospital, during the period march 2018 to May 2018. A total of 54 with HIV-active tuberculos patients were included in the study, all of whom gave their consent to participate. All were adult Sudanese patients admitted to Bashair Teaching Hospital and Abo Anga Teaching Hospital. A comprehensive history was taken with emphasis on neurological symptoms. All patients had a thorough clinical examination. The following investigations were done, when indicated: TWBC and differential, urine analysis, blood urea and electrolyte, ESR., HB% and blood picture, CSF analysis, ELISA and Weston blot., CPK, NC study, EMG, CT brain and serology for toxoplasmosis and syphilis.

IV. Results

24% of 58 patients were found to have neurological manifestations in clinical assessment.

The following table demonstrates the neurological manifestations and their frequency.

Neurological Diagnosis

	Frequency	Percent
normal	44	75.9
AIDS Dementia	3	5.2
Meningitis	2	3.4
Grand mal epilepsy	2	3.4
cerebellar ataxia	1	1.7
GBS	1	1.7
peripheral neuropathy	1	1.7
proximal weakness	1	1.7
spastic quadriplegia	1	1.7
stroke	1	1.7
transverse myelitis	1	1.7
Total	58	100.0

V. Discussion

Three of our patients presented with 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

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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. (21, 22)

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.

Neurological complications, including seizures may arise from HIV itself, tuberculoma, opportunistic infections, tumors, or drugs related complications. Seizures can occur at any disease stage (Nath et al., 2000). Regarding the underlying causes of seizures, the incidence was very high among those who had 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 ,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 De Angelis, 1996.

It did appeared that all the patients had generalized epilepsy, unlike what was reported by Labar and Harden, 1997, where they found that generalized convulsions constituted 50% of seizures among patients with AIDS (Holtzman et al., 1989). The EEGs in our 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. 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. (23, 24)

The study showed that tow of our patients had meningitis and 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. (25, 26) 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

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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. Crytococcosis is the most common systemic fungal infection in AIDS and it is on the rise with the rapid spread of AIDS. Without treatment, Crytococcosis is invariably fatal. The incidence of crytococcal 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). Meningitis may be due to cryptococcus, histoplasmosis, TB or lymphoma. (27, 28) There is a well-known recognized association between brain abscess and toxoplasmosis. 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 Hussein et al. 021 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). (29-30).One of the rare causes of epilepsy is 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).

One patients presented with neuropathy, HIV-active tuberculosis can cause peripheral nerve damage. Other causes of peripheral neuropathy include co-existent opportunistic infections, lymphoma and drugs like AZT and INH. HIV-active tuberculosis patients can present with sensory or motor neuropathy, it can cause polyneuropathy, radiculopathy and mononeuritis multiplex. Guillin-Barrie chronic inflammatory demyelinating chronic inflammatory demyelinating polyradiculoneuro pathy (CIDP). Human immunodeficiency virus (HIV) associated Guillain- Barré syndrome has been reported since 1985. This neuropathy typically occurs early in HIV infection, even at serocon version stage thus it could be the first manifestation of the infection1. It can occur at a later stage also. The pathogenesis of AIDP (acute inflammatory demyelinating polyneuropathy) is probably autoimmune, but in advanced HIV (AIDS) is usually due to CMV infection. (1-3) However, HIV associated neuropathies like distal sensory polyneuropathy and toxic neuropathies have become the most frequent

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neurological disorders in HIV infection. AIDP in HIV is not common.

Transverse myelitis can occur in AIDS with active tuberculous patients. It is a neurological disorder caused by an inflammatory process of the grey and white matter of the spinal cord, and can cause axonal demyelination. One major theory of the cause is that an immune-mediated inflammation is present as the the Result of exposure to a viral antigen. The lesions are inflammatory, and involve the spinal cord on both sides. With acute transverse myelitis. The lesions can be present anywhere in the spinal cord. Symptoms include weakness and numbness of the limbs as well as motor, sensory, and sphincter deficits. Severe back pain may occur in some patients at the onset of the disease. The symptoms and signs depend upon the level of the spinal cord involved and the extent of the involvement of the various long tracts. In some cases, there is almost total paralysis and sensory loss below the level of the lesion. If the high cervical area is involved, all four limbs may be involved and there is risk of respiratory paralysis. Lesions of the lower cervical (C2-T1) region will cause a combination of upper and lower motor neuron signs in the upper limbs, and exclusively upper motor neuron signs in the lower limbs. A lesion of the thoracic spinal cord (T1-12) will produce a spastic paraplegia. A lesion of the lower part of the spinal cord (L1-S5) produces lower motor neuron signs in the lower limb. The degree and type of sensory loss will depend upon the extent of the involvement of the various sensory tracts, but there is often a "sensory level" (at the sensory segmental level of the spinal cord below which sensation to pin or light touch is impaired). This has proven to be a reasonably reliable sign of the level of the lesion. Bladder paralysis often occurs and urinary retention is an early manifestation. (3132)

Myelopathy occurs in AIDS patiénts with active tuberculosis, it is due either to the effect of the virus, associated electrolyte disturbance or to the toxic effect of the drugs. Vaculor myelopathy typically presents as subacute progression of motor and sensory deficits over several months. Parasthesia or numbness of the limbs, if present, is sometimes is difficult to distinguish from symptoms of peripheral neuropathy, moreover, the condition often coexist in patients with advanced HIV disease. Brisk tendon reflexes suggest spinal cord or brain involvement, whereas peripheral neuropathy is associated with depressed reflexes, especially those of the Achilles tendons, a patient with both processes might have brisk knee reflexes and absent ankle jerks.

CVA is due to infarction or hemorrhage. (33, 34) HIV-active tuberculosis increases the risk of both ischemic and hemorrhagic stroke. this increased risk is most apparent in the young HIV infected population in which other risk factors for stroke are seldom evident. The increased risk include opportunistic infectious meningitides and vasculitides, primary HIV vasculopathy, altered coagulation and cardio embolic events, although the cause may be multi factorial or remain cryptic. Higher viral loads increased the risk of stroke, whereas being on antiretroviral therapy for a longer time and having an undetectable viral load decreased the risk.

Only one patient presented with cerebellar ataxia. Cerebellar complications of HIV infection primarily manifested in ataxia usually arise as the result of cerebellar lesions due to HIV encephalopathy, opportunistic infections like toxoplasmosis, vasculitis or neoplastic processes.

VI. Conclusion

HIV-active tuberculosis is a great mimicker. It can present with almost any neurological manifestation. The physician cannot be overcautious to include it in his/her differential diagnosis of otherwise unexplained neurological symptoms and signs.

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