Neurocysticercosis In HIV-Positive Patients

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Abstract

Neurocyticercosis (NCC) is the most common parasitic infection of the nervous system and can cause epileptic attacks in most patients, including signs of intracranial hypertension due to obstruction of the cerebrospinal fluid circulation. Globally, the number of infected individuals is gradually increasing, as well as, among HIV-infected individuals. The immunology, pathophysiology and management of this condition among these patients are discussed. Family doctors could likely modify the course of this epidemic by early diagnosis and aggressive intervention in order to delay the accelerated progression of HIV-infected individuals to AIDS.

INTRODUCTION

An estimated sixty million people globally are infected with the larvae form of Taenia Solium (TS) and in places such as the former Transkei (Region D and E of Eastern Cape Province) in South Africa, the incidence and prevalence of this parasitic disease continue increasing gradually [1]. Neurocisticercosis (NCC) is an infection of the central nervous system (CNS) caused by the larval stage (Cysticercus cellulosae) of the pig tapeworm TS. The adult stage is a parasite exclusively of human, and they are the most common helminth to produce CNS infection in human being.

The occurrences of epilepsy, neuropsychiatry manifestations, dermatological problems, ocular disturbances, and/or raised intracranial pressure in persons living in or visiting regions where taeniasis are endemic or even in one living in close contact with people who have taeniasis should suggest a diagnosis of cysticercosis; the NCC may remain asymptomatic for months to years and commonly a diagnosis is made incidentally when neuroimaging is performed. Symptoms and signs are related both to the parasite which can show a different molecular biology expression from one place to another and to the inflammatory-immunological response of the host. Diagnostic criteria for NCC have been well-established recently [2]; based on these studies, although diagnostic criteria remain controversial, absolute diagnostic criteria is acceptable when the histological demonstration of the parasite from biopsy of the brain or spinal cord lesion is made, or in case of cystic lesion showing the scolex on CT or MRI, or when sub-retinal parasite is visualized by fundoscopy examination. Other less acceptable diagnostic criteria such as major, minor or epidemiologic classification can be reviewed in the Del Bruto's article [2].

The International League Against Epilepsy established that cysticercosis is the single most common cause of acquired epilepsy in the developing world where prevalence rates of active epilepsy are twice those of developed countries [3]. Nearly all infected people live in less-developed countries and the probable link with HIV/AIDS is that chronic parasitic infection down-regulates the cellular immune response that is required to prevent infection by the immunodeficiency virus and Mycobacterium tuberculosis [4]. In South Africa, the MRC has estimated that HIV/AIDS account for 40% of death in adults aged 15-49 in 2000, and may probably kill between 5 and 7 million people by 2010 [5]. Neurocysticercosis is commonly associated to HIV/AIDS, TB and Schistosomiasis in some developing countries and is well known that co-infection by pathogens that elicit oppositing immune response, particularly helminths versus HIV and TB can influence the infection dynamic, progression, and immunoprophylaxis of the disease they cause [5].

Disease model in mice have been manipulated at molecular and cellular levels, in order to demonstrate priming of immune response by contact with viral, bacterial and parasitic organisms. The respective antigenic exposures influence differentiation of T helper 1 (Th1) or Th2 cell, as well as, the associated cytokine profiles and TH1/Th 2 [6].

The parasite inhibit complement activation, lymphocyte activation, and cytokine production and remains viable longer in HIV patients (1), then we observe parasite acting against the immune system and an immune system acting against parasites, with both mechanisms influenced by associated pathological processes such as Tuberculosis, Schistosomiasis and HIV/AIDS. Family doctors, general practitioners, and internists among others can play an important role in the control of this epidemic disease and also they can contribute to delay the progression from HIV to AIDS.

EPIDEMIOLOGY

Poverty, underdevelopment, poor personal hygiene or improper hygiene, and living conditions allowing pig's access to human faeces, are the most important co-factor in the epidemiology of NCC. In densely populated informal settlements in South Africa, co-infections by HIV, Mycobacterium tuberculosis, and TS are usually considered because this parasite is relatively common. Infections by TS can accelerate HIV progression to AIDS because the parasite can modify the immune system of the host by polarizing this immune response to Th2, suppressing interleukin 2, 5 and 6, and TH1 cytokine. NeuroAIDS depends on a number of factors, such as degree of immunosupression, and the molecular biology of the viral strain, particularly its neurovirulence [7].

NCC constitutes a serious health problem in Latin America, India, and China and it is becoming more frequent in Europe and North America, where NCC was exceptionally rare 10 years ago. In South Africa, NCC is localized in well demarked regions of Eastern Cape province and part of KwaZulu Natal where access to employment, cash income, safe and clean water, proper toilet facilities, proper refuse disposal, electricity, telecommunication and medical services are extremely low; that limited access to primary health care system among other factors are perpetuating its dissemination. Because NCC is the commonest cause of new-onset seizure, the incidence of epileptic seizures in the former Transkei is three times more elevated than in developed countries without NCC. Cysticercus in our region, does not invade the eyes as often as India; and skeletal muscles or the subcutaneous tissue are less affected than Asian countries (China). Multiple intracranial lesions are less common in India than in Latin American countries [8] or our region [1].

In the United States of America (USA), TS is becoming more common among immigrants from endemic areas, and around 1,000 news cases have been reported each year. Seroprevalence of NCC infection between 4.9 % and 24 % have been reported in some endemic areas in Mexico, Bolivia, Peru, Ecuador and Guatemala [9] only because the number of seropositive patients represent only those 40 % of cases diagnosed by the absolute criteria; therefore, the prevalence of TS in those country are should be higher. In our area, 6 of 10 epileptic patients attending the Umtata General Hospital Special Epilepsy Outpatient Clinic are affected by NCC and this clinic covers a population of 6.4 million habitants.

PATHOLOGY, IMMUNOLOGY, AND PATHOGENESIS

TS is one of thirty species of cestodes affecting humans. TS requires two host to complete its life cycle. In the first stage, the human host ingest diseased (measly) pork containing viable cysticerci, after ingestion, the scolex evaginates and attaches to the small intestine using its 4 suckers (teaniasis), the tapeworm matures over 3 to 4 months after infection, achieving a length of 2-7 meters. Seven to twelve hundred hermaphrodites proglottids developed from the base of the scolex containing more than 50,000 eggs which are shed passively and intermittently in stools two or three times a week. This explains why stool tests are usually negative for cysticercosis and uncertain to differentiate eggs of TS from eggs of other taenias. Pig becomes infected by ingesting the ova or mature proglottids and in the human small intestines the larvae hatch, and using its double crown of 25 hooklets, erodes the intestine mucosa and enter the bloodstream where the parasites are constantly exposed to the immune system of the host.

In this stage (pre-critical stage), HIV can infect monocytes easily, however if the parasites died at this stage, its may prevent the dominance of Th2 immune response, reducing immune activation and can also alleviate cell anergy, facilitating immunosupression effect by HIV. If the parasite remains alive after this immunological attack, they usually reach the skeletal muscles, eyes and central nervous system (cysticercosis or parachymal localization of the parasite) where the parasites could be found in different stages such as:

1. Vesicular stage: characterized by cysts of 4-30 mm in diameter (or even bigger), the cyst wall is thin (0.4-0.8 mm thick) isodense with the nervous tissue, the cyst fluid is isodense with CSF and there

is minimum inflammatory reaction around the cyst because the parasite elaborate prostaglandins and low-molecular-weight molecules which decrease perilesional inflammation, also secrete proteases that can degrade interleukin (IL)-2 and immunoglobulin, in this stage there is not focal edema; the size of the cyst is related with the resistance of surrounding tissue, i.e on the skeletal muscle the lesions are almost similar in size although smaller in the musculature of the limbs (1-2 cm in diameter) compared with muscular tissue at the trunk (2-3 cm in diameter) and in the CNS cysts are bigger on the subarachnoid space compared with intracerebral tissue where there is a bigger mechanical resistance.

2. Critical stage: long time after primary CNS invasion and due to a successful persistent immunology attack against the cysticercus, due to anti-cysticidal drugs or due to other reasons, in some people then the parasite serine protease secretion increase compared with the previous stage, and decrease the elaboration of prostaglandins by the parasite therefore inflammatory perilesional response is more evident. In spite of the variety of ways used by the parasite to modify host immune response, at this stage, their mechanism of excretory/secretory product fail and its anti-immune properties are weaker, paradoxically these pathologic changes on the parasite membrane and the surrounding tissue (without remarkable edema) are observed, its may be seen in HIV patients with CD4 count > 350 cells/mm3 and viral load rises <55,000 copies /ml or even in window period [10] that such individuals may not qualify for anti-retroviral therapy (ART). At this stage electrophysiological changes suggesting subclinic peripheral neuropathy can be seen, those patients will develop sensory distal symmetrical polyneuropathy later or will manifest peripheral neuropathy as side effect of ART without co-infections like CMV or MAC. We have hypothesized that at this stage there is an increased microglial activation with an associated olygodendrocyte and astroglial changes with a subsequent damage of the axonal functions and blood-brain barrier leading to pathological concentration of macrophage histocompatibility complex, Interleukin-1 and –6, and tumor necrosis factor alpha among other unknown neuro-toxins causing CNS and peripheral nerve disorders. Because HIV does not directly infect neurons, the neuronal injury and/or neuronal death should be related with the interaction of the parasite with chemokine receptors on neurons and astroglias, and the increased concentration of proinflammatory molecules from meningeal macrophages, choroids plexus macrophages, perivascular macrophages, phagocytic macrophages, multinucleated giant cells, and activated microglias-according to the number and location of the cysiticercus. This stage can provoke a collapse of the immune system stimulating intracellular retroviral replication.

3. Colloid stages: characterized by increased cyst fluid density, and perilesional edema, in this stage seizures disorders are common and the previous disorders may be aggravated.

4. Granular stage: parasite is dead, cyst is collapsed or fibrotic, edema can be present.

5. Calcify stage: 2- 10 mm-calcified lesions with perilesional edema (still “active” lesions) or without edema (inactive lesions), epileptic seizures are also frequents. As previously mentioned, the parasites secrete, excrete or shed factors which down-regulate both T cell proliferation and cytokine production [11]. In most of the active-vesicular forms, patients could remains asymptomatic for a period lasting many years or even for life with clinical manifestations dependent upon the number of viable cysts, frequency of recurrent infection, size of the lesion and the perilesional area, site of cysts in the brain, and/or predominance of vesicular, critical, colloid, granular or calcified (with edema) stage and inflammatory-immunological response of the host. Finding cysts in different stages is a rule, sometimes because of re-infections and most of the times because all parasites are not under the same immunological attack along the CNS and some die while other degenerate and another survives without pathological changes; however in immunocompromised patients most of them will survive without major problems, becoming more resistant to external attack and given a false impression of bigger number. In this stage, it is not

certain if TS is also attacked by HIV.

Increased IgG, interleukin-2-5 in serum and interleukin 5-6 plus neopterin in the CSF has been reported [9]. Epidemiological and clinical findings suggest that individual immunological responses to cysticercosis might have a genetic basis [9]. There is also an association with epilepsy in neurocysticercosis with HLA type I [12], therefore HLA differences might also determine the risk of intracranial infection or symptomatic parenchymal disease in NCC [9]. HIV-1 does not directly infect neurons, astrocytes or oligodendroglial cells but seems to be that affected microgial cells dysregulate cytokines and chemokines productions. Maslinska [13] reported the accumulation and phenotype heterogeneity of mast cell (MC) contained immunoreactive tryptase in human brains with NCC. MC are the multifunctional effectors cells of the immune system, MC synthesize and secrete numerous powerful mediators such as endorphins, serotonine, histamine, heparine, kinins, leukotriens, protaglandins, vasoactive intestinal peptide, proteolytic enzymes, cytokines and phospholipases which are well known to have significant pathophysiogical effects on vascular and neuronal tissues. The role of MC accumulated in the CNS regarding host immune tolerance is clear but regulating factors for MC accumulation are not certain. Because MC provide a source of multifunctional cytokines and other potent mediators has been proposed that MC participate in control of cerebral blood flow and the integrity of the blood-brain-barrier. Perilesional edema in calcified lesion is probably related with histamine concentration from MC, inducing vasopermeability and cerebrovascular damage.

CLINICAL PRESENTATION

Most of our patients present with wide variety of epileptic attacks (89 %); signs of intracranial hypertension secondary to CFS flow obstruction and hydrocephalus, meningeal syndrome, and ischemic stroke are very less common [1,10]. Among our patients, focal neurological signs by lesion in the long motor pathways, cranial nerves disorders, cerebella manifestations, and signs of encephalitis have been observed. In HIV-infected patients (CD4 count >350/mm) with NCC, epilepsy is still the most common problem and although new-onset seizures associated with late-stage HIV infection has been documented [14], in our series, epileptic patients were NCC related. Psychiatric symptoms [15], intramedullary lesions [16,17], extra ocular manifestations [18], optic nerve lesions [19], orbital and ocular presentation [20], lesions on the tongue and buccal mucosa [21], and cutaneous manifestations [22] have been reported.

MEDICAL MANAGEMENT

Many tests to confirm HIV infections have been reported and beyond the scope of this report. However, we used ELISA for most of the patients, including the determination of CD4 counts and viral loads, when it was necessary.

For NCC the best investigations to confirm the diagnosis, to establish a trusted prognosis and proper follow-up are CT Scan and/or MRI of the brain, sometimes the diagnosis can be established by excision biopsy of subcutaneous cysticerci mainly in Asian countries (China), although serologic test has shown a high level of sensitivity (90-98%) and specificity in patients without ring-enhancing lesions. Nevertheless, CT scan of the brain showing the scolex in to the cysts is the test of choice. There is abundant information regarding these topics in available medical literature [1,2,8,9,10].

As was previously mentioned, most patients with NCC present with epileptic attack during the critical stages, the colloid and calcify/edema stage. Those patients with tonic-clonic generalized seizure respond very well to anti-epileptic monotherapy, however, HIV-infected patients can present different respond because of the association of other mechanisms, including increased number of parasites in different stages (re-infection plus prolongation of other parasitic stage) for more the 2 years [23]. The medication of choice for intraparenchymal presentation (commonest one) of NCC is praziquantel in spite of its reduced effect when it is associated with anti-epileptic therapy. Praziquantel is an effective isoquinoline for almost all helminthic species and it is absorbed very quickly reaching its peak concentration in serum 1 or 2 hours after oral administration, with the half life being around 2 to 3 hours, and concentration in blood increasing 10 % when high carbohydrate diet is given. Oral doses of 25 mg/kg 6 hourly for 24 hour (followed by 4 days treatment with steroids), can be quite effective (with minimal side effect to patients) producing a spastic paralysis of the parasite musculature, destroying the scolex and affecting the metabolism of the parasitic membrane for patients with recurrent seizures or in status epilepticus in which 100mg/kg/day dosage should be given 1 hourly per os or by nasogastric tube in combination with steroids. Praziquantel is contraindicated in ocular NCC and during pregnancy, but we have found no teratogenic effect in patients under single day treatment. In some anecdotic cases

not responsive to praziquantel, Albendazole, which kills the parasites by inhibition of the glucose up-take, must be prescribed at no less than 15-20mg/kg/day for a week. In HIV-infected patients we recommend the administration of praziquantel in regular cycles of one-day treatment per month for twelve months in combination with 2- 3 days of steroids, mainly for those patients living in endemic areas.

Although some controversial results about praziquantel treatment have been reported [24,25,26,27] we emphasize one-day treatment of praziquantel therapy during one year for those patients with multiple intraparenchymal lesions, and women at the reproductive ages; and for those living in endemic areas with higher risk of re-infections or being HIV seropositive, anti-helminthic treatment even for years should be considered until better life conditions with alleviation of poverty, with proper access to electricity, adequate access to save and clean water and toilets, good sanitary control of the pig population, better hygiene, and more effective primary health care system are implemented. We feel that better results in the program for the control of tuberculosis will help to reduce fatal consequences in HIV-infected patients with NCC. On the other hand, while enormous economic differences between countries persist the immigration rates from endemic regions will continue to increase gradually and NCC will become a worldwide problem, perhaps minimally affecting those in very cold climates and/or extremely well developed primary health care systems. We would like to emphasized that while this situation persists the number of infected immigrants to developed areas will continue to increase [28]. We believe that this disease present more commonly than has been reported; we also believe that massive vaccination of the pigs population without a good primary health care supporting system could be minimally effective and resource intensive.

When the immune system fails to kill the parasites, highly activated members of the macrophage family fuse to form giant cells in an attempt to rid the body of what the immune system could not destroy. Soluble substances released by virally infected or cytokine-stimulated monocyte/macrophages and microglia can activate or disrupt the blood-brain- barrier (BBB) and its related membranes [29]. They also stimulate macrophages in the CNS, augmenting their recruitment and retention. That combination of HIV-NCC appears to drive monocytes towards the activated macrophages phenotype, resulting in the release of matrix-metalloproteinases that degrade extracellular matrix integrity. Brain-resident macrophages and microglia, as well as astrocytes in HIV infected CNS synthesize chemokines, including MIP-1 alpha and MIP-1 beta, which are involved in stimulating monocyte traffic and retention. Injured neurons themselves may participate in recruiting macrophages to the CNS by secreting fracalkine, thereby potentially contributing to a cycle of increasing neuron damage and macrophage recruitment [29].

Finally it is critical to report that a massive anti-helminthic medication campaign without appropriate management of the secondary immunological reactions will not provide safe benefits to affected population, and the lack of health education program will facilitate a new cycles of re-infection with the consequent immunological changes in HIV-positive patients facilitating the progression to AIDS with an increased chance of opportunistic infection, and a higher mortality rate.

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