SCIFED Publishers

Zakaria Mamadou, SF J Neurosci, 2017, 1:1

SciFed Journal of Neuroscience

Review Article Open Access

Peculiarities of Epileptic Seizures in Patients Living with HIV Infection a Review of the Literature

*[1]Zakaria Mamadou, [1]Christian Tanoh, [2]Kouassi Kouamé Léonard, [3]Youssoufa Maiga, [1]Aka-Anghui Evelyne Diarra

*[1]Neurology Department of the University Hospital of Cocody, Abidjan (Côte d'Ivoire)

[2]Neurology Department of the University Hospital of Yopougon, Abidjan (Côte d'Ivoire)

[3]Neurology Department of the University Hospital of Gabriel Touré, Bamako (Mali)

Abstract

The HIV infection is a real public health problem in the world. Central nervous system disorders in people living with HIV are often associated with extremely high morbidity and mortality. Epileptic seizures are very common in HIV-infected patients, especially at an advanced stage of the disease, due to either opportunistic infection of the central nervous system (CNS) or to the HIV infection itself. The type of attack depends on the focal or diffuse lesion of the CNS. The decision to undertake a background antiepileptic drug (AED) must take into account the interaction between AEDs and ARVs regarding the duration of the treatment. The ideal AED in this situation should have low plasma protein binding, non-enzymatic induction. It should not result in an enzymatic induction nor in an increase of viral replication.

Keywords

Epilepsy; HIV; Etiology; Treatment.

Introduction

The nervous system is the second target of HIV. Various manifestations and neurological complications can be observed at all stages of the disease. Encephalitis is the first neurological complication of HIV infection [1, 2].

These include opportunistic infections such as cerebral toxoplasmosis, tuberculous meningoencephalitis, cryptococcal meningitis, cytomegalovirus (CMV) infection, lymphoma, HIV dementia (complex dementia), myelopathy, stroke or sensitive polyneuropathy. The epileptic seizures are a frequent expression of some of these opportunistic infections and are often indicative of HIV-related immune deficiency.

This work is a review of the literature. The objective was to identify epidemiological, pathophysiological, clinical and especially therapeutic peculiarities of epileptic seizures occurring in people living with HIV/AIDS.

Epidemiological Data

The epileptic seizures are frequent symptoms of the HIV infection and of its brain complications. Most of the data on epilepsy in people living with HIV/AIDS come from studies in hospitals.

The prevalence of epileptic seizures varies from region to region. It is estimated to be between 1% and 11% in HIV immune depressed patients [3, 4, 5]. It is of 3% in South Korea [6] and Spain [5], 5% in India [4] and 11% in the United States [3]. In South Africa, this prevalence varies between 3 and 17% [7] and is of 33% in France [8]. A series from Cameroon reported a hospital prevalence of 9.54% and 31.2% [9].

The epileptic seizures during HIV infection are generally observed at a very advanced stage of the disease,

***Corresponding author:** Zakaria Mamadou, Neurology Department of the University Hospital of Cocody, Abidjan (Côte d'Ivoire). E-mail: mamadouzakaria1@hotmail.fr

Received April 19,2017; **Accepted** August 12,2017; **Published** August 26,2017

Citation: Zakaria Mamadou (2017) Peculiarities of Epileptic Seizures in Patients Living with HIV Infection a Review of the Literature. SF J Neurosci 1:1.

and studies have shown a proportional increase in epileptic seizures as a function of decreased CD4 counts [7, 10, 11].

Moreover, these seizures are often inaugural. A review of the literature (1950 and 2010) reports that inaugural seizures in HIV patients vary between 2.6 and 61% [12, 13].

Physio-pathological Aspects

Among the many lesions described on the brain of HIV-AIDS patients, there is a neuronal loss. This observation raises the problem of its mechanism in so far as HIV does not directly infect neurons. The use of an HIV-related toxin may trigger an immunologic reaction responsible for neuronal degeneration. Neuronal death is the result of a series of complex interactions between macrophages, microglial cells, monocytes and astrocytes. These neurotoxic substances would result in a massive release of glutamate or in a decrease in its consumption-utilization. This mechanism involves activation of voltage-dependent calcium channels and N-methyl-D-aspartate (NMDA) receptors, a massive entry of calcium ions into neurons and other cells. The same mechanism, which was proposed in the pathogenesis of HIV-related dementia, may also be retained in the occurrence of both early and late seizures in these patients. The occurrence of generalized seizures as well as a state of epileptic malaise could be linked to cortical hyper-excitability attributed, itself, to an imbalance between excitatory and inhibitory systems [14]. Table 1 summarizes the physio-pathological mechanisms of hyper-excitability [15]. In the context of a neurotoxic mechanism, it should be noted that an increase in the concentration of beta-microglobulin and neopterin in CSF, markers of CNS infection by HIV-1, was found in all patients having no precise cause of the seizures without, however, any evidence of an epileptogenic effect of these chemical elements [16].

Clinical Aspects

The type of epileptic seizure in immune-depressed patients with HIV depends on the etiology. The majority of studies report a predominance of generalized seizures. Mbonda et al, in Cameroon, reported 66% of generalized seizures and 18% of epileptic seizures [17]. The latter were associated with poor prognosis [3, 7, 17]. On the other hand, the frequency of partial seizures was 80% in the study of de Kuaté et al [14]. In India [4] and France [8], the frequency of generalized seizure was 65.2% and 71%, respectively, and those of partial seizures were 34.8% and 29%, respectively.

Table 1: Pathogenesis of HIV-related encephalopathy and epileptic seizures in HIV-positive patients

HIV-related toxins or an immune reaction indirectly leads to neuronal death.
Interactions between macrophages (microglia), astrocytes and neurons produce neurotoxic substances.
The most widely known neurotoxic substances include: eicosanoids, platelet activating factors, quinolines, cysteine, cytokines and free radicals.
Macrophages activated by the protein envelope gp120 of HIV-1 release similar toxins.
The circuit ends with an increase in glutamatergic activity, activation of voltage-dependent calcium channels and channels linked to the N-methyl-D-aspartate (NMDA) receptors.
The massive entry of calcium into the cells eventually leads to neuronal death.
The relative imbalance between excitatory and inhibitory neurotransmitters and the neurotoxicity of other substances in the brain predispose to epileptic seizures.

The high frequency of generalized seizures and epileptic-evil states shows that the HIV-infected brain has a low epileptogenic threshold associated with a process of disinhibition [15].

Partial seizures, less frequent than generalized seizures, are not necessarily linked to expansive focal lesions. Partial seizures secondary to generalized or non-generalized can be observed in diffuse cerebral pathology such as meningitis or HIV encephalopathy [12]. The large proportion of generalized seizure can be explained by a very rapid secondary generalization or the inexperience and difficulties of the entourage or the general practitioners in giving a precise description of the crises and especially their origin [18].

Etiology

Patients living with HIV who have undergone an inaugural epileptic seizure should benefit from extensive paraclinical assessments. These assessments should include a cerebral neuro-imaging (CT or MRI) study, a CSF analysis (cytology, biochemistry, bacteriology, Koch bacillus [KB], cryptococcus, soluble antigen, etc.) and a blood test (fasting blood glucose, blood ionogram, renal

function, blood count) and, for some of them, post-mortem anatomopathological examination. The literature reports that between 50% and 60% of patients have a secondary CNS lesion and may be at the origin of seizures. In spite of the exhaustive paraclinical reports, the undetermined causes vary between 40% and 50% of the cases according to the studies [14].

Elsewhere, hydro-electrolyte and metabolic disorders (renal insufficiency, hyponatremia hypomagnesaemia, etc.) are factors associated with an increased risk of epileptic seizures and their recurrence.

Brain Toxoplasmosis

It is the first opportunistic cerebral infection and also the first etiology of intracranial expansive processes (ICEP), infectious type of HIV. Its frequency varies according to continents; it is 50 to 60% in Europe and Africa and 3 to 10% in the United States. It represents 30% in a Cameroonian study [17]. Its diagnosis is quite easy due of the positivity of the HIV serology, the clinical presence of the Bergman triad (focal neurological deficit, HTIC, infectious syndrome), and evocative CT lesions (predominant hypodense lesion in the central gray nucleus zone, and a clinical improvement in anti-toxoplasmic treatment (sulfadiazine-pyrimethanine or cotrimoxazole).

CNS Lymphoma

It is the second leading cause of intracranial expansive processes in HIV-infected patients and primary CNS lymphoma is the third leading cause of central neurological manifestations after cerebral toxoplasmosis and progressive multifocal leukoencephalopathy (PML). Imaging is useful for the diagnosis of cerebral lymphoma, especially to differentiate it from toxoplasmosis. But sometimes this difference is not obvious and it is after the failure of an antitoxoplasmic therapeutic test that the diagnosis of the cerebral lymphoma can be suspected. The radiological characteristics of lymphomas are: involvement or extension of the lesions to the corpus callosum, exclusive affection of the white substance, peri-ventricular localization, intra-ventricular contrast [19]. It represents 6 cases over 100 patients in the study of Holtzman et al [12] in the United States and 1 over 50 cases in that of Dore et al [11].

Other ICEP

Other causes of ICEP likely to result in epileptic seizures in patients living with HIV include cerebral abscesses, tuberculoma, cryptococcosis, nocardial abscess, syphilitic gum, etc.

Cryptococcosis Neuromeningitis

Its frequency varies between 5.5 and 22% in immune-depressed patients with HIV-AIDS [21]. It is 16% in a Burkinabe study [11] and 15.3% in that of Mbonda et al [17] in Cameroon in 2013. The diagnosis is confirmed by the examination of the CSF with China ink. The Sabouraud's culture and the search for cryptococcus antigen increase the diagnostic probabilities. This disease mainly affects patients with a CD4 cell count of less than 100 cells/µl. The cryptococcal meningitis is the encephalitis meningitis which produces the most epileptic seizures [3].

Tuberculous Encephalitis Meningitis

The epileptic seizures represent 10 to 16% of the tuberculous encephalitis meningitis [21, 22]. The diagnosis is clinical (basal meningitis) and by the microbiological study of the CSF (predominantly lymphocytic leukocytosis, hypoglycorachia, hyper-proteinorachy, hypochlorurachy and positive KB PCR in the majority of cases).

Other Etiologies of Meningitis

The epileptic seizures can sometimes be linked to encephalitis meningitis with various etiologies. These etiologies are caused by opportunistic infections in a proportion of 12 to 16% of cases [15]. The germs involved are syphilis, herpes zoster, toxoplasmosis, cysticercosis, CMV and aseptic encephalitis meningitis [7, 9]. Aseptic meningitis is common cause of seizure in HIV patients.

Progressive Multifocal Leukoencephalopathy (PML)

The PML is a demyelinating disease of the oligodendrocytes, caused by the JC virus. It occurs when the CD4 cell count is inferior to 100 cells/ul. The mechanisms of seizures are explained by the irritative action of demyelinating lesions near the cerebral cortex, the abnormalities of axonal conduction, and an imbalance between neurons and glial cells [23]. The diagnosis of certainty is made by detecting the DNA of the JC virus in the CSF.

Metabolic Causes

The metabolic disturbances are sometimes the cause of epileptic seizures in HIV immune-depressed patients. These disorders include hyponatremia, hypomagnesaemia,

hypocalcemia, hypoglycaemia and renal insufficiency. The hyponatremia is the most frequent, occurring in 35 to 55% of immunodepressed patients in hospitals [24]. This is due to the occurrence of the inappropriate syndrome of the antidiuretic hormone (SIADH), ionic losses of digestive origin or even septicemia.

Drug Causes

These causes are usually forgotten by the clinician whereas they deserve special attention. Indeed, HIV immune-depressed patients, besides their ART, benefit from various other medications which can justify an iatrogenic of seizures. Moreover, the clinician must carefully identify the medications that can lower the epileptogenic threshold. Non-nucleoside reverse transcriptase inhibitors (Effavirenz) are implicated as providers of epileptic seizures [25, 26].

Therapeutic Care

Antiepileptic drugs are needed to prevent the recurrence of seizures and also to improve the quality of life of patients.

Prior to prescribing antiepileptic drugs (AEDs) in patients living with HIV/AIDS under antiretroviral therapy (ART), some drug interactions should be considered.

Enzyme-induced AEMs associated with non-nucleoside reverse transcriptase inhibitors (INNRTI) or protease inhibitors (PIs) result in virological failure; and this relates specifically to the so-called old-fashioned AEMs, namely primidone, phenytoin, phenobarbital and carbamazepine [27], whereas these AEMs are the most accessible in our developing countries.

Other studies show that the carbamazepine and the phenytoin reduce the half-life of the nevirapine (INNRTI) [28]. The carbamazepine also reduces the plasma concentration of the Effavirens [29].

The valproic acid is advantageous because of its broad spectrum on all forms of epileptic seizures and also its lower cost compared to the new AEMs. It remains the drug of choice whereas these new AEMs are inaccessible, for it has two major advantages. In fact, the valproic acid does not induce any drug interactions causing virologic failure and also increases the plasma concentration of Ritonavir, Lopinavir (IP) and other INNTI [30,31].

The AEMs in immune-depressed patients should not be hepatotoxic, having low protein binding, fewer drug interactions, and side effects. The best AEMs recommended by the American Academy of Neurology are Levetiracetam, Lacosamide, Gabapentin and Pregabalin [27].

The duration of treatment for symptomatic seizures (reversible etiology) is 3 to 6 months with imaging control to ensure regression of the lesion. Sometimes, in case of refractory epilepsy, surgery or vagal stimulation may be necessary [32].

Conclusion

Epileptic seizures in patients living with HIV are frequent. Careful management should include an etiologic diagnosis and early treatment with AEMs taking into account their interactions with ARVs. This will allow for a good seizure monitoring and provide patients with a better quality of life. This suggests that in low- and middle-income countries a health policy should be pursued in order to make the new AEMs accessible to the vast majority of the population, especially for people living with HIV.

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