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High mortality rate and aetiologies of central nervous system infections among HIV-1-infected patients from Gabon.

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Abstract

Objective

In sub-Saharan Africa, data on acute central nervous system (CNS) infections observed in HIV-1-infected subjects are very scarce. The goal of this study, conducted in Gabon (Central Africa), was to assess the mortality rate and aetiologies of CNS infections among HIV-1-infected subjects, receiving or not highly active antiretroviral therapy (HAART).

Methods

From November 2009 to April 2010, a prospective case series study was conducted in two Gabonese cities. Standardized clinical, laboratory and imaging data were collected among HIV-1-infected subjects presenting an acute febrile neurological impairment.

Results

Of 22 cases (woman, 54%; median age, 43 years), all but three patients were untreated with HAART. A high proportion (60%) of subjects ignored their HIV serostatus before their neurological impairment. The main clinical presentation was encephalitis (80%). Among the patients who could be clinically followed-up (n=20), 10 (50%) died in a median time of 11 days. All of them were untreated with HAART. Aetiological causes were found in 12 patients as follows: toxoplasmosis (n=5), tuberculosis (n=3), bacterial infection (n=2), *Cryptococcus neoformans* (n=1), and neurosyphilis (n=1). CMV DNA was detected in plasma from six (27%) patients, combined with a HSV DNA positive result for three of them, and a HHV-6 DNA positive result for one.

Conclusion

Our study revealed that, among late-presenting, severely immunosuppressed HIV-1-infected adults, mostly untreated with HAART, acute neurological infections constitute a frequent and severe (mortality of ~50%) clinical entity, with a broad spectrum of aetiologies. It makes their diagnosis difficult to implement in resource-limited settings such as Gabon.

Introduction

By the end of 2010, around 5.0 million people were receiving highly active antiretroviral therapy (HAART) in sub-Saharan Africa. These promising results underline that nearly two thirds of people needing HAART failed to access to medical care and/or were unaware of their HIV serostatus, and consequently remained not treated [1]. In this context, HIV-1-related opportunistic infections (OIs), such as those affecting the central nervous system (CNS), still continue to occur among HIV-1-infected persons.

However, data are very scarce about CNS infections in Africa since infrastructure, access to neurological expertise, diagnostic capabilities (notably molecular techniques) and imaging facilities are quite limited, in comparison with developed countries [2]. Whereas there is a potential role for HIV subtype differences in varying neuropathogenicity [3], paired plasma/CSF HIV-1 RNA concentrations were rarely measured in Africa [4, 5]. For instance, in Gabon (Central Africa) where a high HIV-1 adult prevalence (~7%) and a wide HIV-1 genetic diversity have been previously described [6], the relationship between HIV-1 and neurological signs remains largely unknown.

The main objective of the present study was to assess mortality and aetiologies of acute febrile neurological manifestations observed in patients at different stages of HIV infection, and receiving or not HAART.

Methods

Between November 2009 and April 2010, our study prospectively recruited 22 HIV-1-infected adults admitted to three distinct public Gabonese hospitals from two cities (Libreville, the capital city, and Franceville) for suspected neurological disease. The study was approved by the Gabonese Ethics Committee, and consent was obtained from patients or accompanying relatives. Acute CNS infections were suspected with a fever or history of fever, and at least one of the following signs: reduced level of consciousness (Glasgow coma score <14); severe headache; neck stiffness; focal neurological signs; or convulsions. Patients with slide-positive cerebral malaria were not included in this study.

Patients underwent a full neurologic examination at the time of admission by a trained physician. They were clinically followed-up until day seven, 21 after admission and at the end of hospitalisation. At lumbar puncture, CSF was taken for cell count and differential protein, glucose, gram stain, specific research of *Cryptococcus* and bacterial culture. Blood was taken for toxoplasmosis and syphilis serology when possible. HIV serology was performed for subjects who ignored their HIV serostatus. Data were collected from each subject included gender, age, use of HAART and CD4⁺ lymphocyte T-cell counts (when available). HIV-1 RNA viral load (VL) measurements were done on paired CSF and plasma samples, by using the LTR-based real-time PCR Generic HIV Viral Load assay (Biocentric, Bandol, France) [7] with a low detection limit of 300 copies/ml. Spearman correlation coefficients were calculated to determine the relationship between HIV-1 RNA concentrations in CSF vs. plasma specimens.

The diagnosis of “probable central nervous tuberculosis” was done on the basis of a high level of proteins and a low level of glucose in CSF associated with CT pulmonary scan findings (miliary) and/or results of adenopathy biopsy. A good recovery under specific treatment was also considered for this diagnosis. The diagnosis of “probable cerebral toxoplasmosis” was done on the basis of CT scan findings associated with a good response under specific treatment.

Finally, qualitative home-made real-time PCR assays were performed in CSF and blood for

herpesviruses infections (including cytomegalovirus [CMV], herpes simplex virus [HSV], varicella-zoster virus [VZV] and human herpesvirus type-6 [HHV-6]), enterovirus, influenzae A virus, measles virus, mump virus and arboviruses (Rift valley fever, chikungunya, dengue and West Nile).

Results

Clinical presentation and aetiology spectrum

As shown in Table 1, a total of 22 patients were enrolled during our studied period. Their median age was 43 years (range, 27-68). Women were predominant (54.5%). A high proportion (~60%) of patients ignored their HIV status before their neurological impairment. The majority (73%) of patients were at advanced WHO clinical stages III or IV. All patients but three were untreated with HAART. The main clinical presentation was encephalitis (80%). Altered mental status was the main neurological manifestation with a median Glasgow coma score of 13 during admission. Focal neurological involvement was found in 50% and seizure in 18%. Among the patients who could be clinically followed-up (n=20), 10 (50%) died in a median time of 11 days. All of them were untreated with HAART.

A specific aetiology was identified in 12 patients whereas it remained unknown in 10 individuals (Table 1). The identified aetiologies of acute neurological manifestations in our population were as follows: (i) cerebral toxoplasmosis (n=5); these five patients presented focal neurological signs, seizure or confusion, CT scans were characterized by multiple lesions, associated with contrast enhancement; (ii) multifocal tuberculosis (TB) (n=3); these three individuals showed cerebral involvement associated with miliary or multiple tuberculosis lymphadenitis. All presented clinical signs of meningeal irritation; (iii) bacterial CNS infection (n=2); it included a meningo-encephalitis due to *Streptococcus B* and one case of multiple brain abscesses; (iv) cryptococcal infection (n=1); this patient had a positive cryptococcal antigen test in CSF and the cerebral CT scan disclosed a mass lesion non-enhanced in cerebellum, probably correlated with a cryptococcoma; and (v) neurosyphilis (n=1).

Biological results

As summarized in Table 2, the most common laboratory abnormality was an increase of proteinorachia in CSF (defined by a proteinorachia > 0.5g/l). The two patients who had bacterial

CNS infections showed a significant increase of their leucocyte counts in CSF. The median CD4⁺ T-cell count (n=12) was 78/mm³ (range, 7-494). All patients except two had CSF HIV RNA VL values higher in plasma than in CSF. The median plasma and CSF HIV viral load was 5.34 and 3.65 log₁₀ copies/ml, respectively. A significant correlation was obtained between CSF and plasma HIV-1 RNA levels (R=0.675, p<0.001).

By using real time PCR assays, CMV (n=6), HSV (n=3), and HHV-6 (n=1) DNA were detected in sera samples. Among these, three co-infections HSV/CMV and one co-infection HHV-6/CMV were obtained. Finally, one patient (subject #2) exhibited a positive result for both HSV and HHV-6 in his CSF sample.

Discussion

In sub-Saharan Africa, although behavioural prevention and HAART access efforts continue [8], opportunistic infections, including those affecting CNS, remain a major public health problem. Our study, conducted in Gabon, revealed that, among late-presenting, severely immunosuppressed HIV-1-infected adults, mostly untreated with HAART, acute neurological symptoms constitute a frequent and severe (mortality of ~50%) clinical entity. Further, in our studied population, ~60% of patients ignored their HIV status before their neurological impairment, strongly suggesting that neurological manifestations constituted the initial AIDS-defining illness.

It is well established that HAART significantly improves immune function and decreases HIV RNA levels [9, 10]. Consequently, the incidence of OIs has dramatically decreased, notably in developed countries where HAART coverage is much higher than in developing countries [11]. Unfortunately, in many African countries, such as in Gabon, HAART coverage is still insufficient (~50% in Gabon) [12]. In addition, OIs in these areas continue to occur, particularly in untreated subjects, ignoring their HIV serostatus. In sub-Saharan Africa, efforts to implement prophylaxis for HIV-related OIs are still important in preventing associated morbidity and mortality [2].

In our study, even if we found a correlation between CSF and plasma HIV-1 RNA levels, most of untreated patients showed higher HIV RNA levels in the plasma, suggesting that the CSF viruses may be mostly originated from plasma by diffusion across the blood-brain barrier. However, higher CSF VL values were observed for two patients without HAART, suggesting that the source might be in few cases the CNS itself, by a HIV self-replication within the brain. The clinical usefulness of HIV-1 RNA quantification in the CSF of patients with acute neurological diseases, or the effect of opportunistic diseases on CSF HIV-1 RNA levels remains controversial [5]. Prospective studies are further required to elucidate the clinical consequences of HIV RNA levels in CSF among patients with or without acute neurological infections.

In our resource-constrained setting, we were able to identify aetiological causes for about 50% of neurological HIV-related OIs. Toxoplasmosis and TB were the most frequent causes of febrile

central neurological infection, which is consistent with results obtained in other African countries among HIV-1-infected subjects [13-15]. Besides toxoplasmosis and TB, we were also able to identify other causes (such as bacterial infections, *Cryptococcus*, neurosyphilis), illustrating the large spectrum of aetiologies in HIV-1-infected individuals showing acute CNS signs.

Finally, we were able to detect *Herpesviridae* viruses in the plasma compartment of some patients. More precisely, CMV DNA was detected in six individuals, either alone (n=2) or associated with the presence of HSV (n=3) or HHV-6 (n=1) DNA. In one patient, HSV was also detected in the CSF compartment. As previously described by other researchers [16-20], CMV and HSV reactivations may occur in HIV-infected patients, mostly when they are not treated with HAART. However, their neurological significations remain largely unknown.

Our study has several limitations. The sample size was relatively small and cerebral imaging was not available for all patients. We did not perform PCR assays for tuberculosis, toxoplasmosis, and JC virus which may explain why we found a high proportion of unknown aetiological causes for neurological signs. However, based on our preliminary results, our group has decided to initiate a large-scale evaluation of neurological OIs observed in HIV-positive Gabonese subjects in order to define more precisely their prevalence rates and aetiologies.

In conclusion, our results strongly suggest the need to continue endeavours for providing HIV testing and counselling, to further increase HAART coverage in Gabon (which is around ~50% in 2010), and to use the new World Health Organization 2010 criterion ($CD4 \leq 350/\text{mm}^3$) for earlier treatment initiation. Providing regimens containing ARVs with high CSF penetration should also reduce CSF HIV-1 VL in the CNS and decrease morbidity and mortality by preventing or attenuating acute HIV-1-associated neurological signs. Due to the broad spectrum of aetiologies, the diagnosis of CNS OIs remains difficult in resource-limited settings, such as Gabon.

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