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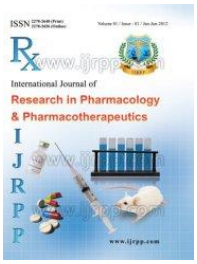

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Adverse neurological events due to antiretroviral therapy in Mali

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ABSTRACT

Introduction

Adverse neurological events during antiretroviral treatment (ART) are frequent and various1-3. Their diagnosis is difficult in developing countries where human resources and infrastructures are most of the time lacking.

Aim

To identify the frequency of neurological side effects in patients under ART in Mali

Methods

We performed a prospective cohort study on patients developing neurological symptoms in a period of 12 months at the Department of Infectious Diseases of the Teaching Hospital "Point G" of Bamako, Mali. Neurological diagnostic was established with the guidance of a neurologist. WHO's sides effects table has been used to characterize and classify the side effects4. Analysis of data was performed with SPSS Software, version 12.0.

Results

A total of 420 HIV seropositive patients under ART have been followed. Of those, 37 cases were found with adverse neurological events (8.08%). The sex ratio M/F was 1.06 and. the mean age was 41.2 years. Of the side effects, polyneuritis alone represented 83.8% of the cases, and polyneuritis associated to vertigo, headache and depression represented the remaining 16.2 %. We didn't notice any these neurological symptoms at the initiation of the ART. The majority of the patients was infected by HIV-1 (91.9 %). Most of the patients, 89.2% were treated with a fixed dose combination of Triomune® (D4T+3TC +Nevirapine). Five cases were at 3rd stage of WHO classification (13.5%), which justified stopping the treatment with d4T.

Conclusions

The use of Triomune® led to neurological adverse events in Mali. Any further new antiretroviral regimens must include a pharmacovigilance to detect eventual neurological side effects.

Keywords: Adverse neurological events, Pharmacovigilance, Antiretroviral therapy**,** Mali

INTRODUCTION

The acquired immunodeficiency syndrome (AIDS) is a global public health threat in many developing countries [1]. In Mali, the prevalence of the infection was 1.3% in 2006 [2]. AIDS has been shown to be associated with opportunistic and tumors development, which result from the infection and destruction of the T-helper lymphocytes [3]. The disease could impact the central nervous system and led to symptoms or disease such as cerebral toxoplasmosis, meningitis seizures, myelopathies, cerebral lymphomas, etc. Peripheral neurological symptoms may be caused by the neurotropism of the HIV itself or by cytomegalovirus or zoster virus [4]. Some studies in Togo indicated 2.4% of neurological symptoms are directly caused by antiretroviral treatment [5]. The most common symptoms were polyradiculoneuritis, mononeuritis and polynephritis [6]. In Mali, no study was conducted before on the neurological symptoms derived from antiretroviral treatment. Therefore, this particular study aimed to determine, the frequency of adverse neurological events associated with the use of ART in the country.

MATERIAL AND METHODS

The study has been conducted in the departments of Neurology and Infectious Diseases of the Teaching Hospital "Point G", where were located patients under antiretroviral therapy who developed neuropathies. It's a prospective cohort of any of those patients in a period of 12 months (from December 1st 2005 to November 30th 2006).

Our study population's sample size (N) was estimated using this formula

$N= \Sigma X^2pq/I^2$ with $\Sigma X= 1.96$ with 5% of margin error, P the estimated prevalence of the disease/condition according to some antiretroviral studies [7,8], q=1-p and I= precision of the results. From this formula, N=37 patients, is the number of patients with adverse events were needed for the study. All the patients had a medical report to collect the needed information. Participants have been well informed of the study and they all consented to participate and to answer our questions, to get physical examined and to undergo laboratory testing: socio-demographic data (age, sex, ethnicity, occupation) clinical data (AIDS stage, neurological symptoms, etc.), para-clinical (serology, CD4 count). Neurological diagnostic was established with the guidance of a neurologist and WHO classification of side effects was used [9]. Data analysis was performed using SPSS software version 12.0. For the ethics' aspect, the consent to participate into the study was required and patients' confidentiality was preserved.

RESULTS

In the 12 months of the study period (December 1th 2005 to November 30th 2006), 420 HIV infected and treated patients were enrolled. Of those enrolled, 37 (8.08%) developed neurological side effects. Of those with side effects, the most predominant sex was females with a ratio of 1.06 and the age range of 31 to 40 years was the most affected with 45.9%, and those with current occupation represented 32% of the cases. Importantly, 45.9% of our patients were classified as 4th grade infection of the WHO table and most of the patients were infected by HIV-1 (91.9%). Furthermore, we found a relationship between the clinical presentations and the etiological diagnostic with p= 0.94. Polyneuritis was confirmed in 83.3% of the cases, and the diagnostic was from the etiology of the disease in 75.7% of the cases (Table I). Of the therapeutic regimens in cause, d4T was the most common with 89.2% (Table II). The time occurrence of the adverse neurological events was most of the time between 1-3 months with 75.7% of the cases (Table III). It's worth to mention that the prognostic was stationer in 59.5% of the cases and B-complex vitamin was used for treatment in 42% of the cases. We also identified 5 cases at 3rd stage of WHO classification (13.5%), which justified halting the treatment with d4T; 11 cases were at 2nd stage (29.5%) and 20 cases at the 1st stage (54%).

Table I: Adverse neurological events

		Grading toxicity of WHO		
Adverse neurological events	Frequency	**Grade I**	**Grade II**	**Grade III**
polyneuritis	**31** (83.8%)	16	9	**5**
headache	3	2	1	0

Polyneuritis+ vertigo	2	1	1	0
Depressant syndrome	1	1	0	0
Total	**37**	**20(54%)**	**11(29.5%)**	**5(13.5)**

Table II: Drug regimens used by the participants

Drug regimen	Frequency	Percentage
D4T + 3TC + NVP	33	89.2
AZT + 3TC + EFV	2	5.4
AZT + 3TC + IDV	1	2.7
AZT + 3TC + DDI	1	2.7
Total	**37**	**100**

Table III: Time occurrence of adverse neurological events

Time	Frequence	Percentage
1 month	6	16.2
1-3 months	28	75.7
>3 months	3	8.1
Total	**10**	**100**

DISCUSSION

Our study was a prospective and descriptive cohort of 37 patients who developed side effects under ART. All the patients were enrolled in the Department of Infectious Diseases of the Teaching Hospital of "Point G" from December 2005 to November 2006. We faced during the study many technically difficulties due to the lack of infrastructures and human resources, and also due to the misunderstanding of some neuropathies by some patients or the existence of other possible causes of neuropathies in some patients. The prevalence of 8.08% observed in our study may not reflect the reality because of factors such as anemia due to the immunodeficiency, the prophylactic treatment by cotrimoxazole, or any treatment other than ART made difficult the positive diagnostic of side effects due to ART. However on the 420 HIV sero positives under ART, we have identified 37 cases (8.08%) of adverse neurological events, with mostly polyneuritis cases. Polyneuritis plus vertigo, migraine and depressive syndromes were also found to be adverse neurological events related to ART. Our prevalence is lower than the one from Mouhari-Touré et al, in Togo where he found 2.4% of adverse neurological events related to ART; however, polyneuritis was also the most frequent in his case [5]. This difference in the prevalence could be explained by firstly the fact that patients in Africa don't sometimes worry much about neuropathies, (and therefore don't report them) secondly, a smallest sample size in our case (37 against 297), and thirdly, their patients used a different regimen, Triomune® (Cipla, India). In our cohort the two genders were present but we had more females with a sex ratio of 1.06, but that may be due to a greater number of seropositive women under ART. The age range of 31-40 years was the most frequent (45.9%), but all the participants ranged from 26 to 66 years old. These results are similar to those of Millogo et al, in Burkina Faso, who found the predominance age range of 31-40 years [10]. These data revealed that the younger population is the most affected. 32% of our patients were from the informal sector, which is the same percentage found by Millogo et al, in Burkina Faso where reported that the majority of the patients were from the informal sector [11]. HIV-1 infection was the most frequent with 91.9% of the cases, and d4T was the first physicians' choice of

treatment. These data are similar to those of Millogo et al, who found 90% [12]. The CD_4 T-cells count has increased after one month of treatment. Millogo et al, have concluded that more the immuno depression is deep more the neurological manifestations associated to ART are particularly frequent [12]. Of our 37 patients, Vitamin B complex has been used with 16 patients and regimen modification has been made with 5 patients (grade 3 toxicity of WHO table). Other symptomatic treatments used were tranquilizers in 17.9% of the cases and tranquilizer + Vitamin B complex in 25% of the patients. It's known that adverse neurological events can be due to neurotoxicity from many antiretrovirals [15-18]. However d4T can induce dose-dependent neuropathies in a period of 3 months, particularly when combined with other anti retrovirals [19]. It is highly possible that one over dosage of d4T or vitamin deficiency during advanced stage of HIV infection could also contribute to increase the frequency of neuropathies. That could possibly explain the neurological side effects seen in our study. Patients with moderate to serious immuno depression are more likely to develop neuropathies [20]. A small CD4 count (<100/µl) is also a risk factor for developing peripheral neuropathies with nucleoside treatment [21].

CONCLUSION

Adverse neurological events during antiretroviral treatment are frequent and various. The neurological events are due to the use of Triomune®. Pharmacovigilance should be absolutely in place for all HIV drugs to detect eventual neurological side effects.

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DECLARATION OF INTEREST

The authors report no conflicts of interest.

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