Impact of alternative treatment approach for cerebral toxoplasmosis among HIV/AIDS patients from a resource-poor setting in Burkina Faso

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ABSTRACT. Cerebral toxoplasmosis is caused by the protozoan Toxoplasma gondii because of reactivation of latent tissue cysts in the Acquired Immunodeficiency Syndrome (AIDS) patients with severe immunosuppression. The objective of this study was to evaluate the benefit of co-trimoxazole in presumptive and prevention of cerebral toxoplasmosis in Human Immunodeficiency Virus (HIV)/AIDS patients at Bobo-Dioulasso Hospital in Burkina Faso from June 2012 to October 2014. ELISA and ELFA were performed on serum for the quantitative determination of IgG and IgM anti-T. gondii, respectively. The seroprevalence of toxoplasmosis was 29.3%. No IgM antibodies for T. gondii were found. Six patients with Toxoplasma-specific antibodies presented cerebral toxoplasmosis. All patients were infected by HIV-1 with the median of CD4⁺ T lymphocytes at 141 cells/µl. No patient was under antiretroviral therapy. No case of cerebral toxoplasmosis was noted in patients receiving co-trimoxazole in prevention. Presumptive treatment of cerebral toxoplasmosis with co-trimoxazole was effective in all patients with a significant clinical improvement in 83.3%. These results attest the benefit of cotrimoxazole in cerebral toxoplasmosis treatment in countries where drug resources are limited when sulfadiazine is not available. Ours finding highlight the importance of establishing toxoplasmosis chemoprophylaxis to HIV with severe immunosuppression patients and positive Toxoplasma serology.

Key words: cerebral toxoplasmosis, AIDS, ART, co-trimoxazole

Introduction

Toxoplasma gondii is an obligatory intracellular pathogen that infects a large proportion of the world population and is a well-recognized cause of illness among patients with AIDS [1]. T. gondii infection typically is latent and remains asymptomatic in both immunocompetent individuals and HIV-infected patients. However, patients with HIV are at 67 risk for developing acute toxoplasmosis due to reactivation of the pathogen if their CD4⁺ T-cell count decreases below 100 cells/µl [2]. Cerebral toxoplasmosis (CT) has become the most serious opportunistic infection due to its frequency, severity, and difficulties in therapeutic management in highly immunosuppressed patients (CD4⁺<100/µl). A low CD4⁺ T-cell count and positive toxoplasmic serology are strongly predictive of CT [2].
Unfortunately, lymphocyte count is not yet a routine examination in developing countries. Given the high risk of CT in advanced stages of HIV infection, anti-toxoplasmic chemotherapy should be widely proposed in HIV-infected patients with toxoplasmic serology. Among the molecules candidates for this primary prevention and currently available, such as pyrimethamine (Malocide), diisulone (Dapsone), macrolides (Clarithromycin), co-trimoxazole or trimethoprim-sulfamethoxazole (Bactrim®) were effectively used. Co-trimoxazole appears more interesting because of its double activity with respect to \textit{Pneumocystis jirovecii} and \textit{T. gondii}. If the superiority of co-trimoxazole to pentamidine aerosols in the prevention of pneumocystosis is confirmed by previous studies in both primary prophylaxis [3] and secondary prophylaxis [4], its efficacy in the primary prevention of toxoplasmosis remains to be demonstrated, in particular by carrying out a prospective study.

In Burkina Faso, particularly in the University Teaching Hospital, there is, to our knowledge, little study on toxoplasmosis among AIDS patients [5]. Co-trimoxazole which is distributed free in the monitoring of patients on anti-retroviral therapy (ART) could have a positive impact in the occurrence of opportunistic infections including CT. We conducted the present study in order to evaluate the benefit of co-trimoxazole in presumptive and treatment of cerebral toxoplasmosis in HIV/AIDS patients at Bobo-Dioulasso Hospital in Burkina Faso, a country where drug resources are limited.

Materials and Methods

Study area and inclusion criteria of patients. A cross-sectional study was conducted, involving 290 HIV-positive patients who were hospitalized for disorders of consciousness such as confusion or coma, epileptic crises, motor deficiency in a febrile or subfebrile context at the Department of Infectious Diseases at the Bobo-Dioulasso University Teaching Hospital from June 2012 to October 2014.

Bobo-Dioulasso Hospital is a reference centre of the West and South-west sub-region of Burkina Faso in the management of HIV-positive patients. This centre has nearly 4,500 people followed as ambulatory patients at the Day Hospital and nearly 350 annual admissions [6]. Screening of HIV-infected individuals for \textit{T. gondii} infection is not a routine practice in health care centres in Burkina Faso. Thus, the therapeutic care of patients with suspicious clinical signs of toxoplasmosis is based on the treatment proof [5].

Data collection. All the patients signed the consent after explanations about the research. For each selected patient, we have collected data during medical hospitalization. These data included socio-demographic, clinical, and biological data. The data of cerebral toxoplasmosis, levels of CD4+ T-lymphocytes, haemogram, and toxoplasmosis treatment, anti-retroviral therapy (ART), and cerebral scanner were obtained using the patients’ medical records.

The blood used for the study was collected by venipuncture in the Department of Infectious Diseases at the Bobo-Dioulasso Hospital, and then centrifuged, with the serum stored at -20°C in Ependorf tubes, and all properly identified. The serological analysis was performed at the Parasitology-Mycology Laboratory at the Bobo-Dioulasso Hospital.

Detection of IgG and IgM anti-\textit{T. gondii}. Enzyme-linked immunosorbtent assay (ELISA) was performed on serum by standard ELISA commercial Kit (AxSYM), Abbott, Laboratories, Abbott Park, III, USA) according to the manufacturer’s instructions. A titer of IgG anti-Toxoplasma antibody \(\geq 3\) IU/ml was considered positive in this study [7,8].

ELFA (enzyme-linked fluorescent assay) using VIDAS system (bioMérieux, Lyon, France), carried out as previously described for the quantitative determination of IgM anti-\textit{T. gondii}, with the following reference value for positive results: IgM > 0.65 [9].

Detection of infectious bacterial and fungal etiology. In case of suspicion of CT, a cerebral spinal fluid (CSF) was performed for the investigation of infectious bacterial and fungal etiology. Routine examination of cerebral spinal fluid (CSF) including direct examination with India ink followed by culture on Sabouraud agar for 3–5 days at 37°C. The preparation was read for about 10 min by two different microscopists. Serum and CSF cryptococcal antigen could not be systematically evaluated. Cryptococcal meningitis cases were retained if India ink preparation and/or culture were positive. At the same time, routine investigation for bacteria was performed including Gram staining, culture on seeding of brain heart infusion bottle, chocolate agar plates, and blood. Standard methods have been foreseen for identifying bacterial isolates.
Statistical analysis. The sample size was calculated based on the number of HIV-positive patients being followed in the Department of Infectious Diseases at the Bobo-Dioulasso Hospital, with a prevalence expectation of 50%, 5% error and confidence level of 95%, the minimum size to be calculated is 249 patients. The number of samples analysed was 290. The data collected were transferred to Epi Data version 3.1 for analysis. Chi-square test was also performed and differences were considered statistically significant when \( p < 0.05 \).

Results

During the study period, 290 persons infected with HIV participated in the project. The age of the patients ranged from 17 to 73 years old (average = 28). The sex ratio F/M was 1.1.

Out of the overall total 290 HIV-seropositive study participants included in this study, 85 (29.3%) were IgG anti-\( T. gondii \) antibody seropositive. The seroprevalence of toxoplasmosis among these 290 HIV patients was 29.3% (85/290).

No IgM antibodies for \( T. gondii \) were found among the HIV-positive patients. All patients with \textit{Toxoplasma}-specific antibodies presented high avidity indexes. No serology was repeated over time.

\textit{T. gondii} seroprevalence of anti-\( T. gondii \) seropositivity increased as age group and occupation status of the study participants increases. The differences were significant (Table 1). \textit{T. gondii} seroprevalence among the female participants was 33.7%. \textit{T. gondii} infection was not significantly associated (\( p > 0.05 \)) with gender of the study participants (Table 1).

According to epidemiological profile, six patients with \textit{Toxoplasma}-specific antibodies presented cerebral toxoplasmosis. The age of the patients ranged from 19 to 64 years old (average = 27) and they were mainly women (sex ratio F/M was 2).

Laboratory investigations showed that all patients were infected by HIV-1. Cerebral toxoplasmosis was inaugural in four cases. According to the levels of CD4\(^+\) T-lymphocytes, all of them presented severe immunodeficiency (less than 200 CD4\(^+\) T-lymphocytes/µl) (Table 1). The CD4\(^+\) T-cell count ranged from 72 to 1519 cells/µl with the median of 141 cells/µl ± 23.

In addition, haemogram noted a lymphopenia with an average of 677.44 ± 201.178 in all patients. Haemoglobin median rate was 10.9 g/dl with extremes from 5.9 to 14.9 g/dl with anaemia in 4 patients.

Moreover, the investigations for detection of infectious bacterial and fungal aetiology have not isolated any case of \textit{Cryptococcus} or bacteria.

Regarding clinical features, the main symptoms were headaches (83.4%) and fever (66.7%), followed by epileptic crisis, convulsions (33.3%) and consciousness disorders type coma, motor deficit (16.7%) (Table 2). One case presented consciousness disorders type coma. This patient benefited from a cerebral scanner performed with and without iodinated contrast medium injection with typical lesions (Fig. 1).

According to treatments characteristics, no
The patient was under antiretroviral therapy. Also, no patient had benefited co-trimoxazole in prevention. No case of cerebral toxoplasmosis was noted in patients receiving co-trimoxazole in prevention. However, the combination of co-trimoxazole (trimethoprim/sulfamethoxazole, TMP-SMX) was first used intramuscularly (15–75 mg TMP-SMX/kg/day without exceeding 12 ampoules/day for 3 to 5 days) and orally (5–25 mg TMP-SMX/kg PO) for 6 weeks [3]. This therapy has been successful in 83.3% of cases (4/5). The average duration of treatment was 43±19 days. Secondary prophylaxis with co-trimoxazole (160–800 mg TMP-SMX per day) was prescribed for five patients. No case of relapse was observed after a median follow up of 36 months of treatment. One patient dies prematurely within the first 48 hours of treatment. The lethality rate was 16.7% (1/6).

**Discussion**

The seroprevalence of anti-\textit{Toxoplasma gondii} IgG antibody noted in our study (29.3%) is higher than 25.4% in HIV-positive patients recorded by Millogo in another study in Burkina Faso [5]. In Gabon, cerebral toxoplasmosis was the most frequent diagnosis with 75 (64.7%) cases of neurological symptoms in HIV infected patients [10]. Shalaka et al. [11] noted 8.4% of cerebral toxoplasmosis among 227 patients analysis of HIV-related hospitalizations at Tripoli Medical Centre. In addition, Yohanes et al. [12] noted seroprevalence of latent \textit{T. gondii} infection at 88.2% among individuals infected with HIV in Arba Minch Hospital, south Ethiopia. In Malaysia, a few previous studies involving HIV-positive patients have reported seroprevalence in a range of 20–51% [13,14]. However, the seroprevalence of toxoplasmosis in HIV infected patients varies according to geographical areas. This variation is linked to eating habits, climatic factors and the age of the study population [14,15].

The non-detection of IgM antibodies in patients in our study is indicative that primo-infection by \textit{T. gondii} has not occurred. The diagnosis of active toxoplasmosis is usually expressed on the presence of IgM antibodies, but in people with HIV/AIDS, it is most often a re-infection, and IgM antibodies are missing since their low immunity response may lead them to produce antibodies at levels undetectable by these techniques [14,16].

Beside, molecular diagnosis using conventional PCR or other kids of PCR technique is also an important tool to detect toxoplasmosis [17,18]. However, in developing countries such as Burkina Faso, these new tools are not easily available for practitioners. Brain biopsy is the definitive diagnostic procedure [19,20]. This procedure should only be considered in patients with negative IgG anti \textit{Toxoplasma} and without good response to treatment [20].

Furthermore, the detection of specific IgG anti-\textit{T. gondii} antibody, therefore, indicates chronic infection with the parasite. Chronic infection of \textit{T. gondii} in HIV-infected patients is a risk for development of cerebral toxoplasmosis (CT), especially when CD4+ T-lymphocyte count falls below 100 cells/\textmu{}l [21,22]. \textit{T. gondii} is an important opportunistic parasitic infection in HIV-infected individuals. Cerebral toxoplasmosis has caused high morbidity and mortality, particularly in AIDS.
patients [23–25]. It is one of the complications reported in the HIV infection in developed countries where it is the first opportunistic disease during this viral disease [1,23]. Therefore, authors published a case of cerebral toxoplasmosis in the immunocompetent individuals. Cerebral toxoplasmosis does not appear only in HIV infected patients [26].

However, previous studies showed that different levels of anti-\(T.~gondii\) IgG antibodies were ineffective to determine a reactivation of cerebral toxoplasmosis [22,27]. Nevertheless, others suggested that high titers in patients might be indicative of the presence of cerebral toxoplasmosis or a higher risk of developing the disease [22,25,27]. In spite of these controversial results, our data confirm the necessity to determine anti-\(T.~gondii\) IgG antibody in the diagnosis of cerebral toxoplasmosis.

In our series, six (6/290) patients with Toxoplasma-specific antibodies presented cerebral toxoplasmosis. Millogo et al. [5] noted the hospital prevalence at 29.8% of CT at the University Hospital of Bobo-Dioulasso. Although the incidence of opportunistic infections has decreased since the introduction of HAART, ocular toxoplasmosis and cerebral toxoplasmosis still occurs in HIV infected patients [23,24]. In fact, Shalaka et al. [11] noted 8.4% of cerebral toxoplasmosis among 227 patients analysis of HIV-related hospitalizations at Tripoli Medical Centre. In addition, Coelho et al. [2] noted the incidence rates of cerebral toxoplasmosis at 6.0, per 1000 persons-year among 2835 HIV infected participants in Rio de Janeiro, Brazil. In another study, Kodym et al. [25] in their cohort of 502 HIV/\(T.~gondii\) co-infected patients recorded 21 cases of cerebral toxoplasmosis.

However, the median number of CD4\(^+\) T-lymphocyte in the six patients was 141 cells/\(\mu\)l. This finding is in agreement with those reported in the literature [2,21,23]. In clinical practice, CD4\(^+\) cell count is considered to be a prognostic or risk factor to monitor the progression of HIV infection individuals with low CD4\(^+\) T-cell count less than 200/\(\mu\)l coinfected with \(T.~gondii\) are at higher risk of reactivating the latent infection [2]. In AIDS patients, most cases of CT are due to reactivation of latent \(T.~gondii\) infection, and incidence of the disease is associated with low CD4\(^+\) T-cell count and \(T.~gondii\) IgG seropositivity [25,27]. These patients are also more at risk of multiple opportunistic infections in a short period of time of hospitalization [2,23,24]. Given the risk of occurrence of CT during the advanced stages of HIV infection, the anti-Toxoplasma chemotherapy should be widely proposed in patients infected with HIV who have a positive toxoplasmosis serology. Hence the need for a prophylactic treatment of toxoplasmosis in these cases. A low CD4 count and a positive toxoplasmosis serology are highly predictive of the occurrence of CT [23,25]. In the absence of anti-Toxoplasma gondii antibodies, dietary advice and hygiene must be reminded to avoid seroconversion which should be sought annually in immunocompromised patients (CD4<200/\(\mu\)l).

Furthermore, anaemia found in some patients was inflammatory and lymphopenia evidence of immunosuppression [25]. Indeed, anaemia and high CD8\(^+\) T-cell counts were factors indicative of cerebral toxoplasmosis in Dakar [28].

In current study, the diagnosis of cerebral toxoplasmosis compared to other brain diseases (microbial, cryptococcal) was performed. Indeed, cryptococcal meningitis is always one of the major AIDS-associated opportunistic infections and its prevalence has not decreased in most African countries [29]. In fact, at the Department of Infectious Diseases of the Bobo-Dioulasso Hospital, every meningeal syndrome is systematically investigated for bacterial and fungal aetiology from CSF. Therefore, these investigations have not isolated any cases of Cryptococcus or bacteria. Cryptococcal antigenemia was not coupled with direct examination and after CSF culture due to the lack of cryptococcal antigen detection kit during the study. The investigation for cryptococcal antigenemia could improve the sensitivity of Cryptococcus detection in our series.

According to cardinal signs of cerebral toxoplasmosis, the symptoms predominantly noted seem to be in accordance with the clinical pictures of CT as demonstrated by the outcomes of several authors [25,28]. Elsewhere, in Brazil, headache, strength deficit and fever were the most frequent signs and symptoms throughout the study conducted [2].

Nevertheless, clinical manifestations of toxoplasmosis are not specific to the disease outside the cerebral location in immunocompromised patients. In the diffuse encephalitic form, the picture is dominated by a confusional syndrome, consciousness disorders and generalized epileptic crisis [1,25]. However, impaired consciousness and
high CD8 T-cell counts were significantly associated with a higher mortality rate in CT [28].

In our study, cerebral scanner was carried out in one patient with CT before and after intravenous administration of iodinated contrast medium with multiplanar reconstructions. Brain lesions were unique or multiple, with peripheral oedema and mass effects. These results are very similar to the radiographic descriptions of cerebral toxoplasmosis [20,21] (Fig. 1). However, Deepak et al. [30] showed multiple ill-defined and nodular enhancing lesions in bilateral supratentorial and infratentorial neuroparenchyma on brain by Magnetic Resonance Imaging (MRI) procedure.

Furthermore, the realization of cerebral scanner, yet fundamental is difficult, due to the lack of financial resources because its cost is twice the Burkinabe minimum guaranteed inter professional salary (MGIS). Our findings show a high prevalence (100%) of chronic T. gondii infection. This, therefore, highlights the need for prevention of CT. Thus, current guidelines recommend the use of a double-strength tablet daily dose of trimethoprim/sulfamethoxazol in Toxoplasma-seropositive patients who have a CD4+ T-cell count below 100 cells/µl [23].

Regarding the therapy strategy, cerebral toxoplasmosis diagnosed early and starting treatment often evolves towards healing but sometimes with squealed [23]. The reference treatment is the pyrimethamine combination (100 mg on first day, then 1 mg/kg/day, 50–75 mg/day associated with 25 mg/day of folinic acid) and sulfadiazine (100 mg/kg/day, divided into 4 doses with a maximum of 6 g/day, for at least 6 weeks and until clinical and radiological response (disappearance of enhancement of lesions by the contrast agent). In the case of intolerance to sulphonamides, the alternative to sulfadiazine is clindamycin (2.4 g/day in 4 administrations trough intravenous or oral route. Others alternative treatments are available. Indeed Goswami et al. [31] among retrospective observational study reported higher efficacy and better tolerability of cotrimoxazole/clindamycin. Moreover, Deepak et al. [30] noted efficacy of trimethoprim/sulfamethoxazol and pyrimethamine/sulfadoxine for 3 weeks with a 20 year old gentleman HIV patient referred for multiple intracerebral lesions due to toxoplasmosis.

Furthermore, the use of intravenous cotrimoxazole (15–75 mg TMP-SMX/kg/day without exceeding 12 ampoules/day) or atovaquone (1,500 mg×2/day during a high-greasy meals and in combination with pyrimethamine or sulfadiazine or azithromycin in combination with pyrimethamine has also been proposed. In addition, presumptive therapy of toxoplasmosis should be started for all HIV positive patients with focal neurological manifestations in the absence of a cerebral scanner. In our study, without sulfadiazine and absence of a cerebral scanner, the combination of sulfadiazine and trimethoprim or cotrimoxazole was first used intramuscularly and orally in presumptive therapy of CT. This therapy has been successful in 83.3% of cases (4/5). This alternative is therefore useful when sulfadiazine is not available. Cotrimoxazole has other advantages such as lower cost, low adverse effects and availability of the generic form. Millogo et al. in the absence of sulfadiazine used sulfadoxine and pyrimethamine combination, firstly intramuscularly and then orally in the Internal Medicine unit of Bobo-Dioulasso Hospital [5]. This therapy has been successful in 75% of intracranial hypertension cases with focal neurological defects. This alternative is therefore interesting when sulfadiazine is not available. Our findings highlight the importance of presumptive therapy of toxoplasmosis for all T. gondii IgG seropositivity in AIDS patients with severe immunosuppression and focal neurological manifestations in the absence of a cerebral scanner.

However, regarding prevention strategy, mixed prevention (pneumocystosis and toxoplasmosis) includes the daily use of one tablet of cotrimoxazole. The low-dose (80/400) tablet provides comparable efficacy and less toxicity than the high-dose (160/800) tablet for the primary prevention of

### Table 2. Clinical and computed tomography characteristics in AIDS patients with cerebral toxoplasmosis in the Department of Infectious Diseases at Bobo-Dioulasso Hospital in Burkina Faso

<table>
<thead>
<tr>
<th>Clinical profile</th>
<th>Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headaches</td>
<td>5</td>
<td>83.4%</td>
</tr>
<tr>
<td>Fever</td>
<td>4</td>
<td>66.7%</td>
</tr>
<tr>
<td>Epileptic crisis/convulsions</td>
<td>4</td>
<td>66.7%</td>
</tr>
<tr>
<td>Consciousness disorders type coma</td>
<td>1</td>
<td>16.7%</td>
</tr>
<tr>
<td>Motor deficit</td>
<td>1</td>
<td>16.7%</td>
</tr>
</tbody>
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pulmonary pneumocystosis. The low dose (80/400) tablet also represents a possible alternative for the prevention of toxoplasmosis. Finally, two weekly discontinuous administration of two high-dose (160/800) tablets per day effectively prevents cerebral toxoplasmosis. No case of cerebral toxoplasmosis was noted in patients receiving co-trimoxazole in prevention treatment Therefore, none of the six patients who presented cerebral toxoplasmosis was under the prophylaxis with co-trimoxazole in our study.

Furthermore, it is important to note that no patient under prevention with co-trimoxazole showed a CT (Table 2). In addition, no patient with CT was on anti-retroviral therapy (ART) at admission. This means a high risk of reactivation of the disease or primo-infection. Antiretroviral therapy is indicated for HIV-positive asymptomatic patients who have CD4+ T-lymphocyte count inferior to 500/µl. Our findings highlight the interest of prevention with co-trimoxazole in countries as Burkina Faso where drug resources are limited in absence of secondary prophylaxis [23]. After an effective attack treatment the risk of recurrence of toxoplasmosis is inevitable in the disease or primo-infection. Antiretroviral therapy is indicated for HIV-positive asymptomatic patients who have CD4+ T-lymphocyte count inferior to 500/µl. Our findings highlight the interest of prevention with co-trimoxazole in countries as Burkina Faso where drug resources are limited in absence of secondary prophylaxis [23]. After a median follow up of 36 months, in our study, secondary prophylaxis with co-trimoxazole (160–800 mg TMP-SMX per day) was prescribed for five patients successfully.

Lethality rate was 16.7% after premature death of one patient within the first 48 hours of treatment. AIDS-associated toxoplasmosis remains a major cause of death, probably underestimated. The reasons are likely to include the advanced stage of HIV infection before treatment due to late screening, exposure to multiple possible opportunistic pathogens in a tropical environment [23].

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