Cerebro-meningeal infections in HIV-infected patients: a study of 116 cases in Libreville, Gabon.

Magloire Ondounda[1], Chinenye Ilozue[2], Caroline Magne[3]

1. Department of Infectious and Tropical Diseases, Hôpital d'Instruction des Armées Omar Bongo Ondimba, BP 20404 Libreville PK9, Gabon. magondounda@yahoo.fr
2. Department of Internal Medicine, Hôpital d'Instruction des Armées Omar Bongo Ondimba, BP 20404 Libreville PK9, Gabon. cilozue@doctors.org.uk
3. Department of Internal Medicine, Hôpital d'Instruction des Armées Omar Bongo Ondimba, BP 20404 Libreville PK9, Gabon. m2caroline@yahoo.fr

Abstract

Background: Cerebro-meningeal pathology is common in human immunodeficiency virus (HIV) infection and the aetiology is often difficult to ascertain with certainty.

Objective: To describe the major suspected and identified causes of meningeal or encephalitic syndromes in HIV infection in Libreville, Gabon.

Methods: A descriptive study using clinical records of patients hospitalised in the Department of Medicine in the Military Hospital of Libreville (Gabon) between January 2006 and May 2010. Clinical features were evaluated using multivariable logistic regression to evaluate association with the outcome of a clinical improvement or death.

Results: The most frequent neurological symptoms were reduced level of consciousness (54.3%), headache (55.2%), motor deficit (38.7%), and convulsions (36.2%). Cerebral toxoplasmosis represented 64.7% of diagnoses, followed by cryptococcal neuromeningitis in 12.9% of cases. Tuberculoma was diagnosed in 4 cases and lymphoma in 2 cases. In 9.5% of cases, no aetiology was determined. Toxoplasmosis treatment led to clinical improvement in 69.3% of cases with suspected cerebral toxoplasmosis. Overall mortality was 39.7%.

Conclusion: The diagnosis of neurological conditions in HIV positive patients is difficult, particularly in a low-resource setting. A trial of treatment for toxoplasmosis should be initiated first line with all signs of neurological pathology in a patient infected with HIV.

Keywords: Cerebral lesion, neuromeningitis, HIV, Libreville, Gabon.

Introduction

Neurological symptoms occur frequently in HIV positive individuals with the brain and meninges often the site of opportunistic pathology due to reduced immunity and the neurotropism of the virus[1,2]. Studies at autopsy have shown that the brain is the second most affected organ after the lungs in patients infected with HIV[3]. The most frequent cause of neurological disease in HIV seropositive patients is an infectious agent, principally Toxoplasma gondii, Cryptococcus neoformans and Mycobacterium tuberculosis in endemic areas[4,5]. These may present as a neuromeningitis syndrome with or without cerebral lesions visible on brain imaging. The differential diagnosis is wide and includes cerebral lymphomas, progressive multifocal leucoencephalopathy (PML), Cytomegalovirus (CMV), Aspergillus and Nocardia infection[1]. In Gabon, the HIV prevalence among adults is estimated at 5.3% and

Corresponding author:
Chinenye Ilozue,
Department of Internal Medicine,
Hôpital d'Instruction des Armées
Omar Bongo Ondimba,
BP 20404 Libreville PK9, Gabon.
P.O. Box 53300, London,
United Kingdom, N3 9AU,
Tel. +44(0)7779 104055
Fax. +44(0)208 3684426
Email: cilozue@doctors.org.uk

the population is also endemic for tuberculosis infection[6]. Toxoplasmosis is common with seroprevalence reaching over 70% in some areas[7]. The accurate diagnosis of these neurological conditions is difficult due to the variation in clinical features and this is even more challenging in a setting with limited technical diagnostic capabilities, notably a lack of cerebral biopsy[2,4]. The diagnostic approach is presumptive, despite evidence that there is poor accuracy of diagnosis without the gold standard of brain biopsy[2]. Most HIV-infected patients presenting with neurological symptoms are presumptively initiated on treatment for toxoplasmosis with the addition of broad spectrum antibiotics and tuberculosis (TB) treatment depending on therapeutic response. Diagnostic guidelines for the industrialised countries of Europe and the USA may not be appropriate for developing countries as the aetiologies of brain lesions differ. Thus the clinical evolution is often the cornerstone for assessing diagnostic accuracy[4].

The objective of this study was to describe the principal diagnoses of neurological diseases in adult patients infected with HIV at the military hospital of Libreville, Gabon. The clinical outcomes of these conditions were also described.

Methods

This retrospective descriptive study was carried out in the department of medicine at the military hospital of Libreville, Gabon (l'Hôpital d'Instruction des Armées Omar Bongo Ondimba, HIA OBO). This is a large tertiary hospital providing medical (internal medicine, cardiology, respiratory, neurology, infectious diseases), surgical (general surgery, cardiothoracics, ear, nose & throat, gynaecology, orthopaedics, ophthalmology), paediatric and maternity services to the local population. Diagnostic facilities are relatively comprehensive and include computed tomography (CT) in the radiology department and laboratory services.

Medical records of patients admitted between January 2006 and May 2010 were examined retrospectively. We included adult patients (age >18 years) with positive HIV-serology, with at least one of the following: A clinical presentation of meningitis or encephalitis, a motor deficit, an abnormal brain scan (CT or magnetic resonanceimaging, MRI) or cytological, biochemical or microbiological abnormalities of cerebrospinal fluid (CSF). There was no post-mortem evidence available from the patients who died to contribute to the definitive diagnosis.

Patients with unknown or indeterminate HIV status and those with incomplete medical records were excluded (all patients presenting for acute admission in the department of Medicine at HIA OBO receive an HIV test and thus this represented a minimum of cases. Many patients had been previously diagnosed with HIV infection and were known to the department of Infectious Diseases). Details of the clinical features and outcome were collected on a standardised data sheet for each case.

The database was created with EpiInfoTM 3.5.1. Demographic and clinical features were analysed to identify any associations with the outcome measures of "clinical improvement" and "death". Multivariable logistic regression was performed using SPSS 17.0.

The study was carried out in full compliance with all ethical principles for medical research involving human subjects as set out in the Declaration of Helsinki

Results

One hundred and sixteen records were included in the series. The median age of the patients was 40 years (range 19-73 years), with a male:female ratio of 1:32. The median delay to consultation was 7 days (range 1-60 days). (Table 1)

The predominant non-pecific symptoms were fever in 62 (53.4%) patients and asthenia in 44 (37.9%). The most frequent neurological symptoms were headache in 64(55.2%) patients, reduced level of consciousness in 63 (54.3%) patients, motor deficit in 46 (38.7%) and seizure in 42 (36.2%). Sixty-four patients exhibited more than one clinical symptom/sign.

Cerebral CT or MRI scan was performed in 88 (75.9%) patients of which 48 (54.5%) had cerebral oedema and 46 (52.3%) had a cerebral abscess with a mass effect in 35(39.8%). Multiple cerebral lesions were found in 31 (35.2%) patients. Twenty-three (26.1%) patients had a normal CT brain scan. CSF analysis was carried out in 64 patients of which 11 (17.2%) had no abnormality. The majority of CSF analyses had subtle abnormalities of glucose and protein.

Cerebral toxoplasmosis was the most frequent diagnosis with 75 (64.7%) cases, of which 44 (58.7%) had cerebral abscesses (26 with multiple lesions) and 6 had another pathology diagnosed on the same admission. The diagnosis was made based on clinical symptoms, features of CT/MRI brain imaging and positive therapeutic response. Cryptococcal neuromeningitis was the second most frequent diagnosis, found in 15 patients (12.9%). This diag-

nosis was confirmed by detection of C. neoformans in the CSF. India ink was positive in 14 cases and cryptococcal polysaccharide antigen was detected in one patient. Bacterial meningitis and stroke occurred in 8 (6.9%) and 6(5.2%) patients respectively. In the absence of a formal diagnosis, the presumptive diagnosis of cerebral tuberculoma (TB) was made in 4 patients and lymphoma in 2 patients. There was dual pathology diagnosed in 7 (6%)

of cases, the majority including toxoplasmosis with tuberculosis (TB), cryptococcal neuromeningitis, immune reconstitution inflammatory syndrome (IRIS), stroke (not definite) and pyogenic abscess. Cryptococcal neuromeningitis with TB was also a dual diagnosis made in 1 patient. In 9.5% of cases (11 patients) the diagnosis was undetermined due to the patients dying before investigations could be carried out. (Table 1)

Table 1: Demographic, clinical and diagnostic profile of total population

	N = 116
Age (years) Median (range)	40.0 (19-73)
Sex: male N(%)	66 (56.9)
Delay to consultation (days) Median (range)	7.0 (1.0 - 60.0)
Length of hospital stay (days) Median (range)	15.0 (1.0 - 72.0)
Diagnosis [n (%)] **Toxoplasmosis**	69 (59.5)
Cryptococcal Neuromeningitis	12 (10.3)
Tuberculosis	2 (1.7)
Bacterial meningitis	8 (6.9)
Stroke (Ischaemic/Haemorrhagic)	5 (4.3)
Lymphoma	2 (1.7)
Joint diagnoses	7 (6.0)
− **Toxoplasmosis & TB,**	1 (0.9)
− **Toxoplasmosis & Cryptococcal NM**	2 (1.7)
− **Toxoplasmosis & IRIS**	1 (0.9)
− **Toxoplasmosis & ?Stroke**	1 (0.9)
− **Toxoplasmosis & pyogenic abscess**	1 (0.9)
− **Cryptococcal NM & TB**	1 (0.9)
Others (unknown)	11 (9.5)
CD4 count (/mm^3) Median (range)	68.0 (1.0 - 764.0)
On ART at time of diagnosis [n/N (%)]	21/78* (26.9)
HIV/AIDS presenting illness [n (%)]	38.0 (32.8)
Outcome [n (%)] - **Improvement**	64 (55.2)
- **No improvement/relapse**	5 (4.3)
- **Died**	46 (39.7)
- **Unknown**	1 (0.9)

NM - neuromeningitis ; IRIS - immune reconstitution inflammatory syndrome ; TB - tuberculosis ; ART - antiretroviral therapy ; HIV - human immunodeficiency virus ; AIDS - acquired immune deficiency syndrome
*78 patients previously diagnosed with HIV.

At the time of diagnosis of the neurological condition, 38 patients (32.8%) were unaware of their HIV status and 26.9% of those with known HIV infection were receiving antiretroviral treatment (ART). The median CD4 lymphocyte count was $68/mm^3$ with a range of $1-764/mm^3$. Sixty-four (55.4%) patients showed clinical improvement, defined as improvement in clinical signs and symptoms within 2 weeks and/or improvement in radiological appearances up to two months after treatment. All of the 75 patients diagnosed with toxoplasmosis received pyrimethamine and sulfadiazine treatment with folic acid, resulting in a clinical improvement in 52 (69.3%). Patients with other diagnoses received various combinations of treatments according to the individual context, namely-antibiotics, antifungals, antiparasitic and antituberculosis treatment. The median length of hospital stay was 15 days (1-72). Overall mortality was 39.7%.

In the multivariable logistic regression analysis, evaluating the clinical features associated with the outcomes of clinical improvement or death, shorter length of stay, male sex and reduced level of consciousness were associated with death. Presence of a cerebral abscess (OR 0.002, 95%CI 0.0001-0.131, p=0.004) and a diagnosis of toxoplamosis (OR 0.02, 95%CI 0.001-0.48, p=0.015) were inversely associated with death. Age, CD4 count, prior ARV therapy and delay to consultation did not appear to have any correlation with mortality in this population. A clinical improvement was associated with a diagnosis of toxoplasmosis and higher CD4 count. Male gender, altered level of consciousness and a cerebral lesion with mass effect had an inverse relationship with a good clinical outcome. (Table 2)

Table 2: Results of multivariable logistic regression analysis of variables associated with clinical outcomes.

Variable	Clinical Improvement n=64 R²=0.641			Died n=46 R²=0.678		
	Median (range) N (%)	Odds Ratio (95% CI)	p-value	Median (range) N (%)	Odds Ratio (95% CI)	p-value
Age (years)	39 (21-67)	0.94 (0.83, 1.07)	0.339	41 (19-73)	0.99 (0.87, 1.13)	0.911
Sex (male)	31 (48.4)	0.08 (0.01, 0.65)	0.018	30 (65.2)	29.2 (1.57, 540.4)	0.024
Length of stay (days)	18 (3-72)	1.04 (0.98, 1.11)	0.228	8 (1-45)	0.92 (0.86, 0.99)	0.027
Delay to consultation (days)	7 (1-34)	0.97 (0.87, 1.08)	0.563	9 (3-60)	1.02 (0.90, 1.14)	0.799
CD4 count (/mm³)	51.5 (3-764)	1.01 (1.00, 1.02)	0.047	79 (1-475)	0.99 (0.985, 1.00)	0.199
Fever	38 (59.4)	2.42 (0.25, 23.6)	0.447	21 (45.7)	0.50 (0.04, 5.77)	0.579
Asthenia	23 (35.9)	0.17 (0.02, 1.58)	0.119	19 (41.3)	8.47 (0.63, 113.2)	0.106
Weight loss	17 (26.6)	0.98 (0.16, 5.89)	0.980	15 (32.6)	0.38 (0.04, 3.37)	0.387
Headache	32 (50.0)	0.73 (0.13, 4.08)	0.721	29 (63.0)	2.14 (0.29, 16.1)	0.459
Reduced consciousness	33 (51.6)	0.09 (0.01, 0.73)	*0.025*	29 (63.0)	21.9 (1.74, 274.1)	0.017
Convulsions	29 (45.3)	2.45 (0.39, 15.5)	0.340	12 (26.1)	0.16 (0.01, 1.92)	0.150
Hemiplegia/Hemiparesis	27 (42.2)	0.57 (0.84, 3.80)	0.558	15 (32.6)	1.19 (0.14, 9.93)	0.873
Psychomotor agitation	20 (31.3)	4.32 (0.50, 37.3)	0.184	7 (15.2)	0.43 (0.04, 4.77)	0.495
Meningism	9 (14.1)	0.67 (0.07, 6.76)	0.733	7 (15.2)	1.21 (0.09, 16.5)	0.884
Visual symptoms	8 (12.5)	0.83 (0.07, 9.95)	0.880	5 (10.9)	0.19 (0.01, 7.21)	0.368
Cerebral abscess	34 (53.1)	148.7 (1.9, 11680.6)	*0.025*	10 (21.7)	0.002 (0.0001, 0.131)	0.004
Multiple cerebral lesions	15 (23.4)	0.14 (0.02, 1.29)	0.083	14 (30.4)	8.26(0.63, 108.4)	0.108
Cerebral oedema	32 (50.0)	7.21 (0.39, 134)	0.186	13 (28.3)	3.02 (0.06, 150.4)	0.579
Cerebral lesion with mass effect	22 (34.4)	0.004 (0.00, 0.38)	0.017	9 (19.6)	48.3 (0.92, 2528.4)	0.055
Normal CT	10 (15.6)	7.72 (0.59, 101)	0.119	13 (28.3)	0.16 (0.01, 2.65)	0.203
Prior ARV therapy	12 (18.8)	5.13 (0.37, 71.2)	0.223	7 (15.2)	0.05 (0.002, 1.299)	0.072
HIV/AIDS presenting illness	20 (31.3)	2.14 (0.24, 18.7)	0.493	15 (32.6)	0.09 (0.01, 1.19)	0.067
Diagnosis of toxoplasmosis	52 (81.3)	54.1 (3.77, 776)	0.003	20 (43.5)	0.02 (0.001, 0.48)	0.015

Discussion

Central nervous system disorders associated with HIV infection occur most commonly at an advanced stage of immunosuppression[8,10]. In Gabon, neurological disease-associated with HIV infection is poorly described, most likely due to the lack of diagnostic resources, particularly stereotactic biopsy. Thirty-eight of our patients were-unaware of their HIV serological status and presented in clinical stage 3 according to the Centre for Disease Control (CDC) criteria[11]. Similar late first presentations of HIV/AIDS have been described in other series. This diagnostic delay may be linked to the poor participation in voluntary testing for HIV due to stigmatisation and-discrimination associated with the diagnosis[12,13]. This is compounded by issues of poor access to health care and cultural and traditional beliefs that cause such late presen-tation in Gabon and other African regions where many people still believe that AIDS is a disease of misfortune and prefer "traditional medicine" interventions[12].

The difficulty in establishing a diagnosis is due to the non-specific nature of the symptoms. Space-occupying intracerebral lesions often present with ill-defined neuro-logical signs and symptoms. Cerebral imaging (CT/MRI), although an important contributor to the diagnosis of brain lesions, is limited by the relatively poor specificity of the images observed. This results in great difficulty establishing a diagnosis with certitude, especially in a set-ting of limited human resources[8,14].

Cerebral toxoplasmosis remains the principal aetiology of intracranial space occupying lesions (SOL) and the number one opportunistic infection of the nervous sys-tem in patients infected with HIV[8,15,16]. Single or multiple cerebral abscesses are most frequently observed, and dif-fuse encephalitis (with normal CT appearance) is rarer[2,8]. In our study, 58.7% of patients suspected of toxoplasmo-sis had one or more space occupying lesions. Toxoplasma gondii serology would have contributed little to the diag-nosis but negative serology may have made the diagnosis less likely[17,18]. Twenty percent of our patients presenting with neurological symptoms had a normal CT brain scan which did not eliminate the diagnosis of cerebral toxo-plasmosis[19]. The problem arises when there is lack of clinical improvement with anti-toxoplasmosis treatment (as judged appropriate). In these cases the difficulty is in

knowing if the case represents an authentic toxoplasmo-sis unresponsive to treatment or another opportunistic or associated pathology, making the evaluation of the pre-sumptive treatment very difficult using outcome criteria alone[2]. Cerebral biopsy, with sensitivity upto 93%,[20] be-comes even more important in such cases.

In our study a trial of treatment with anti-toxoplasmosis agents in those with a presumed diagnosis of toxoplas-mosis led to clinical improvement in 69.3% of patients, a result similar to that found in other studies[21].

In endemic countries the appearance of cerebral tuber-culoma is associated with HIV infection[22,23]. However, in our experience, extrapulmonary forms of TB can often-occur independently of HIV status[24]. The clinical signs of cerebral tuberculoma are generally those of any space occupying lesion and the diagnosis is difficult by means of CT or MRI in the absence of a clinical context of pro-gressive TB. A diagnosis of certitude is made possible by bacteriological data and histopathology. In our study, in-the absence of clinical improvement with anti-Toxoplas-ma treatment, the diagnosis of tuberculoma was made in 4 patients presenting with progressive pulmonary TB disease (miliary TB). Cerebral lymphoma was presumed in 2 cases. Lymphoma represents 2% of cerebral masses in AIDS and appears most often at advanced levels of immunosuppression and lower CD4 counts[25,26]. In this study the median CD4 count was 68/mm^3 with a mini-mum count of 1/mm^3, which is concordant with other studies showing equally advanced stages of immunocom-promise in CNS disease[2,27,28].

Cryptococcal neuromeningitis is another very common cause of neurological disease in HIV positive patients[5,29]. The diagnosis rests on identification of the fungus in the CSF by either india ink staining, the detection of the polysaccharide antigen or culture. However, in AIDS, CSF changes are sometimes atypical and non-specific,making the diagnosis of any neurological infection troublesome[2]. We diagnosed 15 cases of cryptococcal neuromeningitis, representing 12.9% of aetiologies and the second cause of CNS opportunistic infection in this population, simi-lar to that found in other regions of sub-Saharan Africa[5,29,30]. Other neuromeningeal manifestations may be attrib-utable to cytomegalovirus, herpes virus or JC virus. None of these aetiologies were found in our population, likely

due to diagnostic limitations. Seven of the patients had more than one pathology and 11 had no diagnosis made. Previous studies have remarked on the concurrence of several pathologies in a single cerebral lesion in HIV positive patients[2,5].

Overall mortality was 39.7% and there were proportionally fewer deaths in patients diagnosed with cerebral toxoplasmosis compared to other diagnoses. However, several patients died before a diagnosis could be made. In these cases autopsy studies would be of great diagnostic utility[3,9]. In this setting autopsy is not common practice.

The primary limitations are inherent to all retrospective studies: the medical records often had missing information and a number of useful investigations were not carriedout at the time of hospitalisation for a large number of patients. This limits the amount of information that could be obtained and reduces the applicability of the logistic regression models. Secondly, each diagnosis (except cryptococcosis and bacterial meningitis that were proven on CSF) was presumptive, resulting in a limitation in comparative analyses between pathologies. Some HIV positive patients presenting with headache as the only manifestation of neuro-meningeal disease would have been excluded from the analysis, potentially missing important information. There is a risk of selection bias significantly affecting the series in that certain patients may have been excluded due to this lack of neuro-meningeal manifestation and, perhaps, indeterminate HIV test at admission. These potentially HIV positive patients may have been infected by other organisms that have been missed by this series.

This descriptive study of neurological conditions in HIV positive patients identified cerebral toxoplasmosis as the principal diagnosis., As such, empirical treatment for cerebral toxoplasmosis in a HIV positive patient seems reasonable in the context of cerebromeningeal pathology, especially if the CT is suggestive(e.g. demonstrating a cerebral abscess). Other diagnoses such as cryptococcal meningitis, bacterial meningitis and stroke must also be considered as described in this population. The occurrence of multiple pathologies must also be borne in mind by clinicians as demonstrated by the results of this study. The beneficial role of prophylaxis against opportunistic infections is incontestable and must be a priority in the management of HIV positive patients in this setting.

There must also be strengthening of preventative programmes and HIV voluntary testing so that patients are not diagnosed at such late stages of disease.

Conflicts of interest
None to declare

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