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EPIDEMIOLOGICAL ASPECTS, ETIOLOGIES AND CLINICAL OUTCOME OF MENINGITIS IN HIV-INFECTED PATIENTS IN THE SOUTHERN PROVINCE OF RWANDA

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ABBREVIATIONS

AAU	Association of African Universities
AIDS	Acquired Immune Deficiency Syndrome
CD_4	Cluster of Differentiation
CHUB	Centre Hospitalier Universitaire de Butare
CHUK	Centre Hospitalier Universitaire de Kigali
CMV	Cytomegalovirus
CNS	Central Nervous System
CSF	Cerebro-spinal Fluid
EBV	Epstein Barr Virus
HAART	Highly Active Anti Retroviral Treatment
HIV	Human Immune-deficiency Virus
HSV	Herpes Simplex Virus
NUR	National University of Rwanda
PNILT	Programme Nationale Integré de Lutte contre la Tuberculose
TB	Tuberculosis
VDRL	Venereal Disease Research Laboratory
WBC	White Blood Cell

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ABSTRACT

Background: Meningitis associated with HIV/AIDS has an important impact considering morbidity and mortality. In Rwanda yet no study has been conducted on epidemiological aspects, etiologies and clinical outcome of meningitis in HIV-infected patients in the southern province of Rwanda.

Objectives: this study was conducted to assess the epidemiological aspects, the etiologies and the clinal outcome of meningitis in HIV-positive patients.

Methods: Data were collected onto paper questionnaires about socio demographic and clinical data; then entered onto the computerized questionnaires driven by epi-data software. The final analysis was done with the help of SPSS (version 14.0). As threshold for the statistical tests we used a p value of <0.05

Results: Between 2001 and 2006, in a total number of 495 hospitalized HIV-positive patients, 86 cases (17.37%) of meningitis have been recorded. Three types of meningitis where observed: Cryptococcus (64%), tuberculous (24.4%) and bacterial (11.6%). Headache, high fever, neck stiffness, Kernig sign and vomiting are the most frequent signs in all types of meningitis seen in this study. laboratory diagnostic of Cryptococcus meningitis is easier and highly specific using Indian ink (p=0.000), the diagnosis of tuberculous meningitis is presumptive while bacterial meningitis is mainly based on CSF biological findings. The CSF protein were more useful to differentiate between the types of meningitis (p=0.000). Among 55 patients with Cryptococcus meningitis 40% died. 28.6% of TB meningitis patients died. For bacterial meningitis patients, 60% died. The chances to recover are increased in patients who survive the first 14 days of treatment (p=0.001).

Conclusion: This study shows that meningitis still has a high prevalence in HIV-positive patients, with Cryptococcus neoformans being the leading cause.

I. Introduction

Promising developments have been seen in recent years in global efforts to address the AIDS epidemic. But on the other hand the number of people living with HIV continues to grow as does the number of deaths due to AIDS. A total of 39.5 million people were living with HIV in 2006 (2.6 million more than in 2004). Sub saharian Africa continues to bear the brunt of the global epidemic: Two thirds (63%) of HIV-infected persons live in Sub Saharian Africa with its epicentre in southern Africa. One third (32%) of HIV-infected persons live in southern Africa and 34% of all death occur there.

Rwanda is also concerned by this epidemic disease. Of a total population of 8 440 820 in 2005, the estimated number of people living with HIV/AIDS was 190 000. The number of deaths due to AIDS was 21 000.

Frequently HIV doesn't kill directly. Instead, it weakens the body's ability to fight disease. Infections which are rarely seen in those with normal immune systems are life-threatening to those with HIV. Many opportunistic infections cause different severe affections such as several pulmonary diseases, chronic diarrhea, neurological defects, and different bacterial, parasitic and fungal infections. Among those affections meningitis associated with HIV/AIDS has an important impact considering morbidity and mortality.

Different forms of meningitis are associated with HIV infection. They can be classified according to the etiologic agent as cryptococcal, tuberculous, syphilitic, Listeria species, etc. Others are lymphomatous or aseptic. Fungi are common in HIV-positive patients but HIV predisposes to several viral and bacterial infections that can result in meningitis.

In 1996, BERGMAN and KARSTAED (1) showed at Bargwanath Hospital that 37.3% of all HIV infected patients have meningitis. ELI SILBER et al. (5) revealed a co-infection of 66.7% at Goldfields West Hospital in 1999 in the same country. In a prospective study done in Zimbabwe, a meningitis and HIV/AIDS co-infection of 80% was documented by HAKIM et al. (9) in the patients hospitalised in internal medicine department during 2000.

So far two studies (CHUK Department of internal medicine) have been performed on this co-infection in Rwanda. The first was done by BOGAERTS et al. (8) between 1983 and 1992 showing a Cryptococcus meningitis co-infection rate of 19%. The second was done by NDUWIMANA in 2002 and 79.3% of all meningitis cases had the co-infection Meningitis and HIV/AIDS.
As there was no previous similar study done in the southern region we have been motivated to conduct this study with the following objectives:

- Identify epidemiological aspects of meningitis in HIV-Infected patients: prevalence and mortality among patients hospitalized in CHUB
- Identify the frequent etiologies of meningitis in HIV-Infected patients
- Identify the mortality rate of meningitis in HIV-Infected patients
- Identify the prognostic factors of death in affected patients

II. BACKGROUND

II.1. Physiopathology of Meningitis

II.1.1. Meninges

Meninges are three layers of membranes that surround the brain and spinal cord. The outer layer, dura mater, is tough white fibrous connective tissue. The middle layer of meninges is arachnoid, a thin layer resembling a cobweb with numerous threadlike strands attaching it to the innermost layer. The space under the arachnoid, the subarachnoid space, is filled with cerebrospinal fluid and contains blood vessels. Pia mater is the innermost layer of meninges. This thin, delicate membrane is tightly bound to the surface of the brain and spinal cord and cannot be dissected away without damaging the surface.

II.1.2. Cerebrospinal fluid

Cerebrospinal fluid (CSF) is an uncolored fluid with density around 1.005 mg/ml that flows within the ventricles of the brain, the central canal of the spinal cord and out to the subarachnoid spaces surrounding the brain and spinal cord, effectively floating these two structures. The normal protein level is 20 to 30mg/100ml. The lymphocytes are less than 5 per ml. The pH value is 7.3. It serves as a medium for the transfer of substances between the blood and the nervous tissues as well as a liquid buffer, absorbing mechanical shocks to the brain or the cord. Most of CSF is provided by the choroid plexuses that reside in lateral, third and fourth ventricles. In adults, the volume of is 125 to 150 ml. It is in continuous formation, circulation and absorption.

II.1.3. Pathogenesis

II.1.3.1. Definition

Meningitis can be defined as inflammation of the subarachnoidal space and meninigis without direct involvement of brain parenchyma (Hammer and Collony 1992 (6)). If the brain itself is infected the condition is called encephalitis whereas a combination of both is called meningio-encepalitis.

II.1.3.2. Physiopathology

The most common causative organisms of community-acquired bacterial meningitis are S. pneumonia and N. meningitidis. Frequently the patient suffered pneumonia, an acute otitis media or an acute sinusitis before the onset of meningitis. Less commonly L. monocytogenes, gram negative cocci, enteric gram negative bacilli and H. influenza are responsible.
N. meningitides colonizes the nasopharynx even in many healthy people the risk of meningitis depends on the virulence of the bacteria and the immunity of the host.
They are attached to the epithelial mucosa before they pass to general infection by haematogenous invasion. Because of decreased defense of immune system, they will pass over the blood-brain barrier and will proliferate in CSF. This liquid has no sufficient mechanisms of defense and there will be a secretion of inflammation mediators such as cytokine, interleukins 1 and 6, prostaglandins, and so on. These mediators will cause meninges inflammation, and then white blood cells and proteins

will appear in the CSF. The vasogenic oedema of brain is due to an increase of blood-brain barrier permeability combined with effects resulting in secretion of cytokines and leucocytes degranulation; while the cytotoxic oedema of the brain is due to cytotoxic products from micro-organisms. All these effects will increase intracranial pressure.

II.2. Meningites in HIV infected adults

Although HIV-positive individuals are at increased risk of certain types of meningitis, typically cryptococcal and tuberculous, evidence suggests that they are also more likely than the general population to develop community-acquired bacterial or viral meningitis. An early form of aseptic, HIV-associated meningitis develops within days to weeks after HIV infection. It appears as a mononucleosis-like illness and is rarely associated with encephalitis. Meningitides due to Cryptococcus, coccidioidomycosis, histoplasmosis, or other fungal infections are AIDS-defining events and occur typically with very low $CD4^+$ lymphocyte counts.

In Zimbabwe, HAKIM et al. (9) showed a decrease of purulent meningitis in adult hospitalised patients and an increase of TB and Cryptococcus meningitis. This was attributed to a rapid growth of this epidemic infection to HIV/AIDS. In this study meningitis was one of the most severe opportunistic affection in HIV-infected patients.

II.2.1. Main Etiologic germs for HIV/AIDS infection in adults

TABLE 1: Predominantly lymphocytic meningitis

Virus	Bacteria	Parasites	Fungi
Enterovirus: - **Coxsackie A and B virus** - **ECHO virus** - **Poliovirus**	Tuberculosis Syphilis Listeriosis Bucellosis Leptospirosis Rickettsiosis	Toxoplasmosis Trypanosomiasis	Cryptococcosis Candidosis
Paramyxovirus			
Herpes virus: - **HSV1, HSV2** - **HSV6** - **Zona and Varicella virus** - **CMV** - **EBV**			
HIV			
Adenovirus			
Arena virus			
Arbovirus			

Source: Nduwimana JMV, *Méningites associées au VIH/SIDA chez l'adulte au CHK : Aspects diagnostic, thérapeutique, et évolutif. A propos de 82 cas.*

B) Purulent meningitis

TABLE 2: Etiologies of purulent meningitis

Form and Gram	Germs
Gram negative cocci	Neisseria meningitides
Gram positif cocci	*Streptococcus pneumoniae* *Streptococcus agalactiae B* *Staphylococcus epidermidis* *Staphylococcus aureus*
Gram negative bacilli	*Escherichia coli* Salmonnella Pseudomonas aeruginosa Acinetobacter Enterobacter Serratia Proteus *Klebsiella pneumoniae* *Haemophilus influenza* Aeromonas
Gram positive bacilli	Listeria monocytogenes Corynebacteria Bacillus Actinomyces

II.2.2. Diagnostic methods

A) Clinic

A number of symptoms clinically allow to suspect meningitis:

- Symptoms from inflammation of the meninges: a severe headache that won't go away, fever and neck stiffness; were mostly associated with signs from irritation of the meninges such as Kernig and Brudzinski sign
- Signs from increased intracranial pressure: vomiting, bradycardia, arterial hypertension.
- Behavior troubles : trouble of consciousness as agitation, somnolence and even coma

B) Para clinic

TABLE 3: Comparison of CSF founding between Purulent and lymphocytic meningitis

	Purulent meningitis	**Lymphocytic**
Macroscopic aspects	Purulent or xanthochromic CSF	Clear CSF
Opening pressure	High (>180 mmH_20)	Normal or slightly increased
Leukocytes	Increased (frequently >1000 WBC/mm^3 with neutrophilic predominance)	High (10-2000 WBC/mm^3 with lymphocytic predominance)
Ratio CSF glucose/blood glucose	<0.3	>0.6
CSF protein	Increased (frequently >100mg/dl)	Normal or slightly increased
Gram coloration	Positive or negative (50%-80%)	-
Culture	Frequently positive	Negative

Other investigations:

- Funduscopy to investigate Bouchut tubercules, to search for signs of CMV-infection of the retina, papilledema,…
- IDR tuberculin test
- Chest X-ray to exclude pulmonary tuberculosis and pneumonia of other origin
- VDRL if neuro-syphilis is suspected
- Hemoculture can show sometimes the causal germs.
- Soluble antigens (meningococcus, pneumococcus, Cryptococcus,...)
- Sedimentation rate, hemogram and WBC to differenciate between bacterial and viral infection
- Blood smear for malaria

II.2.3.Treatment

A. Predominantly lymphocytic meningitis

TABLE 4: Management of predominantly lymphocytic meningitis

Type of meningitis	Drugs	Dosage	Treatment duration
TB meningitis	2RHZ7E7/7-10RH3	R: 10mg/kg/d H: 5mg/kg/d Z: 30mg/kg/d E: 20mg/kg/d	9 – 12 months[1]
Cryptococcus meningitis	Acute Therapy[2]: - Amphotericine (±Flucytosine) Therapeutic serial lumbar punctures Premedication: - Hydrocortisone - Aspegic Maintenance Therapy[3] Fluconazole	 Amphotericine B: 0.7-1 mg/kg/d Flucytosine: 75-100 mg/kg/d 100mg/dose 1g/dose 200mg/day	 Amphotericine B± Flucytosine for at least 2 weeks followed by Fluconazole 400 mg/day per os to complete a 10 weeks course Lifetime
Syphilitic meningitis	Penicillin G or Ceftriaxone	Penicillin G: 200000-400000 UI/kg/d Ceftriaxone: 1-2g/j	10 days
H. capsulatum meningitis	Amphotericine B or Ketoconazole or	Amphotericine B: 0.5-1 mg/kg/d Ketoconasole and Itraconazole: 400 – 600 mg/d	± 3 months
Viral meningitis **Particular case: Herpetic meningo encephalitis**	Symptomatic Acyclovir	- 10-15mg/kg/dose	Until recovery 14-21 days

[1] National protocol according to PNILT suggests a treatment duration of 6 months
[2] Administered every day
[3] Administered every day for Fluconazole, once or twice for Amphotericine B

B. Purulent meningitis

TABLE 5: First line treatment of purulent meningitis

	Frequent germs	Antibiotics of choice	Dosage
Unknown gram stain	-	Ceftriaxone or Cefotaxime ± Ampicillin	Ceftriaxone:2g/12h Cefotaxime:2g/6h Ampicillin:2g/4h
Gram + cocci	S. pneumonia S. aureus	Ceftriaxone or Cefotaxime+Vancomycine	Vancomycine:1-2g/12h
Gram- cocci	L. monocytogenes	Ampicillin or Gentamicine	Gentamicine:1.5-2.5mg/kg/d
Gram- bacillus	N. meningitis	Chloramphenicol or PenicillinG	Chloramphenicol:1g/8h PenicillinG:4MUI/4h
	H. influenza E. coli Salmonella	Cefotaxime or Ceftriaxone	Idem

Source : Nduwimana JMV, *Méningites associées au VIH/SIDA chez l'adulte au CHK : Aspects diagnostic, thérapeutique, et évolutif. A propos de 82 cas.*

C .Treatment outcomes

A good evolution (recovering) of meningitis associated with HIV/AIDS depends on different factors such as precocity of diagnosis, treatment, prescription and respect of specific drugs and immunity state of the patient. The mean of the healing rate is 60% in all forms of meningitis.

Mortality/Morbidity: Mortality rates and morbidity vary by the etiology of meningitis and its values remain elevated. In 2005, in Malawi Robertson et al. (15) found a mortality rate of 35% in well treated Cryptococcus meningitis patients. Higher mortality rates correlate with poor mental status, high CSF opening pressure at presentation, positive India ink test, extra-CNS manifestations, and higher fungal burdens.

Complications:

- Cryptococcus meningitis may recur after treatment. Without maintenance therapy, 50-70% of patients relapse within 1 year. The rate decreases to 2-7% in patients treated with long-term fluconazole.

- CMV encephaloventriculitis also may recur. As for cryptococcal meningitis, relapse within 1 year is most likely in patients who do not receive maintenance therapy.

III. METHODS

III.1. Study design

The study design is a retrospective descriptive study covering a 6-year period from the 1st of January 2001 to 31st of December 2006.

III.2 Ethical issues

Since we were doing a retrospective study, we were not able to consult the patients or their families to obtain their informed consent.

III.2. Area of the study

It concerns all HIV/AIDS positive patients hospitalized in the Internal Medicine Department of the Butare University Teaching Hospital during the period of our study. CHUB is a referral hospital, specially for the southern region. It also contributes in the training of medical students.

III.3. Inclusion criteria

We included all HIV/AIDS-positive patients who were hospitalized in the time from 01/01/2001 to 31/12/2006 because of meningitis

III.4 Methodology of data collection

III.4.1 Collected data

Questionnaires filled with data from patients folders. The questionnaire contained:

- Socio-demographic data: age, sex, address, profession, matrimonial status.
- Clinical data:
  - Anamnesis: Past medical history, duration of symptoms
  - Physical examination: meningitis clinical signs, HIV/AIDS clinical manifestations
  - Laboratory findings: CSF results
  - Others:
    - Final diagnosis: these data were retrieved from the patient file.
    - Treatment
    - Outcome: categories were “healed”, “dead” and “unknown”. Information about sequelae were rare in the files.

III.4.2 Data management

Data were collected onto paper questionnaires and entered onto the computerized questionnaires driven by epi-data software. The final analysis was done with the help of SPSS (version 14.0). Please find the questionnaire in the annexes. As threshold for the statistical tests we used a p value of <0.05.

III.5. Limitations

- Some patients' files were incomplete and we lacked information on many items such as CD4 count, complications, since when the patient is living with HIV, past medical history and so on.
- Specific diagnosis of meningitis was sometimes not available because of lack of more specific diagnostic tests for bacterial (syphilitic), viral and parasitic meninges infections.

IV. RESULTS

Between 2001 and 2006, in a total number of 495 hospitalized HIV-positive patients, 86 cases (17.37%) of meningitis have been recorded.

Table 6: Comparison of meningitis and other pathologies in HIV-positive patients in our study

Pathology	Number	Percentage
Meningitis	86	17.37%
Other pathologies	409	82.63%
Total	495	100%

Table 7: Distribution of HIV patients hospitalized from 2001-2006

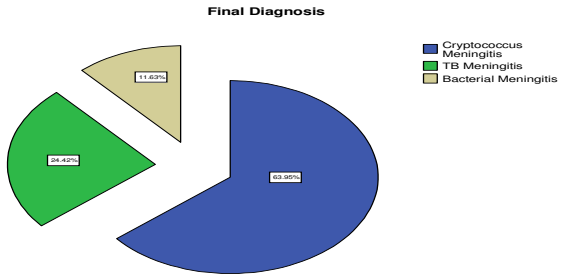
Year	2001	2002	2003	2004	2005	2006
Number of HIV-positive patients	63	63	97	124	73	76
Number of meningitis	13	14	17	14	14	13
Prevalence (%)	20.63	22.22	17.52	11.29	19.17	17.10

IV.1 Description of the study population

Due to the inclusion criteria, all the 86 patients of our study had a co-infection of HIV and meningitis. Three types of meningitis including Cryptococcus, TB and Bacterial meningitis were observed. No case of viral, parasitic or candida meningitis was recorded over the period of study.

Table 8: Types of meningitis

		Number of patients	Percent
Type of meningitis	Cryptococcus	55	64.0
	TB	21	24.4
	Bacterial	10	11.6
	Total	86	100.0



Graph 1: types of meningitis observed

IV.2 Socio-demographic profile of the study population

IV.2.1 Origin

On a total number of 86 patients included in our study, 76 (88,4%) are from the southern province, 1 from the eastern province, 3 from the western province and 6 from Kigali City.

Table 9: Origin of the patients

	Number of patients	Percent
south	76	88.4
east	1	1.2
west	3	3.5
MVK	6	7.0
Total	86	100.0

IV.2.2 Age of the patients

In our study 72 patients (83.7%) are less than 45 years old. The 26-45 age group is the most affected by HIV-meningitis co-infection with 70 patients (81.4%) and Cryptococcus neoformans was the most frequent cause of meningitis in the same group (61.4%). The difference is not statistically significant (p=0.696). The mean age was 38.6 and ranging from 20 to 75. (Table 10)

Table 10: Distribution of HIV-meningitis co-infection by age group

		Type of meningitis			Total
		Cryptococcus	TB	Bacterial	
Age	<= 24	2	0	0	2
	25 - 29	6	3	0	9
	30 - 34	10	5	5	20
	35 - 39	13	1	3	17
	40 - 44	12	7	1	20
	45 - 49	4	3	1	8
	50 - 54	4	0	0	4
	55 - 59	2	0	0	2
	60 - 64	0	1	0	1
	70 - 74	0	1	0	1
	75+	1	0	0	1
Total		54	21	10	85

IV.2.3 Sex

In 86 HIV-positive patients who developed meningitis 51 were female (59.3%) and 35 male (40.7%) with a male/female ratio of 0.68. Cryptococcus meningitis was the most prevalent type in both sexes. The difference is not statistically significant (p=0.405).

Table 11: Distribution of HIV-meningitis co-infection by sex

			Type of Meningitis			Total
			Cryptococcus	TB	Bacterial	
Sex:	F	Count	34	10	7	51
		%	66.7%	19.6%	13.7%	100.0%
	M	Count	21	11	3	35
		%	60.0%	31.4%	8.6%	100.0%
Total		Count	55	21	10	86
		%	64.0%	24.4%	11.6%	100.0%

IV.2.4 Occupation

The majority of HIV-positive patients affected by meningitis were farmers (60), followed by state employees (24), and one private sector employee.

Table 12: Distribution of HIV-meningitis co-infection by occupation

			Type of meningitis			Total
			Crypto	TB	Bacterial	
Profession	Farmer	Count	38	15	7	60
		%	63.3%	25.0%	11.7%	100.0%
	State	Count	16	5	3	24
		%	66.7%	20.8%	12.5%	100.0%
	Private	Count	0	1	0	1
		%	.0%	100.0%	.0%	100.0%
	Other	Count	1	0	0	1
		%	100.0%	.0%	.0%	100.0%
Total		Count	55	21	10	86
		%	64.0%	24.4%	11.6%	100.0%

IV.2.5 Marital status

Table 13: Repartition of HIV-meningitis co-infection by marital status

			Type of Meningitis			Total
			Cryptococcus	TB	Bacterial	
Marital Status:	Single	Count	9	3	0	12
		%	75.0%	25.0%	.0%	100.0%
	Married	Count	21	9	4	34
		%	61.8%	26.5%	11.8%	100.0%
	Separated	Count	1	1	0	2
		%	50.0%	50.0%	.0%	100.0%
	Widow	Count	10	3	2	15
		%	66.7%	20.0%	13.3%	100.0%
Total		Count	41	16	6	63
		%	65.1%	25.4%	9.5%	100.0%

IV.2.6 Distribution of patients according on the period of study

Table 14: Distribution of patients by year of hospital stay

			Type of Meningitis			Total
			Cryptococcus	TB	Bacterial	
Year:	2001	Count	12	0	1	13
		%	92.3%	.0%	7.7%	100.0%
	2002	Count	8	4	2	14
		%	57.1%	28.6%	14.3%	100.0%
	2003	Count	11	3	3	17
		%	64.7%	17.6%	17.6%	100.0%
	2004	Count	7	6	1	14
		%	50.0%	42.9%	7.1%	100.0%
	2005	Count	9	4	1	14
		%	64.3%	28.6%	7.1%	100.0%
	2006	Count	7	4	2	13
		%	53.8%	30.8%	15.4%	100.0%
Total		Count	54	21	10	85
		%	63.5%	24.7%	11.8%	100.0%

p=0.478

IV.3 Past medical history and Clinical aspects

IV.3.1 Past medical history

Among 86 patients with meningitis 20 (23%) had a history of tuberculosis, 6 (7%) a history of meningitis, 3 (3.5%) a history of pneumonia. Only one patient with Cryptococcus meningitis had a previous history of facial palsy. Past history of meningitis were more frequent in patients with Cryptococcus meningitis with a statistically significant difference (p=0.035).

Table 15: Distribution of patients according to past morbid history and type of meningitis

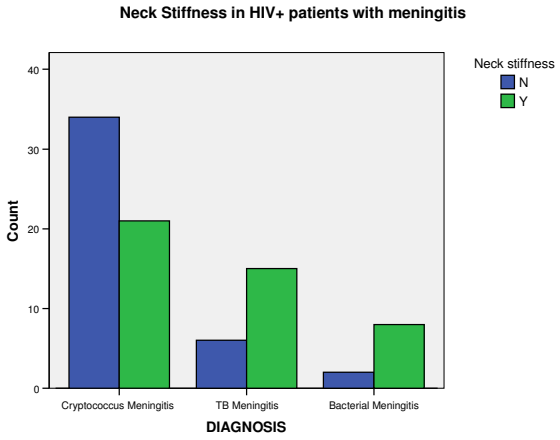
		Type of meningitis			P value (chi-Square)	Statistic decision
		Cryptococcus Meningitis	TB Meningitis	Bacterial Meningitis		
		%	%	%		
Tuberculosis	Y	25.5	23.8	10.0	0.075	Not Significant
Meningitis	Y	12.7	9.5	10.0	0.035	Significant
Pneumonia	Y	3.6	4.8	0.0	0.088	Not Significant
Others (facial palsy)	Y	1.8	0.0	0.0	0.752	Not significant

IV.3.2 Clinical signs of meningitis in HIV-positive patients

Headache (p=0.163), high fever (p=0.961), neck stiffness (p=0.005), Kernig sign (p=0.181) and vomiting (p=0.941) are the most frequent signs in all types of meningitis seen in our study. There is no statistically significant difference of clinical signs between the different types of meningitis except for neck stiffness which is more associated with bacterial meningitis than others (p=0.05).

Table 16: Distribution of patients according to clinical signs and types of meningitis

		Type of meningitis			P value (chi-Square)	Statistic decision
		Cryptococcus meningitis	TB meningitis	Bacterial meningitis		
		%	%	%		
Headache	Y	85.5	81.0	60.0	0.163	Not significant
Fever	Y	65.5	66.7	70.0	0.961	Not significant
Neck stiffness	Y	38.2	71.4	80.0	0.005	Significant
Kernig sign	Y	16.4	28.6	40.0	0.181	Not significant
Conscious troubles	Y	34.5	23.8	30.0	0.662	Not significant
Photophobia	Y	3.6	0.0	0.0	0.739	Not significant
Motor and sensory deficits	Y	5.5	0.0	0.0	0.416	Not significant
Vomiting	Y	45.5	42.9	40.0	0.941	Not significant



Graph 2: Neck stiffness in HIV-positive patients affected by meningitis

IV.3.3 Clinical manifestation of HIV/AIDS

Dermatosis, condylomas and vaginal candidiasis have been only seen in patients with a cryptococcus meningitis co-infection. Meanwhile progressive wasting is more associated with tuberculous meningitis with a statistically significant difference (p=0.047). (Table 17).

Table 17: Distribution of patients according to clinical manifestation of HIV and type of meningitis

		Type of meningitis			P value (chi-Square)	Statistic decision
		Cryptococcus meningitis	TB meningitis	Bacterial meningitis		
		%	%	%		
Progressive wasting	Y	14.5	33.3	0.0	0.047	Significant
Long lasting fever	Y	12.7	9.5	10.0	0.913	Not significant
Chronic diarrhoea	Y	1.8	4.8	0.0	0.654	Not Significant
Chronic cough	Y	10.9	4.8	10.0	0.709	Not significant
Oral Candidosis	Y	30.9	33.3	10.0	0.361	Not significant
Zona	Y	3.6	4.8	0.0	0.792	Not significant
Other (condyloma, dermatosis, vaginal candidosis)	Y	5.4	0.0	0.0	0.941	Not significant

IV.3.4 Distribution of patients according to type of meningitis and CSF biochemical parameters

a. CSF macroscopic aspect

Table 18: Distribution according to the macroscopic aspects of CSF

			Type of meningitis			Total
			Cryptococcus	TB	Bacterial	
Macroscopic aspect	Clear	Count	49	18	0	67
		%	73.1%	26.9%	.0%	100.0%
	Xanthochromic	Count	2	0	1	3
		%	66.7%	.0%	33.3%	100.0%
	Purulent	Count	1	1	9	11
		%	9.1%	9.1%	81.8%	100.0%
	Hematic	Count	1	1	0	2
		%	50.0%	50.0%	.0%	100.0%
Total		Count	53	20	10	83
		%	63.9%	24.1%	12.0%	100.0%

P=0.000

b. CSF glucose and protein

CSF biochemical parameters were measured in 73 patients. Among them 54 had hypoglycorrhachia (59.3% with Cryptococcus meningitis), 15 had normal CSF glucose level and 4 had hyperglycorrhachia. All the patients with bacterial meningitis had diminished CSF glucose. The difference is not statistically significant (p=0.351). (Table 19). The CSF protein level is higher in bacterial and tuberculous meningitis (p=0.001 using Kruskal Wallis test)

Table 19: Distribution of patients according to CSF glucose and type of meningitis

			Type of meningitis			
			Cryptococcus	TB	Bacterial	Total
CSF Glucose (mg/dl)	<= 45	Count	32	15	7	54
		%	59.3%	27.8%	13.0%	100.0%
	46 - 80	Count	12	3	0	15
		%	80.0%	20.0%	.0%	100.0%
	81+	Count	2	2	0	4
		%	50.0%	50.0%	.0%	100.0%
Total		Count	46	20	7	73
		%	63.0%	27.4%	9.6%	100.0%

Table 20: Distribution of patients according to LCR proteins and type of meningitis

	Type of meningitis	N	Mean Rank
LCR Proteins	Cryptococcus meningitis	46	27,80
	TB	20	52,05
	Bacterial	7	54,43
	Total	73	

c. CSF white blood cells

CSF WBC count shows hypercytosis with neutrophilic predominance, normal WBC count in Cryptococcus meningitis. A moderate hypercytosis is noticed in tuberculous meningitis (p=0.002)

Table 21: Distribution of patients by CSF WBC count and type of meningitis

			Type of meningitis			Total
			Cryptococcus	TB	Bacterial	
Leucocytes	<= 5	Count	6	1	0	7
		%	85.7%	14.3%	.0%	100.0%
	6 - 250	Count	25	8	2	35
		%	71.4%	22.9%	5.7%	100.0%
	251+	Count	11	10	8	29
		%	37.9%	34.5%	27.6%	100.0%
Total		Count	42	19	10	71
		%	59.2%	26.8%	14.1%	100.0%

IV.4 Outcome

Among 55 patients with Cryptococcus meningitis 43.6% recovered and 40% died for the rest we did not have the information on whether they recovered or not. 28.6% of TB meningitis patients died and 47.6% recovered. For bacterial meningitis patients, 60% died and 30% recovered. The difference is not statistically significant with p=0.550 (Table 19)

Table 22: Outcome after treatment according to the type of meningitis

		Type of Meningitis			Total
		Cryptococcus	TB	Bacterial	
Heal	Count	24	10	3	37
	%	43.6%	47.6%	30.0%	43.0%
Death	Count	22	6	6	34
	%	40.0%	28.6%	60.0%	39.5%
Unknown	Count	9	5	1	15
	%	16.4%	23.8%	10.0%	17.4%
Total	Count	55	21	10	86
	%	100.0%	100.0%	100.0%	100.0%

IV.5 Duration of stay in hospital

The mean hospitalization duration was 15.6 days in Cryptococcus meningitis, 28.25 days in TB meningitis, and 12.0 days in bacterial meningitis. The difference of hospitalization duration is not statistically significant (p=0.140).Table (20)

Table 23: Duration of hospitalization according to the type of meningitis

		Type of meningitis			Total
		Cryptococcus	TB	Bacterial	
Days	<= 14	31	6	7	44
	15 - 30	17	10	2	29
	31+	4	4	1	9
Total		52	20	10	82
Mean		15.67	28.25	12.00	
Minimum		1	3	1	
Maximum		110	120	32	

IV.6 Prognostic

There is an association between duration of treatment and the outcome. Among 35 patients hospitalized less than14 days, 25 died and among 32 hospitalized more than 15 days 7 patients died. The difference is statistically significant (p=001).

Table 24: Outcome according to the duration of treatment

		Outcome		
		heal	death	Total
Duration of treatment	<= 14	10	25	35
	15 - 30	19	6	25
	31+	4	3	7
Total		33	34	67

V. DISCUSSIONS AND COMMENTS

V.1 General view

The internal medicine service of CHUB is among the sites receiving the highest number of HIV-positive patients in Rwanda. In our study 495 HIV-positive patients have been hospitalized in the same service between 2001 and 2006. Among them 86 (17.3%) where hospitalized for meningitis with lymphocytic meningitis predominance (p=0.000). Since 2003, the co-infection rate is slightly decreasing probably due to a better management of HIV-positive patients (free antiretroviral drugs available for eligible patients).

In France 2004, Dromer et al. (4) , demonstrated a 46% decreased incidence of Cryptococcus infection after the introduction of HAART.

V.2 Socio-demographic profile of study population

V.2.1 Origin of the patients

The majority of our patients (88.4%) are from the southern region of Rwanda. This is due to the geographic situation of CHUB, most of its patients coming from south.

V.2.2 Types of meningitis according to sex and age

In our study, 51 women and 35 men have been recorded (sex ratio men/women: 0,7). This female predominance is not statistically significant (p=0.405). The mean age was 38.6, ranging from 20 to 75, the most affected age group was 26-45.

In Rwanda (CHUK), in 1992, BOGAERTS et al. (8) found a male predominance with men/women sex ratio of 1.5 for Cryptococcus meningitis, 1.17 for TB meningitis, with a mean age of 36.3. In Burundi (Bujumbura), in 1990, LAROCHE, et al. (14) found a male/female ratio 1.7 with a mean age of 37, ranging from 23 to 66 in patients with Cryptococcus meningitis.

The female predominance mainly in Cryptococcus meningitis might be due to the fact that Rwandese women and girls are constantly in agricultural work and in other activities and thus exposed to Cryptococcus germ which is staying in such environment.

V.3 Etiologies of meningitis in HIV-positive patients

In 86 cases of HIV-meningitis, 3 etiologies of meningitis were observed: Cryptococcus meningitis (64%), TB meningitis (24.4%) and bacterial meningitis (11.6%). In general Cryptococcus and TB are very common in HIV-positive patients. The high prevalence of Cryptococcus meningitis could be related to the high prevalence of HIV/AIDS (3%) in our country which contributes to the proliferation of this causal germ in nature. As discussed already in chapter III.5 (Limitations) it is likely that not all etiologies were diagnosed. This can be explained by the lack of the diagnosis tests for viral meningitis, syphilitic meningitis and parasitic infections (e.g. toxoplasomosis). (13)

The prevalence of TB meningitis could also be related to the high prevalence of active tuberculosis at another site in HIV/AIDS patients. In Ivory Coast, LUCAS SB et al. (11), in 1993, observed 20% of TB meningitis within HIV-positive patients with tuberculosis.
In 1994, in Malawi, MAHER et al. (12) and in 1992 DE COCK et al. (3) in South Africa, documented Cryptococcus and TB meningitis as the main etiologies of HIV-meningitis association. In Rwanda (CHUK) in 2001 KARASI (10) found a cryptococcal predominance in 2160 cases of meningitis.

V.4 Clinical aspects

V.4.1. Clinical signs

Headache, fever, neck stiffness, vomiting, was the most frequent clinical manifestations of meningitis in HIV-positive patients in our study.

Our results are also supported by a study done by Chuck and Sande (2), in 1989 where the patients infected with HIV cryptococcal meningitis typically present with fever, headache, nausea and vomiting, and cognitive dysfunction. Meningeal signs and photophobia are less common than in patients who are HIV negative; focal findings and seizures may be seen but are uncommon. Although the onset of disease can be acute, it is more often chronic or insidious.

Among the clinical signs of HIV infection, progressive wasting (p=0.047), oral candidosis (p=0.361) and long lasting fever (0.913) were the most frequent observed manifestations in our study population.
This can be explained by the fact that Cryptococcus meningitis as well as progressive wasting, oral candidosis and long lasting fever onset occur at later stages of HIV/AIDS infection.

Similarly in 2002, NDUWIMANA (7), observed in CHUK that in HIV patients with meningitis, clinical manifestations of AIDS were led by progressive wasting (p=0.0000), long lasting fever (p=0.0004), chronic cough (p=0.0006) and oral candidosis (p=0.003).

V.4.2 Past medical history

Among 86 patients in our study, 20 (23.2%) had a history of Tuberculosis (p=0.075). This can be explained by the fact that HIV-infected patients are morelikely predisposed to tuberculosis at any anatomical site. In South Africa ELI SILBER et al. (5) documented a history of tuberculosis in 55% patients with HIV-meningitis association.

In our study, 6 (6.97%) patients had a history of meningitis. Unfortunately there was no further information about the type and circumstances of the previous meningitis. Recurrent meningitis is very common in cryptococcal meningitis.

V.5 Para clinic aspects

Of a total number of 66 patients with lymphocytic meningitis more than 71.21% had low CSF glucose level (<45mg/dl) and high CSF protein (>45mg/dl). Normal values were mainly observed in Cryptococcus meningitis patients. All patients with bacterial meningitis had an association of low CSF glucose and high CSF protein, as it was expected.

In Zimbabwe, HAKIM et al. (9) found 10% of normal CSF within cryptococcal meningitis patients.90% had an association of hypercytosis, low CSF glucose level, and high CSF protein level.

In South Africa, SILBER et al. (5) documented 33% of normal CSF results mainly within patients affected by cryptococcus meningitis while 67% had classic CSF abnormalities. Normal CSF findings have been also noticed by ZUGER et al. (18) in cryptococal meningitis.

V.6 Outcome in the hospital

Among 86 patients of our study a clinical improvement have been noticed for 43.0%.The difference between three types of meningitis is not statistically significant (p=0.550). This low number of clinical improvement can be explained in some cases by low income for some patients. This lack of possibilities to buy themselves the indicated drugs creates irregularities in meningitis management.
In South Africa BERGMAN and KARSTAEDT (1) documented a clinical improvement of 50% while ZUGER (18) in America found a clinical improvement in more than 60% of his patients. In one study from Malawi, availability of fluconazole has decreased the mortality of cryptococcal meningitis from 100% to 35% (Robertson et al, 2005).

The number of deaths was 34 (39.5%) among 86 patients of our study, among them 64.7% are from Cryptococcus meningitis. The high mortality rate (40%) of cryptococcal meningitis can be explained by poor prognosis of this type of meningitis and the severe HIV/AIDS immuno-depression. Particularly the lack and the elevated cost of anti fungal drugs have probably contributed in increasing the cryptococcal meningitis related mortality.

In Zimbabwe, HAKIM et al. (9) found a mortality rate of 68% in HIV-positive patients with an acute meningitis co-infection. NDUWIMANA in 2002 in CHUK (7), observed that in patients with meningitis 59,5% of deaths were due to Cryptococcus meningitis

Compared with patients who have ‘‘conventional’’ bacterial meningitis, patients with lymphocytic meningitis typically have stayed in the hospital for a longer time. This can be explained by the fact that these types of meningitis are more likely to undergo a chronic stage.

V.7. Prognostic factors

There is an association between the duration of stay in hospital and the outcome. If you survive the first 14 days, the chances get better to recover. The lack of some information limited our further investigations in factors that affect the outcome after treatment.

In 1997, a study by van der Horst and colleagues (17), found in HIV-positive patients with cryptococcal meningitis managed with Amphotericine B and Floconazole that mortality was 5.5% in the first 2 weeks of treatment and 3.9% in the subsequent 8 weeks.

VI. Conclusions and recommendations

VI.1. Conclusions

a) Epidemiological aspects

- Meningitis remains among the most common HIV/AIDS opportunistic diseases in internal medicine department of CHUB (17.37%).
- The most affected age group is the one from 26-45, note that this group is the economically active group.

b) Etiologic view

We observed a high prevalence of cryptococcal and tuberculous meningitis in HIV-infected patients:

- In our study (among HIV-infected patients) Cryptococcus neoformans was the most common causal germ of meningitis (64.0%).
- Tuberculous meningitis is also a common causal germ of meningitis in patients infected by HIV (24.4%).

c) Clinical aspects

- Headache, high fever, neck stiffness, Kernig sign and vomiting are the most frequent signs in all types of meningitis seen in our study.
- Neck stiffness is more associated with tuberculous and Bacterial meningitis (p=0.005)

d) Para clinic aspects

- The laboratory diagnostic of Cryptococcus meningitis is easier and highly specific using Indian ink (p=0.000).
- Because CSF smear and culture are insensitive, diagnosis of tuberculous meningitis is often presumptive. It is then based on compatible clinical findings and CSF profile, risks for tuberculosis. Only in a few patients active tuberculosis can be identified at another anatomical site.
- The diagnostic of bacterial meningitis is mainly based on bacteriological and biological findings. It is easily established in presence of turbid CSF, hypercytosis (neutrophilic predominance), low CSF glucose level and high CSF protein level.
- According to our findings the CSF protein level is more significant than CSF glucose level to differentiate between on one hand cryptococcal meningitis and on other hand tuberculous and bacterial meningitis (p=0.001).

e) Management and outcome

- Management of Cryptococcus meningitis using Amphotericin B is efficient, but its elevated costs have limited its accessibility and this leads to an increased mortality due to this type of meningitis. Furthermore severe side effects influence the duration of the treatment.
- The national protocol for management of tuberculosis is valid in HIV-positive patients with TB meningitis.
- Chances to recover are increased after the first 2 weeks of treatment

VI.2 Recommendations

Our study is a modest contribution about the HIV-meningitis association in the department of Internal Medicine of CHUB. Nevertheless some recommendations are expressed to:

The Ministry of Health:

- Considered the fact that anti fungal drugs are hardly affordable to our population, it is necessary to supply all referral and district hospital with Amphotericine B and Fluconazole to be freely given to all the patients with Cryptococcus meningitis.
- Provide hospitals with necessary materials to perform Indian ink and cryptococcal antigen tests for an early diagnosis of Cryptococcus meningitis.

The physicians:

- Elaborate more precise and systematic patients' folders, with well organized data to facilitate future studies
- Do systematically lumbar puncture and measure CSF outlet pressure, essentially focus on Ink Indian in HIV-positive patients suspicious of meningitis.
- Establish a consistent system for follow up of those patients to manage further complications of meningitis.

The NUR faculty of medicine:

- Future research should address the coinfection HIV and meningitis and the socio-economic impact of this condition (on the patient and his family as well as on society). Further studies on its prevention would be desirable.
- A prospective design of this future study would be desirable.

REFERENCES

1. BERGMAN and A.S. KARSTAED. The spectrum of meningitis in a population with high prevalence of HIV disease. QJ Med 1996; 89:499-504
2. Chuck SL, Sande MA. Infections with Cryptococcus neoformans in the acquired immunodeficiency syndrome. N Engl J Med 1989;321:794–799.
3. DE COCK KM, SORO B, COULIBARY IM, LUCAS SB. Tuberculosis and HIV infection in sub-Saharan Africa J Am Med Assoc 1992; 268:1581-1587.
4. Dromer F, Mathoulin-Pelissier S, Fontanet A, et al. Epidemiology of HIV-associated cryptococcosis in France (1985–2001): comparison of the pre- and post-HAART eras. AIDS 2004;18:555–562.
5. ELI SILBER, PAMELA SONNENBERG, KEVIN C.HO, HENDRIK J.KOORNHOF, SHAUN EINTRACHT, LYNN MORRIS et al. Meningitis in a community with a high prevalence of tuberculosis and HIV infection.
6. Hammer and Collony, Viral aseptic meningitis in the limited states: clinical features, viral etiologies and differential diagnosis
7. Nduwimana JMV, Méningites associées au VIH/SIDA chez l'adulte au CHK : Aspects diagnostic, thérapeutique, et évolutif. A propos de 82 cas.
8. J. BOGAERTS, D.ROUVROY, H.TAELAMAN, A. KAGAME, M.A. AZIZ, D. SWINNE et al. AIDS associated cryptococcal meningitis in Rwanda (1983-1992) :Epidemiologic and diagnosis features. Journal of infection 1999; 39:32-3
9. James G. HAKIM , INNOCENT T.GONGAIZDO, ROBERT S.HEYDERMAN, JENS MIELKE, EBBAH MUSHANGI, ALBERT TAZIWA et al. Impact of HIV infection on meningitis in Harare, Zimbabwe: a prospective study of 406 predominantly adults patients. AIDS 2000; 14:1401-1407. Journal of the Neurological sciences 1999; 162:20-26
10. KARASI J.C. Les meningites bacteriennes : étude microbiologique. A propos de 2160 cas. Mémoire de la faculté de Médecine. 2001
11. LUCAS SB, HOUNNOU A, PEACOCK C et al. The mortality and pathology of HIV infection in a West Africa city. AIDS 1993; 7:1569-1579
12. MAHER D, MWANDUMBA H. Cryptococcal meningitis in Lilongwe and Blantyre. Malawi J infect 1994; 28:59-64.
13. Marra, Christina M, Infections of the central nervous system in patients infected with HIV. Continuum Neurology, 2006; 12(2): 111-132
14. R. LAROCHE, et al., Cryptococcus in Bujumbura Burundi: apropos of 80 cases observed in 42 months, Bull. Soc. Pathol. Exot. Fil. 83 159 1990
15. Robertson K, Kopnisky K, Mielke J, et al. Assessment of neuroAIDS in Africa.J Neurovirol 2005; 11:7-16
16. UNAIDS, AIDS epidemic update December 2006
17. Van der Horst CM, Saag MS, Cloud GA, et al. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Mycoses Study and AIDS Clinical Trials Group. N Engl J Med 1997;337:15–21.
18. ZUGER A, LOUIS HOLZMAN RS SIMBERKOFF MS, RAHAL JJ. Cryptococcal disease in patients with the acquired immunodeficiency syndrome: diagnostic features and outcome of treatment. Ann Int Med 1986; 104:234-240

ANNEXES