Mortality and Survival of Patients with Central Nervous System Disorders: Prognostic Factors of at the University Hospital Point G, Bamako, Mali

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Abstract
The department of infectious and tropical diseases is the referral for all HIV positive patients in need of hospitalization. HIV has modified the epidemiology of central nervous system (CNS) disorders in Mali.

Objective: *Our objective was to study the prognostic factors of the mortality and survival of patients with CNS disorders in the department of infectious and tropical diseases at the University hospital Point G, Bamako, Mali.*

Methods: *We collected data retrospectively from the medical records inpatients between 1st January 2013 and 31st December 2017 and we used R software version 2.12.2 to analyze data.*

Results: *In five (5) years, we registered 1,315 hospital admissions with CNS disorders with a morbidity rate of 21.14% (278/1315) and 71.7% (125/278) were HIV positive. In bivariate analysis (Log-rank test), there was a statistically significant difference between survival and alcohol consumption (p=0.001) and smoking (p<0.001); history of tuberculosis (p=0.006); presence of dementia syndrome (p<0.001) and positive HIV serology (p=0.01). Multivariate analysis (Cox model) identified dementia [adjusted Hazard Risk, HR=13.02 (2.62 - 64.8)], previous tuberculosis [adjusted HR=13.33 (1.05 - 102.63)], alcohol use [adjusted HR=3.08 (1.67 - 5.69)] and smoking [adjusted HR= 2.9 (1.05 - 7.99)] as poor prognostic factors for survival. According to the Kaplan Meier method, the overall median survival of patients was 37 days [CI 95%; (35-55 days)].*

Conclusion: *Notion of TB, alcohol use and smoking were poor prognostic factors of the survival of HIV positive inpatients with CNS disorders.*

Keywords: Disorders, *Central nervous system, survival, prognostic factors*. Inpatients, Point G.

Introduction

Disorders of the central nervous system (CNS) are common, serious diagnostic and therapeutic emergencies with high mortality rates of up to 10% [1,2]. Cerebromeningeal infectious pathology is fairly similar in its clinical presentation despite its various etiologies (bacterial, parasitic, viral or fungal) [3]. The advent of HIV has changed the epidemiology of CNS disorders. CNS disorders are as prevalent as 40% to 70% in HIV positive patients and can occur at any stage of HIV/AIDS infection [4].

Several studies have been conducted to identify their etiologies and therapeutic approaches. Certainly, few studies have looked in general at survival and prognostic factors according to nosologically entities. This study was aimed at investigating the prognostic factors of mortality and survival of HIV positive inpatients from 1st January 2013 and 31st December 2017 in Bamako, Mali.

Methods

Site of study: This study took place in Bamako, the administrative and economic capital of Mali with a population of around 3 337 122 inhabitants. Bamako is located in the south of the country. This study was conducted in the infectious diseases department of the university hospital of Point G, one of the five university hospitals in the country. This department is the main reference structure for infectious and tropical diseases in Bamako.

Study design: This was a study of the survival and prognosis of inpatients with CNS pathologies from 1st January 2013 to 31st December 2017 (*i.e. over five years*) in the department of infectious and tropical diseases. Data on follow-up factors were collected from 'patient's medical records'. The time (delay) of participation for each patient was either the interval between the first day of hospitalization and the date of the last appointment after discharge or the date of patient's death.

Data collection

We included all the files of inpatients hospitalized for a CNS pathology, diagnosed on the basis of clinical examination (infectious syndrome associated with a confusional or encephalic syndrome, or cerebellar syndrome, or dementia, or focal neurological deficits, and/or Bergman's triad), biological evaluation (evidence of the germ or pathogen in the cerebrospinal fluid) and radiological evaluation (abnormality detected by brain CT Scan). Sometimes, the diagnosis has been retained because of the strong clinical presumption and the favorable clinical evolution of the patients under treatment.

Operational definitions

We considered as:

- Encephalic syndrome, a combination of meningeal syndrome (headache, increased sensitivity to stimuli, sometimes vomiting and stiff neck),
- intracranial hypertension syndrome (nausea, easy vomiting in jet, dizziness, seizures, papillary oedema at the bottom of the eye or on the Computed Tomography (CT) scan) and behavioral disorders.
- Confusional syndrome was defined by a decrease in vigilance, temporo-spatial disorientation, slowing down and diffuse disturbance of intellectual activities, illusions or hallucinations, disturbance of the sleep-wake cycle.
- Dementia was defined as impairment of short-term memory, impairment of intellectual reasoning and judgment, impairment of general activity and emotional state, and social behavior with an impact on social or professional life.
- Bergman's triad combined focal neurological signs (hemiplegia, hemiparesis, convulsions, cranial nerve palsy, ataxia, and visual blurring), an infectious syndrome and an intracranial hypertension syndrome.
- We grouped the CNS disorders by etiology: parasitic (cerebral toxoplasmosis, cryptococcal meningitis and cerebral malaria), bacterial (bacterial meningitis, bacterial brain abscess and tuberculosis meningitis), viral, tumoral or vascular.
- The diagnosis of cerebral malaria (CM) was based on coma with a Glasgow score of less than 15 or convulsion associated with *Plasmodium falciparum* infection and no other apparent cause of convulsion or coma. Cases of Cryptococcal meningitis were confirmed by microscopic evidence of the cryptococcus after staining with China ink.
- Progressive multifocal leukoencephalopathy (PML) was suspected when the disease was generally insidious, unifocal at the beginning, but progressed without remission to a multifocal brain disease. The CT scan showed hypodense lesions without contrast. It was not confirmed in suspected cases even in post mortem.

Data analysis

The data were analyzed with R software version 2.12.2. The Kaplan Meier method was used to estimate the median overall survival of patients. To compare survival rates, the log-rank test was used, taking into account each follow-up factor. To explain survival by all follow-up factors and to identify prognostic factors, the Cox proportional hazard model was applied.

Results

In five (5) years, 1,315 patients were hospitalized in the department, including 278 cases of disorder central nervous system (*proportional morbidity of 21.14%*). Among the 278 included, 126 were HIV-positive (*proportional seroprevalence of 70.8%*).
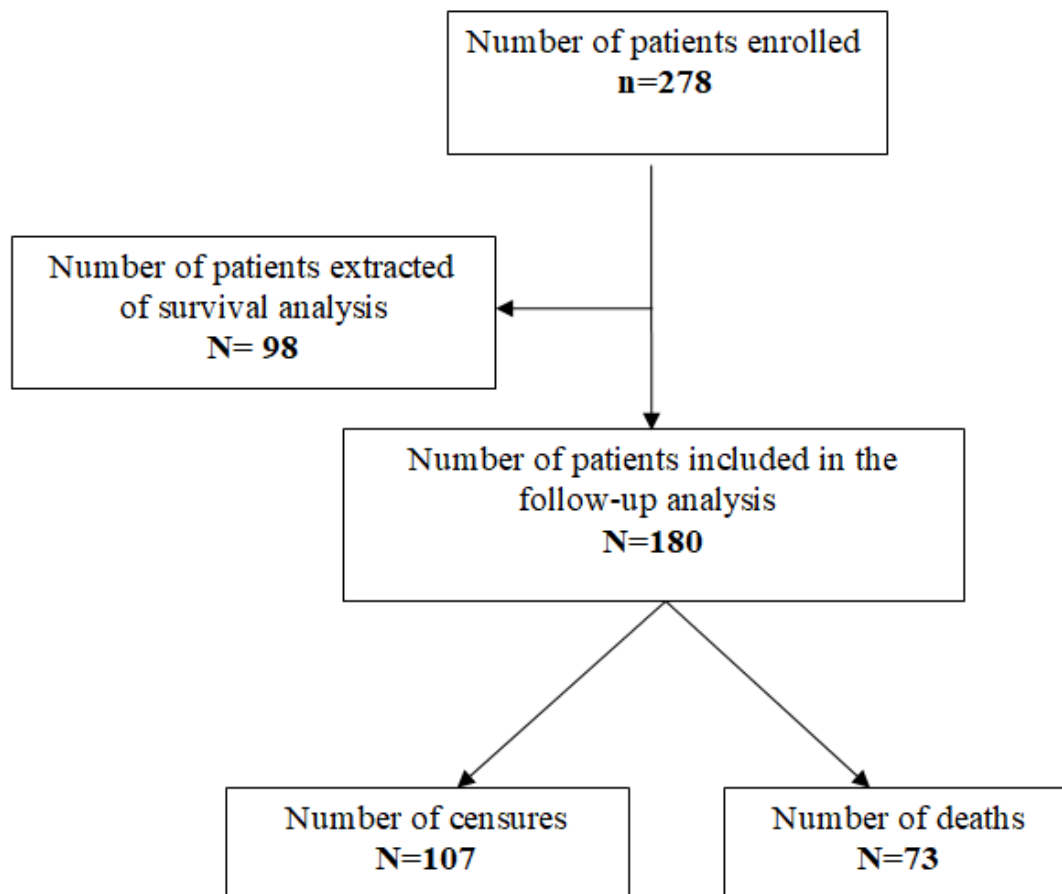
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                    ┌──────────────────────────────┐
                    │   Number of patients enrolled │
                    │            n=278              │
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Figure 1: Flow chart of study participants inclusion.

Characteristics of the study population

We found a predominance of women (52.2%) with a sex ratio of 0.91. The majority of subjects were married (57.2%) with a median age of 33 years old [11-58 years old]. As a lifestyle, 13.3% had a notion of alcohol use and 2.8% tobacco smoking. We found the following medical histories: arterial hypertension (1.1%), diabetes (0.6%), peptic ulcer (2.8%) and tuberculosis (0.6%). The patients were referred in 34.4% of cases by community and district health centers. Table 1 summarizes the description of the study population.

Table 1: Description of sociodemographic characteristics of the study population

Variables		Effectif (N=180)	Percentage
Gender	Male	86	47.8%
	Female	94	52.2%
Marital status	Single	77	42.8%
	Married	103	57.2%
Age (years old)*	16 - 25	28	15.6%
	26 – 34	66	36.7%
	≥ 35	86	47.8%
Alcohol use	Yes	24	13.3%
	No	156	86.7%
Tobacco smoking	Yes	5	2.8%
	No	175	97.2%
Arterial hypertension	Yes	2	1.1%
	No	178	98.9%
Diabetes	Yes	1	0.6%
	No	179	99.4%
Peptic ulcer disease	Yes	5	2.8%

	No	175	97.2%
Notion of Tuberculosis	Yes	1	0.6%
	No	179	99.4%
Referred patients	Yes	62	34.4%
	No	118	65.6%

Average age (Min. – Max.): 33.16 (11-58 years old)

Clinical and biological characteristics

The physical examination revealed Bergman's syndrome (24.4%), dementia syndrome (1.1%) and meningeal syndrome (40%). CNS disorders were parasitic (53.3%), bacterial (39.4%), viral (5.6%), tumoral (lymphoma (0.6%) and cerebral vascular accident (1.1%).

HIV serology was positive in 70% of cases.

Table 2: Clinical and biological characteristics of the study population

Characteristics		Effectif (N=180)	Percentage (%)
Clinical factors			
Bergman's syndrome	Yes	44	24.4%
	No	136	75.6%
Meningeal syndrome	Yes	72	40%
	No	108	60%
Disorder	Cerebral vascular accident	2	1.1%
	Lymphoma	1	0.6%
	Bacterial etiology (Neurobacteriosis*)	71	39.4%
	Parasitic etiology (Neuro parasitosis*)	96	53.3%
	Viral etiology (Neurovirosis*)	10	5.6%
Biological parameters			
Hemoglobin (g/dl)	*Average (Min. – Max.)*	9,47 (3 – 16)	
Average Overall Volume	*Average (Min. – Max.)*	85,57 (27 – 110)	
Blood haemoglobin concentration	*Average (Min. – Max.)*	30.50 (10 – 93)	
Leukocyte count	*Average (Min. – Max.)*	7516 (260 – 201000)	-

Bivariate analysis

The bivariate analysis with the log-rank test concluded that there was no difference in survival regarding the gender (log-rank test, p=0.69), married and single people (log-rank test, p=0.56) and different age groups (log-rank test, p=0.57). On the other hand, there is a statistically significant difference between the survival of alcohol drinkers and non-drinkers (Log-rank test, p=0.001), and between tobacco smokers and non-smokers (Log-rank test, p<0.001). A history of tuberculosis in the patient resulted in a significant difference in survival (Log-rank test, p=0.006) as did the presence or absence of a dementia syndrome (Log-rank test, p<0.001) or positive or negative HIV serology (Log-rank test, p=0.01). There was a trend of difference in survival between the central nervous system diagnostic groups (Log-rank test, p<0.07).

Table 3: Bivariate analysis comparing survival between follow-up factors

Monitoring factors		Effectif	Number of deaths	Log-rank test
Gender	*Male*	86	35	*0.69*
	Female	94	38	
Marital status	*Married*	103	45	*0.56*
	Single	77	28	
Age group	*16 – 25 years*	28	10	*0.57*
	26 – 34 years	66	26	
	≥ 35 years	86	37	
Alcohol use	*Yes*	24	14	*0.001*
	No	156	59	
Tobacco consumption	*Yes*	5	5	*< 0.001*

		175	68	
High blood pressure	Yes	2	1	0.56
	No	178	72	
Peptic ulcer disease	Yes	5	1	0.90
	No	175	72	
Tuberculosis	Yes	1	1	0.006
	No	179	72	
Referred patients	Yes	62	29	0.07
	No	118	44	

Table 4: Bivariate analysis comparing survival between follow-up factors

Monitoring factors		Effectif	Number of deaths	Log-rank test
Bergman's syndrome	Yes	44	18	0.82
	No	136	55	
Meningeal syndrome	Yes	72	26	0.34
	No	108	47	
Intracranial hypertension syndrome	Yes	36	14	0.09
	No	144	59	
Dementia syndrome	Yes	2	2	< 0.001
	No	178	71	
HIV	Positive with HIV+	126	52	0.01
	Negative by HIV-	54	21	
HAART	Yes	51	19	0.55
	No	129	54	
Tuberculosis	Cerebral vascular accident	2	1	0.07
	Lymphoma	1	0	
	Bacterial etiology (Neurobacteriosis*)	71	28	
	Parasitic etiology (Neuro parasitosis*)	96	39	
Hemoglobin (g/dl)	≤ 10 g/dl	127	56	0.09
	> 10 g/dl	53	17	
Mean Blood Volume	≤ 90 fL	111	47	0.04
	> 90 fL	69	26	
Leukocyte count	≥ 4000/mm3	102	41	0.53
	< 4000/ mm3	78	32	

Overall patient survival

According to the Kaplan Meier method, the overall median survival of patients was 37 days (95% CI [35-55 days]).
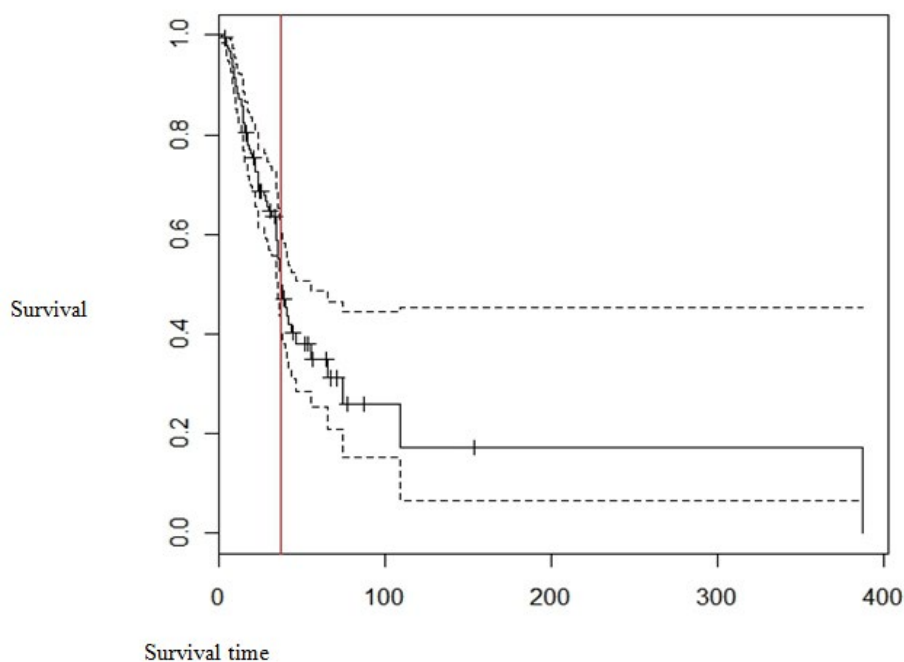
Figure 2: Patient survival figure according to the Kaplan Meier model.

Multivariate analysis

Multivariate analysis of the Cox model identified the following as poor prognostic factors for survival: dementia syndrome [adjusted HR=13.02 (2.62- 64.8)], previous tuberculosis (HR=13.33 [1.05 - 102.63]), and alcohol (HR=3.08 [1.67 - 5.69]) and tobacco (HR= 2.9 [1.05 - 7.99]). The only protective factor was the hemoglobin level (HR=0.81 [0.72 - 0.92]).

Table 4: Multivariate analysis of the Cox model

Pronostic factor	HR brut (IC 95%)	Adjusted HR (IC 95%)	Wald test	Likelihood test
Dementia syndrome				
No (reference.)				
Yes	14.06 (3.2 – 61.72)	13.02 (2.62 – 64.8)	*0.002*	*0.014*
History of tuberculosis				
No (ref.)				
Yes	10.29 (1.37 – 77.46)	13.33 (1.05 – 102.63)	*0.013*	*0.071*
Tobacco smoking				
No (ref.)				
Yes	4.97 (1.98 – 12.45)	2.9 (1.05 – 7.99)	*0.041*	*0.066*
Alcohol use				
No (ref.)				
Yes	2.56 (1.42 – 4.62)	3.08 (1.67 – 5.69)	*<0.001*	*0.001*
Hemoglobin level				
≤ 10 g/dl				
> 10 g/dl	0.82 (0.73 – 0.93)	0.81 (0.72 – 0.92)	*<0.001*	*<0.001*

Discussion

Central nervous system (CNS) disorders are a frequent reason for hospitalization with a proportional morbidity of 21.14% in the infectious diseases department of the Point G University Hospital. It appears to be higher than that reported by Soumare et al in Dakar, where the prevalence of disorders of central nervous system in the infectious diseases department of the Fann University Hospital was 11.4% [2]. The advent of HIV has profoundly changed the epidemiological profile of patients with central nervous system disorders in Africa, where HIV seroprevalence remains high compared to the North.

According to the Kaplan Meier method, the overall median survival of our patients was 37 days (95% CI; [35-55 days]). We have found few studies on survival in CSN disorders or pathologies. However, Correa RB et al, in a study of the impact of neurological manifestations on the survival of Brazilian AIDS patients, reported that 43.7% of their patients had a survival of less than one month after the onset of the disorder and 45.6% had a survival of between one (1) and six (6) months [6]. This decrease in survival in our context would be related to the severity of the pathology, particularly in the case of HIV, but also to the late treatment in relation to a rather long and complex therapeutic route. Most often, Malian patients consult the traditional practitioner first, then the first level of care, without counting the high frequency of self-medication.

The bivariate analysis with the Log-rank test allowed us to conclude with respect to socio-demographic characteristics that there was no difference in survival between men and women ($p=0.69$), married and single people ($p=0.56$) and the different age groups compared ($p=0.57$). All these categories therefore have the same risk of disorders of central nervous system but also the same probability of death. However, there was a significant difference between survival according to lifestyle such as alcohol use ($p=0.001$) and tobacco smoking ($p<0.001$). Some authors have reported that alcohol consumption increases the risk of death in certain central nervous system diseases [7]. Alcohol and tobacco progressively destroy the nervous system (functional and injury toxicity), which worsens the damage and increases the risk of death in CNS disorders [8, 9].

A history of tuberculosis in the patient resulted in a significant difference in survival ($p=0.006$) in our study. Although tuberculous meningitis is specific to immunodepression or AIDS, tuberculosis is the most common opportunistic infection during AIDS in Africa. In Mali, tuberculosis is a public health problem with an estimated incidence of 56 (37-79) cases per 100 000 persons in 2016. The therapeutic success rate is 77%, with a mortality rate of 7.7% (*National Tuberculosis Control Programme Reports 2015 and 2016*). Tuberculosis is the second most common cause of meningoencephalitis in France in the general population not infected with HIV [10]. In pulmonary tuberculosis, however, meningeal involvement is ten (10) times more frequent in the context of AIDS than in the general population. This requires systematic assessment of the CSF in these cases. This is the case for tuberculous meningoencephalitis (2.3%) with a case fatality rate of 45.5%.

Multivariate analysis of the Cox model identified dementia syndrome as a poor prognostic factor for survival ($p<0.001$, HR=13.02 [2.62 - 64.8])]. Indeed, this syndrome has been observed during probable progressive multifocal leukoencephalitis (PML) and HIV-related encephalitis without pathological evidence being established. In Canada, Walsh et al reported that 19% of patients had evidence of HIV-1 associated dementia before death and at autopsy. Twelve (12) of the 16 cases had neuropathological lesions and the most common diagnoses were HIV-1 encephalitis, progressive multifocal leukoencephalopathy, toxoplasmosis and primary central nervous system lymphoma [12].

There was a significant difference in survival between positive and negative HIV status (Log-rank test, p=0.01).

Conclusion

Disorders CNS are an important part of inpatient care in our department. Their epidemiology has changed in infectious diseases departments since the advent of HIV. Early referral for appropriate management and consideration of prognostic factors may help to improve patient survival. It is also necessary to strengthen the technical platform and improve access to para-clinical examinations. It is also necessary to strengthen the capacity of resources through training.

Acknowledgements

Conflict of interest

The authors declare no conflict of interest.

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